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REVIEW ARTICLE

Japanese Gastric Cancer Association Task Force for Research Promotion: clinical utility of ^{18}F-fluoro-2-deoxyglucose positron emission tomography in gastric cancer. A systematic review of the literature

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Abstract Since April 2010, the Japanese Public Health Insurance System has covered the costs incurred for performing ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) imaging for patients with advanced gastric cancer. The aim of this review was to evaluate the clinical impact of PET for patients with gastric cancer. A systematic literature search was performed in PubMed/MEDLINE using the keywords "gastric cancer" and "PET" to search for relevant articles published from January 2000 to September 2010. The clinical impact of selected articles was assessed by the authors to evaluate the following: (a) tumor staging, (b) diagnosis for recurrent disease, (c) evaluation of treatment response, and (d) screening for gastric cancer. FDG uptake increases in papillary adenocarcinoma, tubular adenocarcinoma, and solid-type poorly differentiated adenocarcinoma. This uptake is also associated with glucose transporter 1 expression. The sensitivity and specificity of FDG-PET for metastatic lymph node detection were 21–40% and 89–100%, respectively. The sensitivity and specificity for distant metastasis detection were 35–74% and 74–99%, respectively. Treatment response can be detectable at an earlier stage by PET than by computed tomography (CT), because FDG uptake by cancer cells decreases according to the treatment response. In summary, although PET has limitations such as frequent false-negative cases in signet-ring cell carcinoma and non-solid type poorly differentiated carcinoma, it can contribute to the selection of a more appropriate treatment modality by detecting distant metastases and treatment response.

Keywords PET · Gastric cancer · Systematic review

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Introduction

Since April 2010, the Japanese Public Health Insurance System has covered the costs incurred for performing ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) imaging for patients with advanced gastric cancer. Because the medical expense of a PET examination is more than 100,000 yen (1,200 US dollars), appropriate indications for PET examination should be used to maximize the clinical impact of this modality. Therefore, the Japanese Gastric Cancer Association Task Force for Research Promotion (directed by Dr. Motoki Ninomiya) assigned the authors to evaluate the clinical impact of PET examination by reviewing recent publications. On the basis of the present systematic review, prospective clinical studies can be planned to elucidate the clinical utility of PET.

Article selection

A computer-aided search of the PubMed website (http://www.ncbi.nlm.nih.gov/sites/entrez) was conducted to find relevant articles on PET imaging used for gastric cancer. The keywords "gastric cancer" and "PET" were used to search for relevant articles published from January 2000 to September 2010. Studies investigating the clinical impact of PET and/or PET/computed tomography (CT) fusion used for assessing patients with gastric cancer were selected. Several articles, focusing on the esophagogastric junction, included many cases of squamous cell carcinomas. Therefore, we excluded those articles that included squamous cell carcinomas, which accounted for more than 50% of the total number of cases in the literature. Furthermore, case reports, non-English-language articles, and studies that investigated other tracers such as methionine were also excluded.

Four researchers (H.S., S.O., M.K., and K.M.) reviewed all the articles, and after applying the inclusion and exclusion criteria, we arrived at a consensus about articles to be selected at a working meeting. A total of 198 articles were selected from the PubMed database. After exclusions as per the criteria, 96 articles were selected, of which 52 articles were selected as references for the present review article.

Physiological FDG uptake in gastric mucosa

Focal FDG uptake in normal gastric mucosa and significantly different accumulation levels that depend upon the histological type of gastric cancer are crucial issues in assessing a PET image of gastric cancer. Focal FDG uptake in the gastrointestinal tract with a standard uptake value (SUV) of approximately 2.5 can generally be detected by PET/CT even in patients without known gastrointestinal malignancy [1]. In other studies, the SUV in the upper third of the stomach was significantly higher than that in the lower third of the stomach. Furthermore, a significant difference in FDG uptake was observed among the three portions of the stomach: upper third > middle third > lower third; the physiological gastric FDG uptake was significantly higher at the oral end. Therefore, stronger gastric FDG uptake at the anal end would suggest pathological uptake [2, 3].

Heusner et al. [4] evaluated esophagogastric FDG uptake in 546 patients without esophagogastric malignancies. They concluded that elevated esophagogastric FDG uptake does not predict cancer development and should not be investigated further if CT shows no unusual features. Takahashi et al. [5] reported the association between the endoscopic view, *Helicobacter pylori* infection, and FDG accumulation in 272 patients who underwent a PET examination during a health check-up. They found FDG accumulation in 81 cases (30%), which they classified according to the following 2 patterns: (a) localized accumulation only in the fornix (Group A, $n = 32$) and (b) diffused accumulation throughout the stomach (Group B, $n = 49$). The *H. pylori* infection rate was higher in Group B than in Group A. Considering the endoscopic view, FDG uptake corresponded largely to mucosal inflammation, including superficial gastritis and erosive gastritis, and therefore, inflammatory mucosa was assumed to be the main cause of non-specific FDG accumulation.

To reduce non-specific FDG accumulation in the gastric mucosa, Kamimura et al. [3] proposed that the patient should consume additional water to distend the stomach before PET examination. The mean SUVs in each portion of the stomach before and after the consumption of additional water were as follows: upper-third portion, 2.41 ± 0.75 versus 1.82 ± 0.66; middle-third portion, 2.28 ± 0.73 versus 1.73 ± 0.56; and lower-third portion, 1.61 ± 0.89 versus 1.48 ± 0.49, respectively. The mean SUVs in the upper-third portion and middle-third portion after the consuming of additional water decreased significantly. Additional milk intake immediately before PET imaging is also an effective method for suppressing physiological FDG uptake in the stomach [6]. Ingestion of milk approximately 1 h after FDG injection had no significant influence on FDG accumulation in the heart, mediastinum, and liver, whereas the percentage of FDG uptake in the stomach decreased from 60 to 11%. With the normal gastric wall distended, malignant lesions were observed with higher contrast and clearer outlines. In addition, some small ($\sim$12 mm) malignant lesions were detected at an early stage with mild uptake. The recommended conditions for PET imaging for gastric cancer are shown in Table 1.

Differences of histology and glucose transporter 1 expression in gastric cancer

Cellular FDG uptake is predominantly related to glucose transporter 1 (GLUT1) expression. GLUT1 is ubiquitously

Table 1 The recommended conditions for ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) imaging of suspected gastric cancer

No inflammation around the tumor
Serological, bacteriological, and endoscopical tests are needed
Appropriate distension of the gastric wall
Appropriate tumor size according to the resolution of the PET apparatus
Cohesive histological type

expressed in almost all cell types, but is frequently overexpressed in malignant tissue, leading to the intracellular accumulation of FDG, which can then be visualized by FDG-PET. In gastric carcinoma, GLUT1 is expressed late in carcinogenesis, and increased amounts are associated with tumor progression and patient survival [7–9].

Kawamura et al. [7] analyzed GLUT1 protein expression in 617 carcinomas and 50 tubular adenomas of the stomach. None of the adenomas expressed GLUT1, whereas 182 of the 617 carcinomas (30%) were positive for GLUT1 expression. Furthermore, signet-ring cell carcinoma and mucinous adenocarcinoma showed very low positive values for GLUT1 expression (2 and 6%, respectively). Among the other histological types, papillary adenocarcinoma (44%) showed slightly higher positive values for GLUT1 expression than tubular (32%) or poorly differentiated adenocarcinomas (28%).

Yamada et al. [8] evaluated the association between FDG uptake and histopathological type in 40 patients with gastric carcinoma among whom 19 patients (48%) showed detectable FDG uptake. Cohesive carcinomas (papillary adenocarcinoma, tubular adenocarcinoma, and solid-type poorly differentiated adenocarcinoma) were more significantly detectable than non-cohesive carcinomas (signet-ring cell carcinoma and non-solid type poorly differentiated carcinoma) (65 vs. 14%, respectively). Multiple regression analysis revealed that the depth of invasion and histological types were independent factors associated with the detection rate of FDG uptake, and GLUT1 expression was the most important factor for determining the degree of FDG uptake. Alakus et al. [9] supported this significant association between FDG uptake and GLUT1 expression in 35 patients with gastric cancers. Only 4 of 17 (24%) signet-ring cell carcinoma cases showed GLUT-1 expression. GLUT1-positive signet-ring cell carcinomas revealed higher median SUVs than GLUT1-negative tumors (6.9 vs. 3.1). The authors concluded that the FDG uptake in gastric cancer depended on GLUT-1 expression. It is important to note that early or non-cohesive gastric carcinoma may not show sufficient FDG uptake to produce a positive PET image.

Clinical utility of PET for staging of gastric cancer

According to the data of the National Comprehensive Cancer Network [10], the accuracy of PET/CT, PET alone, and CT alone to evaluate tumor stage is 84, 63, and 64%, respectively. In the National Oncologic PET Registry, 21,000 patients underwent 23,000 scans. Of these, 24% were for cancer diagnosis, 28% for initial staging, 24% for restaging after treatment, and 24% for the evaluation of suspected recurrence. The investigators reported that PET resulted in a change in intended management in 37% of 3025 scans for gastric cancer [11]. PET is relatively more sensitive than CT for detecting stage IV disease (74 vs. 47%) with distant lymph node involvement and/or accidental double cancer. However, the sensitivity of PET for the detection of locally advanced gastric carcinomas is dependent on the microscopic growth type of the tumor. Stahl et al. [12] showed that only 24 of 40 (60%) locally advanced gastric carcinomas were detected by PET. The detection rate for intestinal tumors was significantly higher than that for non-intestinal tumors (83 vs. 41%). The overall low detection rate (30–50%) of gastric carcinomas is attributable to the frequent occurrence of diffusely growing and mucus-containing tumors. A marked increase in FDG uptake is more commonly observed in the carcinomas with intestinal growth than in the non-intestinal carcinomas (83 vs. 41%), probably because of the abundance of intra- and extracellular mucus content and the lack of GLUT1 expression on the cell membrane of the non-intestinal carcinomas. Namely, in poorly differentiated adenocarcinoma, the sensitivity of PET to detect tumors is low, and FDG uptake is not associated with biological malignant potential [13, 14]. A summary of the clinical utility of FDG-PET imaging for gastric cancer is shown in Table 2.

Depth of tumor

Tumor detection rates for early tumors have been reported to be 0–44% [15–17]. Even for advanced tumors, detection rates have been reported to range from 34 to 94% [18–20]. These studies found a significant association between FDG uptake and the depth of tumor invasion and tumor size. Because of the limitations of resolution and physiological FDG accumulation, tumor depth could not be accurately evaluated. Mochiki et al. [21] reported an association between primary tumor depth and PET positivity in 85 patients. Detection rates of PET for each tumor depth were 40% for T1 tumors ($n = 25$), 88% for T2 tumors ($n = 32$), 90% for T3 tumors ($n = 21$), and 100% for T4 tumors ($n = 7$). Although detection rates of various levels were

Table 2 Clinical utility of FDG-PET imaging for gastric cancer

Assessment variables	Clinical utility
Depth of tumor	Not useful
Lymph node metastases	Useful for distant lymph nodes
Distant metastases	Low sensitivity but high specificity
Peritoneal metastases	Useful and high specificity
Recurrent disease	May be useful, but controversial
Treatment response	May be useful
Screening	Not useful

reported , specificity was reported to be consistently around 90% [16–18, 20, 21]. Although PET-positive tumors were more likely to be classified as T2 or above, the tumor detection rate even for advanced tumors was not sufficient for evaluating tumor depth.

Lymph node status (Table 3)

Regarding the detection of lymph node involvement, it is important to note that multidetector CT (MD-CT) can cover almost all positive lymph nodes. Tsujimoto et al. [17] reported that 85% of cN0 patients were staged correctly and no stage of cN1 patients was underestimated by MD-CT.

Lerut et al. [22] reported that for the diagnosis of locoregional nodes, PET had lower accuracy than the conventional combination assessment by CT and endoscopic ultrasound (48 vs. 69%) because of a significant lack of sensitivity (22 vs. 83%). However, the accuracy for distant nodal metastasis was significantly higher for PET than that for the combined use of CT and endoscopic ultrasound (86 vs. 62%). Mochiki et al. [21] also reported that PET scans had lower accuracy for diagnosing locoregional lymph nodes than CT because of a significant lack of sensitivity (23 vs. 65%). These authors reported that although some of the patients were upstaged by PET with the detection of distant lymph node metastases, PET was not useful for evaluating the number of metastatic lymph nodes and perigastric nodes.

Kim et al. [23] reported that 70 of 73 (96%) patients with advanced gastric cancer had PET-positive tumors. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PET for lymph node metastasis were 40, 95, 91, and 56%, respectively. Employing multiple logistic regression, the authors concluded that the SUV for primary tumors was the only independent variable that was significantly related to the sensitivity of lymph node metastasis. Furthermore, two Korean groups [24, 25] have reported a similar tendency (sensitivity 31 and 34%, specificity 97 and 96%, and accuracy 55 and 72%). These two groups concluded that PET exhibited good specificity for lymph node staging of gastric cancer.

Regarding the detection of lymph node involvement in patients with T1 tumors, Mukai et al. [20] assessed FDG uptake in 27 patients with T1 tumors and found that 7 (26%) patients were PET-positive and 20 patients were PET-negative. Two of the 7 PET-positive patients had nodal involvement, and the primary tumors of both patients were the intestinal type. In contrast, none of the 20 PET-negative patients had nodal involvement. The sensitivity of detection of nodal involvement by PET was lower than that of CT (35 vs. 62%). However, the specificity of PET was higher than that of CT (97 vs. 88%), while the accuracy of CT was higher than that of PET (68 vs. 76%). The most recent report by Kim et al. [26] compared the value of PET/CT with that of contrast-enhanced CT in an evaluation of metastatic lymph nodes in 71 patients with advanced gastric carcinoma. For regional lymph node metastasis, the sensitivity, specificity, PPV, NPV, and the accuracy of PET/CT versus contrast-enhanced CT were 41 versus 75%, 100 versus 92%, 100 versus 98%, 26 versus 42%, and 51 versus 77%, respectively. Overall, the sensitivity and accuracy of PET/CT were inferior to those of contrast-enhanced CT in the diagnosis of regional lymph node metastases. The diagnostic ability of PET to detect lymph node metastases is summarized in Table 3.

Distant metastases (Table 4)

Positron emission tomography (PET) is useful for detecting distant metastases, including metastases to organs, and metastases more than 10 mm in size to peritoneum and distant lymph nodes. Yoshioka et al. [27] reported that the overall sensitivity, specificity, and accuracy of PET to detect distant metastases were 71, 74, and 73%, respectively. The sensitivities and specificities were 85 and 74% for the detection of liver metastasis, 67 and 88% for lung

Table 3 Diagnostic ability of FDG-PET to detect lymph node metastases

References	Number of patients	Sensitivity (%)	Specificity (%)	Accuracy
Tsujimoto et al. [17]	205	21	89	85%
Kim et al. [23]	73	40	95	46%
Mukai et al. [20]	62	35	97	68%
Lerut et al. [22]	42	22	90	Regional = 48% Distant = 86%
Mochiki et al. [21]	85	23	100	69%
Yang et al. [24]	78	31	97	55%
Yun et al. [25]	81	34	96	72%

Table 4 Diagnostic ability of FDG-PET to detect distant metastases

References	Number of patients	Sensitivity (%)	Specificity (%)	Accuracy (%)
Yoshioka et al. [27]	22	71	74	73
Lim et al. [28]	112	35	99	89
Turlakow et al. [29]	24	57	93	96
Yang et al. [30]	141	74	93	88

metastasis, 24 and 76% for ascites, 4 and 100% for pleural carcinomatosis, and 30 and 82% for bone metastasis, respectively.

Two patterns of FDG uptake are known to be indicators of peritoneal metastasis, as follows: (a) diffuse uptake spreading uniformly throughout the abdomen and pelvis, obscuring visceral outlines; and (b) discrete foci of uptake located randomly and anteriorly within the abdomen or independently within the pelvis and unrelated to solid viscera or nodal stations [28, 29]. Lim et al. [28] demonstrated that although the sensitivity of PET to detect peritoneal metastasis was significantly lower than that of CT (35 vs. 77%), the specificity of PET was significantly higher than that of CT (99 vs. 92%).

Turlakow et al. [29] compared the sensitivities of PET and CT in 24 patients with suspected peritoneal tumors. PET was positive in 14 patients, of which one was false-positive; CT was positive in 10 patients; and either PET or CT was positive in 18 patients. This yielded sensitivities of 57, 42, and 78% and uniformly high positive predictive values of 93, 100, and 95% for PET, CT, and PET or CT, respectively. PET provides additional information compared with that obtained from conventional imaging in staging peritoneal carcinomatosis. Yang et al. [30] compared the diagnostic impact of PET/CT to detect peritoneal dissemination with that of CT. PET/CT had an accuracy of 88%, sensitivity of 74%, specificity of 93%, PPV of 81%, and NPV of 91%; these values were significantly higher than those of CT, at 78, 39, 94, 72, and 79%, respectively. The authors concluded that PET/CT was useful for predicting peritoneal metastasis. Because peritoneal dissemination is more likely to be the non-cohesive type rather than distant metastatic lymph nodes, the diagnostic impact of PET was reported to be relatively low.

To summarize the clinical utility of PET for staging, PET has high specificity for detecting distant metastases, but it is not useful for the detection of regional lymph nodes or T1 tumors.

Utility of PET in detecting recurrent gastric cancer

Positron emission tomography (PET) is often useful for detecting different patterns of recurrence, such as local recurrence involving the remnant stomach, regional lymph nodes, peritoneal dissemination, liver metastases, and remote metastases. PET is an advantageous imaging tool because it enables the evaluation of the entire body at once. Physiological FDG accumulation in remnant gastric mucosa can be excluded by inducing gastric distension by having the patient drink a glass of water before scanning. This seems to be a simple, cost-effective method to improve the diagnostic accuracy of PET. Visual analysis with special attention to the configuration of FDG activity after water ingestion seems to be more useful than the change in SUV for the evaluation of remnant stomach [1, 3, 31]. De Potter et al. [32] retrospectively assessed the accuracy of PET for diagnosing gastric cancer recurrence in 33 patients. The sensitivity and specificity of PET to detect recurrence were 70 and 69%, respectively. PPV was 78%, and NPV was 60%. In the patient group with proven recurrence, the mean survival for the PET-negative group was 18.5 $\pm$ 12.5 months, which was significantly longer than that for the PET-positive group (6.9 $\pm$ 6.5 months).

Recently, a combined PET/CT scanner has been more commonly used rather than a dedicated PET scanner. Sun et al. [33] evaluated the clinical role of PET/CT in the detection of gastric cancer recurrence after initial surgical resection in 23 patients. Overall, the accuracy of PET/CT was 83%, NPV was 78%, and PPV was 86%. The 2 false-positive PET/CT findings were actually chronic inflammatory tissue lesions. For the 2 patients with false-negative PET/CT findings, the final diagnosis was recurrence of mucinous adenocarcinoma. PET/CT revealed extraabdominal metastases in 7 patients and an additional esophageal carcinoma in one patient. Clinical treatment decisions were changed in 30% of the patients after the introduction of PET/CT into the authors' conventional postoperative follow-up program. Sim et al. [34] compared the sensitivity and specificity of PET/CT and contrast CT in 38 patients with confirmed recurrent gastric cancer. The sensitivity was 68 and 89% and the specificity was 71 and 64%, for PET/CT and contrast CT, respectively. An additional PET/CT to contrast CT showed no further increase of the PPV regardless of the site. The sensitivity and specificity of PET/CT for the detection of gastric cancer recurrence was similar to that of contrast CT, with the exception of peritoneal seeding. However, an additional PET/CT using contrast CT did not increase diagnostic accuracy in the detection of recurrent gastric cancer.

Park et al. [35] analyzed 105 postoperative patients with suspected gastric cancer recurrence. Among the 105 patients, 75 were confirmed to have true recurrence, at 108 sites. The sensitivity, specificity, PPV, NVP, and accuracy of PET/CT in diagnosing true recurrence were 75, 77, 89, 55, and 75%, respectively. On a per-lesion basis, 75 of the 108 (69%) true recurrences showed positive FDG uptake, while on a per-person basis, 75 of 84 (89%) patients with positive FDG uptake were confirmed to have a true recurrence. PET/CT may be helpful in confirming the presence of recurrence, particularly in patients in whom recurrence is highly suspected, because of its high positive predictability. Bilici et al. [36] analyzed 34 patients with suspected recurrent gastric cancer. In total, 23 of the 34 (68%) patients had documented recurrent disease, whereas 11 patients had no evidence of recurrent disease. PET/CT

correctly confirmed recurrent disease in these 23 patients with suspected recurrence. However, PET/CT was false-negative in one patient, but recurrent disease was confirmed by histopathology. The overall sensitivity, specificity, accuracy, PPV, and NPV of PET/CT were significantly superior to those of CT (96 vs. 63%, 100 vs. 10%, 97 vs. 47%, 100 vs. 63%, and 91 vs. 10%, respectively) for the detection of recurrent gastric cancer. The PET/CT results changed the patients' management in 18 (53%) cases.

Sohn et al. [15] compared the clinical value of CT and PET/CT in detecting recurrent gastric cancer after endoscopic submucosal dissection in 212 patients. The local recurrence rate was 5% during the study period. However, conventional CT and PET/CT scans could not detect local recurrence of cancer in any patient. Nakamoto et al. [37] performed a retrospective review of 92 consecutive patients who underwent PET—either integrated PET/CT or manual fusion of dedicated PET and CT—scans for post-treatment surveillance of gastric cancer. Of these patients, 46 were suspected of having a recurrence based on the findings of other imaging modalities (Group A), recurrence was predicted in 19 patients by tumor markers without definite findings (Group B), and the remaining 27 patients underwent a PET scan without evidence of recurrence (Group C). Gastric cancer recurrence was confirmed in 31 patients (67%) in Group A, in 11 patients (58%) in Group B, and in 2 patients (7%) in Group C. On a per-patient-basis, the sensitivity, specificity, and diagnostic accuracy of PET for recurrence were 81, 87, and 83% in Group A; 73, 88, and 79% in Group B; and 50, 88, and 85% in Group C. Therapeutic management was influenced by the 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 a second primary cancer. Suga et al. [38] evaluated the prevalence of positive findings of PET in 303 patients with high serum carcinoembryonic antigen (CEA) levels. The prevalence of PET-positive cases was higher with an increase in the absolute CEA level, and more than 90% of the patients were PET-positive when CEA levels were above 20 ng/mL.

Therefore, PET is a useful modality for the diagnosis of recurrent gastric cancer. However, PET also has limitations such as frequent false-negative cases, either in early cancer or in non-cohesive types.

Usefulness of PET in evaluation of treatment response

The glucose metabolism of cancer cells decreases according to the level of treatment response. Therefore, that response to treatment is expected to be apparent at an earlier stage on PET than on CT, allowing early changes in treatment for responsive tumors. Several recent reports involving patients with gastric cancer have demonstrated that the response to preoperative chemotherapy can be predicted by PET early in the course of therapy [39].

Chemotherapy is indicated for advanced cancer, and the tumor size can easily be evaluated by several modalities, especially by MD-CT using a three-dimensional (3D) volume rendering high-resolution method [40, 41]. Because PET evaluates tumor activity by estimating rates of glucose metabolism, this qualitative diagnostic characteristic makes treatment evaluation possible even before the morphological decrease of tumor size. Several articles reported early treatment evaluation by PET that predicted responders and non-responders [42, 43]. However, FDG also accumulates in inflammatory cells, and false-positive findings are found in the inflammatory stage after treatment. Considering these characteristics of PET, the usefulness of early response evaluation after the initiation of the treatment has been reported by several institutions [40–44]. The ideal examination times and criteria have not been determined [41]. Ott et al. [43, 44] reported that the best evaluation time was 2 weeks after the initiation of treatment. They classified the tumors that demonstrated more than 35% reduction of FDG uptake as a responder group and the tumors that demonstrated less than 35% reduction of FDG uptake as non-responders. For these PET responders, "metabolic responders", the treatment should be continued, and for non-responders another treatment strategy should be employed [44]. On the other hand, PET reassessment after the completion of neoadjuvant chemotherapy did not detect significant correlations between the SUVs of the major and minor responder groups [45]. Therefore, PET may be considered to be a reliable modality to reflect treatment response at an early phase. A typical case of gastric cancer with uterine metastases was detected by whole-body PET imaging before surgery. Strong accumulation in the uterus was reduced after chemotherapy according to the treatment response (Fig. 1).

Currently, evaluation of the response to chemotherapy by PET is expected at an early stage of the treatment course, but the ideal evaluation time and criteria remain to be determined because several factors have to be studied further, such as histological types and the choice of drugs for treatment. On the other hand, the evaluation of neo-adjuvant therapy requires not only the response of the main tumor but also the response of metastatic lymph node. The relationship between the prognosis of patients who have received neoadjuvant treatment and FDG uptake in metastatic lymph node after treatment should be studied, and prognostic criteria of FDG uptake after neo-adjuvant therapy should be established [46].

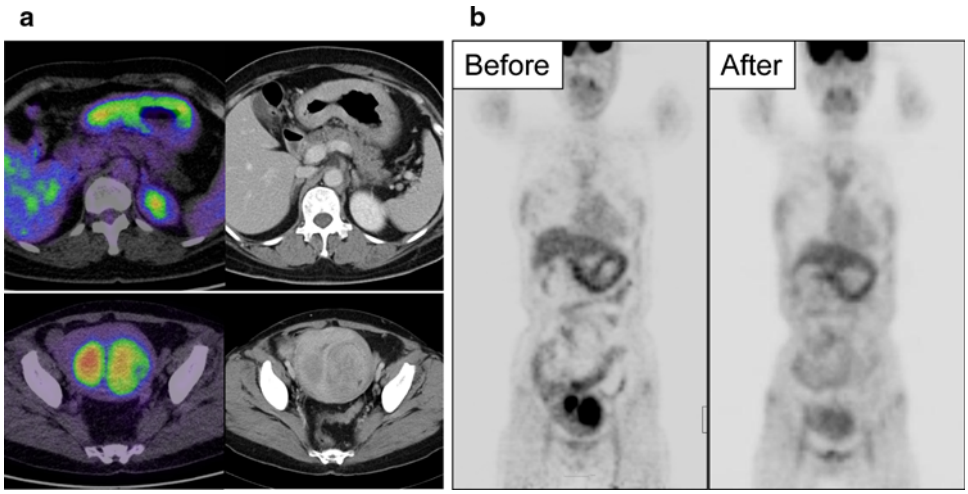

Fig. 1 Diagnostic ability of ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) in detecting distant metastases and evaluating treatment response in patients with scirrhous-type tumors. **a** Weak FDG accumulation in gastric cancers but strong accumulation in uterine metastases. **b** Decreased FDG uptake according to treatment response after chemotherapy

Efficacy of PET for the screening of gastric cancer

Although PET has recently been proposed as a promising cancer screening test [47, 48], the utility of PET in gastric cancer screening has not been evaluated. For gastric cancer screening, the usefulness of PET is limited because of physiological FDG uptake in the normal gastric wall and differences of FDG uptake according to the histological type of the tumor [1, 2]. Physiological FDG deposits in the stomach may increase false-positive findings, although these deposits can be decreased by expanding the gastric wall by the patient consuming water or milk just before imaging acquisition [4, 5]. As Koga et al. [2] have reported, physiological gastric FDG uptake was shown to be significantly higher at the oral end; thus, strong gastric FDG uptake at the anal end suggested pathological uptake. These authors [1, 2, 4, 5] concluded that FDG accumulation in the stomach suggested a high probability of the presence of inflammatory change in the gastric mucosa froming a background for the development of cancer or malignant lymphoma; thus, FDG accumulation in the stomach requires further endoscopic examinations.

Israel et al. [49] retrospectively analyzed unexpected focal FDG uptake in the gastrointestinal tract. They found that 58 of 4390 (1%) patients had unexpected focal uptake. Of the 34 cases for which follow-up data were available (4 with sites in the stomach, 2 in the small bowel, and 28 in the colon), gastrointestinal tumor was confirmed in 24 patients (71%). Of these, 11 were malignant tumors, including 3 gastric cancers, 2 small bowel cancers, and 6 colon cancers. Shoda et al. [50] compared the sensitivity of PET with that of upper gastric endoscopy in gastric cancer screening for 2861 asymptomatic subjects. Positive PET results were obtained in only 2 of 20 (10%) patients with gastric cancer, including 18 T1 tumors.

Lee et al. [51] reported that of 1336 asymptomatic subjects who underwent PET/CT as part of a cancer screening program, along with some other diagnostic tests, malignant tumors were found in 16 participants (thyroid cancer 9, lung cancer 2, stomach cancer 2, and 3 other cancer types). The 47 cases of positive PET/CT findings were as follows: 11 cases were true-positive, 36 were false-positive, and 5 cases were false-negative. Two cases of early gastric cancer, which were found on endoscopy, were included in the false-negative group. The overall detection rate of PET/CT was 0.8%, and the sensitivity, specificity, PPV, and NPV of PET/CT were 69, 97, 23, and 99%, respectively.

In addition, Terauchi et al. [16] demonstrated that among 2911 asymptomatic subjects, PET detected cancer in 28 subjects, although 129 cases of cancer were PET-negative. The overall detection rate, sensitivity, specificity, and PPV were estimated to be 1, 18, 95, and 11%, respectively. In conclusion, the efficacy of screening gastric cancers using PET is not high. When PET shows accumulation in the stomach (especially in the lower part or as localized uptake), a subsequent endoscopy or close follow-up study for the patient is indispensable.

According to a multi-institutional study conducted by the Japanese Society of Nuclear Medicine and the Japan Radioisotope Association for cancer screening including PET, 30 cases of gastric cancer were found in 50,558 healthy subjects [47]. PET showed a relative sensitivity of 27% and PPV of 16%. Twenty-two of the 30 gastric cancers were detected by gastric endoscopy, 2 cases of gastric cancer were detected by PET alone, and 6 cases with positive findings were detected by PET and tumor markers. Eight cases of PET-negative Stage I and 1 case of Stage III cancer were found. The most common benign diseases that were PET-positive were gastritis (29 cases) and polyps (9 cases).

Based on these results, it was concluded that PET is a poor detector of gastric cancer, and that additional endoscopy and other diagnostic methods are to be recommended to avoid overlooking early gastric cancer.

Conclusions and suggestions for future clinical research topics in clinical utility of PET in gastric cancer

In conclusion, based on the present systematic review of the literature, PET may be useful for detecting distant metastases and/or recurrent disease with high specificity and high PPV. Furthermore, it may be useful for evaluating treatment response. However, PET is not useful for gastric cancer screening because of its low ability to detect cancer at an early stage. Because FDG uptake is affected by GLUT1 expression and/or the histological type of cancer cells, the NPV of PET is unreliable. Currently, CT is the most frequently used imaging modality for the preoperative staging and follow-up of affected patients. However, PET may be superior to anatomic imaging modalities for detecting distant and significant nodal metastases. In addition, PET may play a valuable role in monitoring treatment response and patient survival, because FDG uptake has been reported to be associated with biological malignant potential and/or the viability of cancer cells [52].

Based on the present systematic review, the following clinical research topics should be investigated in future: (a) determine how often the PET finding led to changes in the treatment modality, (b) the clinical utility of the SUV in predicting patient survival, (c) whether the clinical ability of PET in detecting suspected recurrent disease improves patients' survival, and (d) the optimal timing of PET examination and optimal criteria to evaluate treatment response.

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References

1. Kamimura K, Fujita S, Nishii R, Wakamatsu H, Nagamachi S, Yano T, et al. An analysis of the physiological FDG uptake in the stomach with the water gastric distention method. Eur J Nucl Med Mol Imaging. 2007;34:1815–8.
2. Koga H, Sasaki M, Kuwabara Y, Hiraka K, Nakagawa M, Abe K, et al. An analysis of the physiological FDG uptake pattern in the stomach. Ann Nucl Med. 2003;17:733–8.
3. Kamimura K, Nagamachi S, Wakamatsu H, Fujita S, Nishii R, Umemura Y, et al. Role of gastric distention with additional water in differentiating locally advanced gastric carcinomas from physiological uptake in the stomach on 18F-fluoro-2-deoxy-D-glucose PET. Nucl Med Commun. 2009;30:431–9.
4. Heusner TA, Hahn S, Hamami ME, Kim UH, Baumeister R, Forsting M, et al. Gastrointestinal 18F-FDG accumulation on PET without a corresponding CT abnormality is not an early indicator of cancer development. Eur Radiol. 2009;19:2171–9.
5. Takahashi H, Ukawa K, Ohkawa N, Kato K, Hayashi Y, Yoshimoto K, et al. Significance of (18)F-2-deoxy-2-fluoro-glucose accumulation in the stomach on positron emission tomography. Ann Nucl Med. 2009;23:391–7.
6. Zhu Z, Li F, Mao Y, Cheng W, Cheng X, Dang Y. Improving evaluation of primary gastric malignancies by distending the stomach with milk immediately before 18F-FDG PET scanning. J Nucl Med Technol. 2008;36:25–9.
7. Kawamura T, Kusakabe T, Sugino T, Watanabe K, Fukuda T, Nashimoto A, et al. Expression of glucose transporter-1 in human gastric carcinoma: association with tumor aggressiveness, metastasis, and patient survival. Cancer. 2001;92:634–41.
8. Yamada A, Oguchi K, Fukushima M, Imai Y, Kadoya M. Evaluation of 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography in gastric carcinoma: relation to histological subtypes, depth of tumor invasion, and glucose transporter-1 expression. Ann Nucl Med. 2006;20:597–604.
9. Alakus H, Batur M, Schmidt M, Drebber U, Baldus SE, Vallböhmer D, et al. Variable 18F-fluorodeoxyglucose uptake in gastric cancer is associated with different levels of GLUT-1 expression. Nucl Med Commun. 2010;31:532–8.
10. Podoloff DA, Ball DW, Ben-Josef E, Benson AB 3rd, Cohen SJ, Coleman RE, et al. NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Canc Netw. 2009;7(Suppl 2):S1–26. (Review).
11. Hillner BE, Siegel BA, Shields AF, Liu D, Gareen IF, Hunt E, et al. Relationship between cancer type and impact of PET and PET/CT on intended management: findings of the National Oncologic PET Registry. J Nucl Med. 2008;49:1928–35.
12. Stahl A, Ott K, Weber WA, Becker K, Link T, Siewert JR, et al. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. Eur J Nucl Med Mol Imaging. 2003;30:288–95.
13. Esteves FP, Schuster DM, Halkar RK. Gastrointestinal tract malignancies and positron emission tomography: an overview. Semin Nucl Med. 2006;36:169–81. Review.
14. Rosenbaum SJ, Stergar H, Antoch G, Veit P, Bockisch A, Kühl H. Staging and follow-up of gastrointestinal tumors with PET/CT. Abdom Imaging. 2006;31:25–35. Review.
15. Sohn YJ, Jang JS, Choi SR, Kwon HC, Jung GJ, Kim MC, et al. Early detection of recurrence after endoscopic treatment for early gastric cancer. Scand J Gastroenterol. 2009;44:1109–14.
16. Terauchi T, Murano T, Daisaki H, Kanou D, Shoda H, Kakinuma R, et al. Evaluation of whole-body cancer screening using 18F–2-deoxy-2-fluoro-D-glucose positron emission tomography: a preliminary report. Ann Nucl Med. 2008;22:379–85.
17. Tsujimoto H, Sugasawa H, Ono S, Ichikura T, Yamamoto J, Hase K. Has the accuracy of preoperative diagnosis improved in cases of early-stage gastric cancer? World J Surg. 2010;34:1840–6.
18. Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, et al. Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. Cancer. 2005;103:2383–90.
19. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. Gastric Cancer. 2009;12:6–22. Review.
20. Mukai K, Ishida Y, Okajima K, Isozaki H, Morimoto T, Nishiyama S. Usefulness of preoperative FDG-PET for detection of gastric cancer. Gastric Cancer. 2006;9:192–6.

21. Mochiki E, Kuwano H, Katoh H, Asao T, Oriuchi N, Endo K. Evaluation of 18F–2-deoxy-2-fluoro-D-glucose positron emission tomography for gastric cancer. World J Surg. 2004;28:247–53.
22. Lerut T, Flamen P, Ectors N, Van Cutsem E, Peeters M, Hiele M, et al. Histopathologic validation of lymph node staging with FDG-PET scan in cancer of the esophagus and gastroesophageal junction: a prospective study based on primary surgery with extensive lymphadenectomy. Ann Surg. 2000;232:743–52.
23. Kim SK, Kang KW, Lee JS, Kim HK, Chang HJ, Choi JY, et al. Assessment of lymph node metastases using 18F-FDG PET in patients with advanced gastric cancer. Eur J Nucl Med Mol Imaging. 2006;33:148–55.
24. Yang QM, Kawamura T, Itoh H, Bando E, Nemoto M, Akamoto S, et al. Is PET-CT suitable for predicting lymph node status for gastric cancer? Hepatogastroenterology. 2008;55:782–5.
25. Yun M, Lim JS, Noh SH, Hyung WJ, Cheong JH, Bong JK, et al. Lymph node staging of gastric cancer using (18)F-FDG PET: a comparison study with CT. J Nucl Med. 2005;46:1582–8.
26. Kim EY, Lee WJ, Choi D, Lee SJ, Choi JY, Kim BT, et al. The value of PET/CT for preoperative staging of advanced gastric cancer: comparison with contrast-enhanced CT. Eur J Radiology 2010 (Epub ahead of print).
27. Yoshioka T, Yamaguchi K, Kubota K, Saginoya T, Yamazaki T, Ido T, et al. Evaluation of 18F-FDG PET in patients with advanced, metastatic, or recurrent gastric cancer. J Nucl Med. 2003;44:690–9.
28. Lim JS, Kim MJ, Yun MJ, Oh YT, Kim JH, Hwang HS, et al. Comparison of CT and 18F-FDG PET for detecting peritoneal metastasis on the preoperative evaluation for gastric carcinoma. Korean J Radiol. 2006;7:249–56.
29. Turlakow A, Yeung HW, Salmon AS, Macapinlac HA, Larson SM. Peritoneal carcinomatosis: role of (18)F-FDG PET. J Nucl Med. 2003;44:1407–12.
30. Yang QM, Bando E, Kawamura T, Tsukiyama G, Nemoto M, Yonemura Y, et al. The diagnostic value of PET-CT for peritoneal dissemination of abdominal malignancies. Jpn J Cancer Chemother. 2006;33:1817–21.
31. Yun M, Choi HS, Yoo E, Bong JK, Ryu YH, Lee JD. The role of gastric distention in differentiating recurrent tumor from physiologic uptake in the remnant stomach on 18F-FDG PET. J Nucl Med. 2005;46:953–7.
32. De Potter T, Flamen P, Van Cutsem E, Penninckx F, Filez L, Bormans G, et al. Whole-body PET with FDG for the diagnosis of recurrent gastric cancer. Eur J Nucl Med Mol Imaging. 2002;29:525–9.
33. Sun L, Su XH, Guan YS, Pan WM, Luo ZM, Wei JH, et al. Clinical role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in post-operative follow up of gastric cancer: initial results. World J Gastroenterol. 2008;14:4627–32.
34. Sim SH, Kim YJ, Oh DY, Lee SH, Kim DW, Kang WJ, et al. The role of PET/CT in detection of gastric cancer recurrence. BMC Cancer. 2009;9:73.
35. Park MJ, Lee WJ, Lim HK, Park KW, Choi JY, Kim BT. Detecting recurrence of gastric cancer: the value of FDG PET/CT. Abdom Imaging. 2009;34:441–7.
36. Bilici A, Ustaalioglu BB, Seker M, Kefeli U, Canpolat N, Tekinsoy B, et al. The role of (18) F-FDG PET/CT in the assessment of suspected recurrent gastric cancer after initial surgical resection: can the results of FDG PET/CT influence patients' treatment decision making? Eur J Nucl Med Mol Imaging. 2010 (Epub ahead of print).
37. Nakamoto Y, Togashi K, Kaneta T, Fukuda H, Nakajima K, Kitajima K, et al. Clinical value of whole-body FDG-PET for recurrent gastric cancer: a multicenter study. Jpn J Clin Oncol. 2009;39:297–302.
38. Suga T, Nakamoto Y, Saga T, Higashi T, Hara T, Ishizu K, et al. Prevalence of positive FDG-PET findings in patients with high CEA levels. Ann Nucl Med. 2010;24:433–9.
39. Wong WL, Chambers RJ. Role of PET/PET CT in the staging and restaging of thoracic oesophageal cancer and gastro-oesophageal cancer: a literature review. Abdom Imaging. 2008;33:183–90. (Review).
40. Lee SM, Kim SH, Lee JM, Im SA, Bang YJ, Kim WH, et al. Usefulness of CT volumetry for primary gastric lesions in predicting pathologic response to neoadjuvant chemotherapy in advanced gastric cancer. Abdom Imaging. 2009;34:430–40.
41. Suttie SA, Welch AE, Park KG. Positron emission tomography for monitoring response to neoadjuvant therapy in patients with oesophageal and gastro-oesophageal junction carcinoma. Eur J Surg Oncol. 2009;35:1019–29. (Review).
42. Di Fabio F, Pinto C, Rojas Llimpe FL, Fanti S, Castellucci P, Longobardi C, et al. The predictive value of 18F-FDG-PET early evaluation in patients with metastatic gastric adenocarcinoma treated with chemotherapy plus cetuximab. Gastric Cancer. 2007;10:221–7.
43. Ott K, Fink U, Becker K, Stahl A, Dittler HJ, Busch R, et al. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. J Clin Oncol. 2003;21:4604–10.
44. Ott K, Herrmann K, Lordick F, Wieder H, Weber WA, Becker K, et al. Early metabolic response evaluation by fluorine-18 fluorodeoxyglucose positron emission tomography allows in vivo testing of chemosensitivity in gastric cancer: long-term results of a prospective study. Clin Cancer Res. 2008;14:2012–8.
45. Vallböhmer D, Hölscher AH, Schneider PM, Schmidt M, Dietlein M, Bollschweiler E, et al. [18F]-Fluorodeoxyglucose-positron emission tomography for the assessment of histopathologic response and prognosis after completion of neoadjuvant chemotherapy in gastric cancer. J Surg Oncol. 2010;102:135–40.
46. Dassen AE, Lips DJ, Hoekstra CJ, Pruijt JF, Bosscha K. FDG-PET has no definite role in preoperative imaging in gastric cancer. Eur J Surg Oncol. 2009;35:449–55. (Review).
47. Minamimoto R, Senda M, Uno K, Jinnouchi S, Iinuma T, Ito K, et al. Performance profile of FDG-PET and PET/CT for cancer screening on the basis of a Japanese Nationwide Survey. Ann Nucl Med. 2007;21:481–98.
48. Nishizawa S, Kojima S, Teramukai S, Inubushi M, Kodama H, Maeda Y, et al. Prospective evaluation of whole-body cancer screening with multiple modalities including [18F]fluorodeoxyglucose positron emission tomography in a healthy population: a preliminary report. J Clin Oncol. 2009;27:1767–73.
49. Israel O, Yefremov N, Bar-Shalom R, Kagana O, Frenkel A, Keidar Z, et al. PET/CT detection of unexpected gastrointestinal foci of 18F-FDG uptake: incidence, localization patterns, and clinical significance. J Nucl Med. 2005;46:758–62.
50. Shoda H, Kakugawa Y, Saito D, Kozu T, Terauchi T, Daisaki H, et al. Evaluation of 18F–2-deoxy-2-fluoro-glucose positron emission tomography for gastric cancer screening in asymptomatic individuals undergoing endoscopy. Br J Cancer. 2007;97:1493–8.
51. Lee JW, Kang KW, Paeng JC, Lee SM, Jang SJ, Chung JK, et al. Cancer screening using 18F-FDG PET/CT in Korean asymptomatic volunteers: a preliminary report. Ann Nucl Med. 2009;23:685–91.
52. Hur H, Kim SH, Kim W, Song KY, Park CH, Jeon HM. The efficacy of preoperative PET/CT for prediction of curability in surgery for locally advanced gastric carcinoma. World J Surg Oncol. 2010;8:86.