Clinical Value of Whole-body FDG-PET for Recurrent Gastric Cancer: A Multicenter Study

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Objective: The purpose of this multicenter study was to evaluate the clinical usefulness of positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) for suspected recurrent gastric cancer.

Methods: We performed a retrospective review of 92 consecutive patients who underwent PET [either integrated PET/computed tomography (CT) or manual fusion of dedicated PET and CT] scans for post-treatment surveillance of gastric cancer between June 2006 and December 2007. Of these patients, 46 patients were suspected of recurrence by other imaging modalities (Group A), 19 patients were suspected of recurrence by tumor markers without definite findings (Group B) and the remaining 27 patients underwent a PET scan without evidence of recurrence (Group C). The diagnostic performance and prevalence of the clinical impact of FDG-PET were analyzed.

Results: Recurrence of gastric cancer was confirmed in 31 patients (67%) in Group A, in 11 patients (58%) in Group B and in 2 patients (7%) in Group C. In addition, colon cancer (n = 3), lung cancer (n = 1) and pulmonary carcinoid (n = 1) were identified in five patients (5%). In patient-basis, the sensitivity, specificity and diagnostic accuracy of PET for recurrence were 81%, 87% and 83%, respectively, in Group A, 73%, 88% and 79%, respectively, in Group B and 50%, 88% and 85%, respectively, in Group C. Therapeutic management was influenced by PET results in 22 patients (48%) in Group A, in 8 patients (42%) in Group B and in 2 patients (7%) in Group C, including cases in which PET was helpful for detecting second primary cancer.

Conclusions: PET with FDG yielded useful information in patients with suspected recurrent gastric cancer, especially when recurrence was suspected in the clinical setting.

Key words: 18F-FDG – PET – gastric cancer – recurrence

INTRODUCTION

Gastric cancer is a common malignant disease, especially in eastern Asian countries. In spite of the recent dramatic progress of diagnostic and/or therapeutic strategies, it is still the second cause of cancer death in Japan. When gastric cancer is found in the early stage, the prognosis is reasonably fair (1), but in advanced cancer, the prognosis remains poor (2,3). In making a therapeutic strategy based on the patients’ quality of life, an accurate diagnosis acquired by recent imaging techniques is indispensable. Morphological imaging modalities, including endoscopy and computed tomography (CT), are usually conducted for postoperative tomography, but it is sometimes difficult to accurately detect recurrent or metastatic foci.

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) is a non-invasive technique for determination of metabolically active lesions, which has

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been widely used for re-staging or follow-up after treatment in various malignant diseases (4–6). In particular, in the alimentary tract, there are already many reports describing the clinical usefulness of FDG-PET or PET/CT for esophageal (7–9) and colorectal cancers (10–13). However, there are only limited reports on gastric cancer (14–16), although a few reports about PET/CT studies for suspected recurrent gastric cancer have been published recently (17,18).

The purpose of this study was to evaluate the diagnostic accuracy of FDG-PET or PET/CT in the diagnosis of recurrent gastric cancer and to assess its clinical impact in making decisions.

**PATIENTS AND METHODS**

**PATIENT ENROLLMENT**

We performed a multicenter (Kyoto University Hospital, Tohoku University Hospital, Hitachi General Hospital, Dokkyo Medical University Hospital, National Cancer Center Hospital East, National Cancer Center Hospital and International Medical Center of Japan) retrospective observation study. Inclusion criteria (i) postoperative state of gastric cancer and (ii) PET scans (either integrated PET/CT or manual fusion of dedicated PET and CT) were performed for surveillance of recurrent gastric cancer with or without suspicion of recurrence. Patients who had taken oral anticancer drugs were included in this study, whereas patients who had a PET scan for evaluating the therapeutic effect after chemotherapy were excluded.

Between June 2006 and December 2007, a total of 114 scans in 107 consecutive patients were performed for postoperative surveillance of gastric cancer. Among the patients, 13 patients had no or insufficient follow-up. In two patients, primary colon cancer was found by colonoscopy before PET examinations, and a PET scan was ordered for pretherapeutic staging of colon cancer. After excluding these 15 patients, 92 patients were analyzed for this investigation. If patients had repeated PET scans, we only analyzed results for the first PET study after the end of initial surgery for gastric cancer. Patients' profile including initial stage and histopathology is demonstrated in Table 1.

Of these 92 patients, 61 were males and 31 were females, with a mean age of 67 years old, ranging from 31 to 87 years old. These patients were classified into the following three groups according to their status at PET examination: Group A (n = 46), patients who were suspected of having recurrence by other imaging modalities such as CT or gastroendoscopy; Group B (n = 19), patients who were suspected of having recurrence by tumor markers without definite findings on prior imaging modalities; and Group C (n = 27), patients who were not suspected of having recurrence, but a PET scan was ordered just for follow-up, based on physicians’ or patients’ requests. In this investigation, patients in Group A were suspected of having recurrence when a new or growing mass had been depicted on morphological modalities, such as CT, or regrowth of tumor was observed by endoscopy, which were confirmed to be recurrent tumor histopathologically.

Patients gave written informed consent, as required in each Institutional Review Board.

**FDG-PET OR PET/CT SCANS**

FDG-PET (n = 47) or PET/CT (n = 45) scans were performed after patients had fasted for at least 4 h. Sixty minutes after intravenous administration of 250–370 MBq FDG, imaging of the trajectory of the upper thigh to skull base was performed using a dedicated full-ring BGO-based dedicated PET scanner (Advance, GE Healthcare), a BGO PET/CT scanner (Discovery LS/ST, GE Healthcare), an LSO PET/CT scanner (Biograph, CTI/Siemens) and a GSO PET/CT scanner (Gemini, Philips Medical Systems). PET images were reconstructed with attenuation correction by the
ordered-subsets expectation maximization algorithm, but specific parameters for image reconstruction were dependent on each institutional method. All PET studies were conducted under the guidelines issued by the Japanese Society of Nuclear Medicine.

**IMAGE INTERPRETATION**

A lesion on PET was considered suspicious if the metabolic activity was higher than the background activity allowing for normal biodistribution. In PET/CT studies, at least two experienced board certified radiologists/nuclear medicine physicians interpreted the PET, CT and fused images visually by consensus on a display in each institute. In dedicated PET studies, after achieving image fusion between PET and CT images manually on a workstation (AquariusNetStation, TeraRecon), PET, CT and fused images were read by at least two experienced radiologists/nuclear medicine physicians. Since CT images acquired by a standalone CT scanner were available in all cases, there were no cases in which PET was interpreted without making fused images. For interpreting these images, the physicians had knowledge of the clinical findings, including tumor markers, and of the results of all the available imaging studies. Semi-quantitative analysis using standardized uptake value (SUV) was not performed in this study, and any cut-off values for SUV were not set for differentiating lesions in interpreting PET images.

**DATA ANALYSIS**

Patient-based sensitivity, specificity and diagnostic accuracy were calculated, and the prevalence of clinical impact obtained by FDG-PET for therapeutic strategy was evaluated for each group. In addition, we have compared the diagnostic accuracy between PET/CT ($n = 45$) and software-based fusion of PET and CT ($n = 47$). We have also analyzed the diagnostic performance whether or not the histology was signet ring cell carcinoma.

**STANDARD REFERENCE**

Final diagnoses were obtained by histopathological examination ($n = 23$) or clinical follow-up ($n = 69$). Of these 69 patients, 21 patients had true positive lesions. They were confirmed by follow-up CT in 19 patients, in whom tumors were growing in 16 patients and decreased after chemotherapy in 3 patients, and by magnetic resonance imaging in 2 patients. There were seven patients with false-negative lesions, which increased in size on CT or PET/CT in six patients and decreased on CT after chemotherapy in one patient. In addition, there were 37 of 69 true-negative cases, in which follow-up CT demonstrated no recurrence in 32 patients, lesions did not change or decreased in size without any treatment on CT in 2 patients, carcinoembryonic antigen level decreased without treatment in 2 patients and endoscopy revealed no recurrence in 1 patient. There were four patients who were confirmed to be false-positive findings. For these patients, follow-up CT showed no changes of suspected lesions without therapy. One patient died of recurrent disease of gastric cancer 130 days after the PET examination. When this patient was excluded, the follow-up period ranged from 186 to 733 days with an average of 376 days.

**RESULTS**

Of the 92 patients evaluated in this study, 44 patients were confirmed to have recurrent disease, 5 patients had no recurrence but had other tumors not related to prior gastric cancer, such as lung cancer ($n = 1$), pulmonary carcinoid ($n = 1$) and colon cancer ($n = 3$), and the remaining 43 patients were considered negative for recurrence, according to the final diagnoses. The numbers of patients with specific metastatic foci are presented in Table 2.

Tables 3 and 4 demonstrate the diagnostic performance of PET in our population. In Group A, 31 of 46 patients (67%) had recurrence of gastric cancer. In the remaining 15 patients without recurrence, 1 patient had colon cancer and 1 patient had primary lung cancer, as a second primary cancer. PET findings affected the patients’ therapeutic strategy in 22 patients (48%), including patients with a second primary cancer.

In Group B, 11 of 19 patients (58%) were confirmed to have recurrence and two patients had colon cancer. Of 11 patients with recurrence, PET accurately interpreted 8 patients as positive, but the remaining 3 patients were negative. Among the three patients, two patients had multiple peritoneal metastases and one patient had small nodal metastasis. With regard to the colon cancer in two patients, PET detected a primary colon cancer in one patient, but not in the other patient. Therapeutic strategy was influenced by PET findings in 8 of 19 patients (42%) in this group, including 1 patient with colon cancer.

**Table 2. Number of cases according to metastatic foci**

<table>
<thead>
<tr>
<th>Location</th>
<th>No. of cases with confirmed recurrence</th>
<th>No. of PET positive cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>4</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Lymph node</td>
<td>19</td>
<td>15 (79)</td>
</tr>
<tr>
<td>Liver</td>
<td>6</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Lung</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Bone</td>
<td>5</td>
<td>4 (80)</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>15</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

PET, positron emission tomography.

aThis category includes recurrence at the anastomotic site.

bTwo more lesions were suspected by PET in two patients who were excluded from the table because they were confirmed to be primary lung cancer and a pulmonary carcinoid tumor.

cMetastases to the ovary ($n = 2$) and the spleen ($n = 1$).
In Group C, only 2 of 27 patients (7%) had recurrence of gastric cancer, which included bone metastasis in 1 patient and nodal metastasis in the other. In addition, PET detected a pulmonary nodule, and a carcinoid tumor was confirmed by surgery in one patient. Therapeutic strategy was influenced by PET findings in only 2 of 27 patients, including a patient with carcinoid tumor in the lung.

Tables 5 and 6 demonstrate the diagnostic accuracies of PET/CT, manual fusion of PET with CT and overall data in our population. The sensitivity, specificity and diagnostic accuracy of manual fusion of PET + CT \((n = 47)\) for suspected recurrent gastric and second primary cancer were 65%, 89% and 79%, respectively, whereas those of PET/CT \((n = 45)\) were 86%, 94% and 89%, respectively. When limited to patients who had been suspected of having recurrence clinically, i.e. Groups A and B, those of manual fusion \((n = 25)\) were 65%, 88% and 72%, respectively, whereas those of PET/CT \((n = 40)\) were 86%, 100% and 90%, respectively.

In addition, we have analyzed only PET/CT data in terms of whether or not histology had been signet ring cell carcinoma at initial surgery. The sensitivity, specificity and diagnostic accuracy in cases of non-signet ring cell carcinoma \((n = 29)\) were 94%, 91% and 93%, respectively, whereas those in cases of signet ring cell carcinoma \((n = 8)\) were 50%, 100% and 75%, respectively.

Overall, therapeutic management was determined by PET results in 32 patients (35%). Among these, unexpected or inconclusive lesions were found to be true recurrence or metastatic tumors with confidence in 18 patients, for whom surgery or chemotherapy was initiated, based on PET results. In 10 patients, lesions that were suspected as recurrence before PET were regarded as negative because of lack of abnormal uptake, and scheduled treatment was altered or cancelled. In the remaining four patients, colon cancer \((n = 2)\), lung cancer \((n = 1)\) and pulmonary carcinoid \((n = 1)\) were depicted by PET, and they were all confirmed by histopathological examination after surgery.

**DISCUSSION**

There are many reports on the clinical value of FDG-PET for recurrence of colorectal cancer, but there are limited studies for recurrent gastric cancer. In this investigation, we found

<table>
<thead>
<tr>
<th>Table 3. Diagnostic performance for recurrent gastric cancer only according to clinical status*</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>A ((n = 44))</td>
</tr>
<tr>
<td>B ((n = 17))</td>
</tr>
<tr>
<td>C ((n = 26))</td>
</tr>
</tbody>
</table>

*The number of cases with a second primary cancer identified by PET is excluded.

<table>
<thead>
<tr>
<th>Table 4. Diagnostic performance for recurrent gastric cancer and second primary cancer according to clinical status</th>
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<tbody>
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<td>Group</td>
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In Group C, only 2 of 27 patients (7%) had recurrence of gastric cancer, which included bone metastasis in 1 patient and nodal metastasis in the other. In addition, PET detected a pulmonary nodule, and a carcinoid tumor was confirmed by surgery in one patient. Therapeutic strategy was influenced by PET findings in only 2 of 27 patients, including a patient with carcinoid tumor in the lung.

Tables 5 and 6 demonstrate the diagnostic accuracies of PET/CT, manual fusion of PET with CT and overall data in our population. The sensitivity, specificity and diagnostic accuracy of manual fusion of PET + CT \((n = 47)\) for suspected recurrent gastric and second primary cancer were 65%, 89% and 79%, respectively, whereas those of PET/CT \((n = 45)\) were 86%, 94% and 89%, respectively. When limited to patients who had been suspected of having recurrence clinically, i.e. Groups A and B, those of manual fusion \((n = 25)\) were 65%, 88% and 72%, respectively, whereas those of PET/CT \((n = 40)\) were 86%, 100% and 90%, respectively.

In addition, we have analyzed only PET/CT data in terms of whether or not histology had been signet ring cell carcinoma at initial surgery. The sensitivity, specificity and diagnostic accuracy in cases of non-signet ring cell carcinoma \((n = 29)\) were 94%, 91% and 93%, respectively, whereas those in cases of signet ring cell carcinoma \((n = 8)\) were 50%, 100% and 75%, respectively.

Overall, therapeutic management was determined by PET results in 32 patients (35%). Among these, unexpected or inconclusive lesions were found to be true recurrence or metastatic tumors with confidence in 18 patients, for whom surgery or chemotherapy was initiated, based on PET results. In 10 patients, lesions that were suspected as recurrence before PET were regarded as negative because of lack of abnormal uptake, and scheduled treatment was altered or cancelled. In the remaining four patients, colon cancer \((n = 2)\), lung cancer \((n = 1)\) and pulmonary carcinoid \((n = 1)\) were depicted by PET, and they were all confirmed by histopathological examination after surgery.

**DISCUSSION**

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<th>Table 5. Diagnostic performance of PET/CT and PET + CT for recurrent gastric cancer and second primary cancer in all patients</th>
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<tbody>
<tr>
<td>Group</td>
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<tr>
<td>-------</td>
</tr>
<tr>
<td>PET/CT ((n = 45))</td>
</tr>
<tr>
<td>PET + CT ((n = 47))</td>
</tr>
<tr>
<td>Overall ((n = 92))</td>
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*The number of cases with a second primary cancer identified by PET/CT or PET + CT is included.

<table>
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<tr>
<th>Table 6. Diagnostic performance of PET/CT and PET + CT for recurrent gastric cancer and second primary cancer in patients with suspected recurrence</th>
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<tbody>
<tr>
<td>Group</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>PET/CT ((n = 40))</td>
</tr>
<tr>
<td>PET + CT ((n = 25))</td>
</tr>
<tr>
<td>Overall ((n = 65))</td>
</tr>
</tbody>
</table>

*The number of cases with a second primary cancer identified by PET/CT or PET + CT is included.
that PET is also applicable for evaluating recurrent gastric cancer with a clinical impact of 30–40% of the cases, which is similar to other malignant diseases. Therapeutic management was influenced mainly in the suspected recurrent groups, i.e., Groups A and B, with only a limited number of cases in which PET findings affected therapeutic management in Group C. In Group C of our population, unexpected recurrence or second primary cancer was finally diagnosed in 3 of 27 cases (11%), but of these 3 cases, colon cancer was not accurately identified by PET in 1 patient. When considering cost-effectiveness, the higher cost of PET examination makes it difficult to conduct in routine clinical use for follow-up. Therefore, based on our data, PET or PET/CT should be considered for further examination after getting inconclusive or equivocal findings by conventional imaging modalities. When recurrence is not suspected in clinical setting, such as initial surveillance after surgery or just follow-up, PET or PET/CT would not be necessary and recommended because expected useful information is limited.

The diagnostic performance of PET with CT and PET/CT was reasonably high, which is similar to previous reports. For example, Sun et al. (17) reported that the accuracy, positive predictive value and negative predictive value of FDG-PET/CT for recurrent gastric cancer were 83%, 78% and 86%, respectively. Park et al. (18) found that the sensitivity, specificity and diagnostic accuracy of PET/CT were 75%, 77% and 75%, respectively, for suspected recurrent gastric cancer, and they concluded that PET/CT would be a helpful imaging tool, particularly in patients who are suspected of recurrence.

Compared with manual fusion of PET and CT, an inline PET/CT system yielded more diagnostic accuracy in this investigation, as has been observed in other cancers. On the other hand, we did not compare the diagnostic accuracy of PET or PET/CT with CT alone, gastroendoscopy and tumor markers. It is important to assess the diagnostic accuracy among the modalities in order to determine the most optimal method during follow-up to avoid futile medication. However, information obtained by tumor markers and gastroendoscopy is different from what is brought by cross-sectional modalities. Even if tumor markers have inferior diagnostic accuracy, they would be still considered due to its non-invasive and easy procedure. If a PET examination is regarded as a useful diagnostic tool for a whole body, the endoscopy would not be omitted for evaluation of an anastomotic site within the lumen. In addition, in order to compare the diagnostic accuracy between PET and CT, we need to perform both scans around the same time, but the data acceptable for comparison were limited in our population.

With regard to location, PET could identify metastases or recurrence in most locations except for the stomach, including anastomosis, although the number of cases was limited. Due to physiological uptake in the bowel, a sufficient tumor-to-background ratio cannot be obtained, especially in small lesions located in the lumen of the alimentary tract, which can be evaluated only by endoscopy. The number of patients with nodal or peritoneal metastasis was large, with relative lower sensitivity probably because of the small size of the lesions. As previously reported in nodal staging in esophageal cancer (19) or colorectal cancer (20), as well as in evaluating peritoneal metastasis in recurrent ovarian cancer (21), there is a limitation on the detection of small foci by PET. In addition, it is difficult to detect small lung lesions, including metastasis, by PET, and CT is considered a first choice modality. In this study, three pulmonary nodules were identified by PET, and surgical resection was performed for these patients, with a sensitivity of 100% for malignant pulmonary nodules, including primary lung cancer. However, we should be cautious in concluding that PET could be useful for detecting malignant pulmonary lesions because tiny lesions in the lung field tend to be missed. Further studies with more lesions are needed to determine the feasibility of PET for pulmonary lesions.

There were 13 cases with signet ring cell carcinoma in this study. It has been reported that signet ring cell carcinoma showed significantly low rate of FDG uptake (22,23). Our results were consistent with those data in that lower sensitivity and accuracy were acquired in patients with signet cell carcinoma, although the number of patients was not large.

Almost all of the patients in this study had a history of total or partial gastrectomy, which is considered a unique treatment for curative purposes. Patients who received chemotherapy before surgery were excluded from the study. Therefore, the clinical usefulness of PET for evaluating the therapeutic effect of chemotherapy, such as neo-adjuvant chemotherapy before surgery, was not determined in this investigation.

There were three cases of colon cancer, one case of lung cancer and one pulmonary carcinoid tumor, which were not related to prior gastric cancer. Agress and Cooper (24) reported that in 1750 patients, the frequency of unexpected PET findings was 3.3% and the incidence of proven malignant and premalignant tumors was 1.7%. Ishimori et al. (25) reported that second primary cancer was detected in at least 1.2% of the cases when PET/CT images were reviewed. In our population, second primary cancer was confirmed in 5 of 92 cases (5%), and PET yielded helpful information in 4 of these 5 cases before other imaging modalities were performed. Although the prevalence of second primary cancer may not be very high, PET can provide us with the clinical impact even in patients without recurrent disease. When interpreting PET images, the possibility of second primary cancer as well as metastasis from prior treated cancer should be considered.

This study has certain limitations. First, all of the lesions were not always evaluated histopathologically. Therefore, there was the possibility of including cases in which false-positive lesions were treated as true-positive lesions by anticancer drugs, or true-positive lesions were not identified in the clinical setting. In addition, images were interpreted at each institute, followed by registration and analysis of the
data. The diagnostic accuracy might have been changed if images were interpreted by specific readers all at once. However, data acquisition was performed according to the guidelines, and only visual analysis was performed by experts with more experiences. There should be minimal differences in diagnostic performance, as has been reported by Suzuki et al. (26).

CONCLUSION

PET with FDG is a useful diagnostic tool for recurrent gastric cancer. Although its clinical value may be limited in patients who are not suspected of having recurrence, PET is worth considering for making a therapeutic decision in patients with suspected recurrent disease, as is the case with other various cancers.

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Conflict of interest statement

None declared.

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