

Review

The role of [18F]FDG PET/CT for gastric cancer management

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Abstract

Gastric cancer (GC) is a common cause of cancer-related deaths in the world. In addition to the patient's clinical history and clinical examination, nuclear medicine tools are required for diagnosis. [¹⁸F]FDG PET/CT has been commonly used for cancer patients for staging, restaging, evaluation of treatment response. This study aimed to review the current literature on the role of [¹⁸F]FDG PET/CT for GC management.

KEY words: gastric cancer; PET/CT; [18F]FDG

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Introduction

Gastric cancer (GC) is a common neoplasm and GC is the third most widespread cause of cancer-related deaths worldwide. GC generally affects men higher than women. Various factors such as Helicobacter Pylori, bad diet habits and smoking give rise to GC [1]. GC is a cancer type usually diagnosed at an advanced stage. Patient history, physical examination, endoscopy and biopsy is essential for the diagnosis of this disease. Diagnostic imaging modalities including endoscopic ultrasound (EUS), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography/computed tomography (PET/CT) are used for the initial evaluation of GC. Fluorine-18 fluoro-2-deoxy-D-glucose ([18F]FDG) PET/CT is recommended if there is no evidence for metastasis and if clinically indicated according to National Comprehensive Cancer Network (NCCN) guidelines. PET/CT might be useful for the evaluation of therapy response before surgery, recurrence and determination of occult metastatic tumour [2]. In this review article, the role of [18F]FDG PET/CT for GC management is evaluated in light of the current literature.

Detection of primary tumours and prediction of prognosis

A cancer screening programme for detecting GC found that FDG-PET had 37.9% sensitivity. Furthermore, FDG-PET had lower

Correspondence to: Ebru Salmanoglu Department of Nuclear Medicine, Kahramanmaras Sutcu Imam University, Faculty of Medicine, Avsar Kampus 46040, Kahramanmaras, Turkey e-mail: ebrusalmanoglu@yahoo.com sensitivity than endoscopy. FDG-PET demonstrated early-stage GC in some cases. However, many of them were shown with a combination of endoscopy. Therefore, the combination of endoscopy was helpful for the detection of tumours at an early stage [3].

Dual time point imaging (DTPI) [¹⁸F]PET/CT was analysed to differentiate malignant and benign disease of GC patients (n = 74) with focal increased gastric uptake on imaging. The maximum standardized uptake value (SUVmax) of the early PET/CT imaging was 5.0 \pm 1.4, the SUVmax of the delayed PET/CT imaging was 5.9 \pm 2.7. The study concluded that DTPI can play an important role in differentiating malignant disease from the benign gastric disease [4].

The utility of [¹⁸F]FDG PET/CT was investigated for detecting primary GC in suspected GC patients (n = 68). After fasting wholebody PET/CT imaging, the patients drank a measured amount of milk with Diatrizoate Meglumine. Local gastric PET/CT imaging was also performed. Whole-body PET/CT had 92.9% sensitivity, 75.0% specificity, 94.5% PPV, and 69.0% negative predictive value (NPV) for detecting primary tumour. Local gastric PET/CT had 91.1% sensitivity, 91.7% specificity, 98.1% PPV, and 68.8% NPV. The mean ratio of the tumour's SUVmax/the adjacent gastric Wall SUVmax was significantly increased with local gastric PET/CT. It was concluded that gastric distention might be useful for tumour visibility. However, gastric distention may not significantly improve diagnostic accuracy [5].

[¹⁸F]FDG uptake was investigated for the detection of regional lymph nodes (LNs) in preoperative GC patients (n = 156). Tumour size (≥ 3 cm) and LN metastasis were significantly associated with [¹⁸F]FDG uptake in LN. When the SUVmax of the primary tumour > 3.75, PET/CT had 73.5% sensitivity and 74.5% specificity for the detection of LN metastasis. While the SUVmax of the primary tumour > 4.35 and FDG uptake of LN was positive, PET/CT

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had 58.8% sensitivity and 91.6% specificity for the prediction of non-curative surgery [6].

Histopathologic characteristics of primary GC affect the FDG uptake and tumour detection rate on FDG PET/CT. In a study of 50 patients with preoperative locally advanced gastric adenocarcinoma (GA), FDG uptake of the primary tumour was investigated. Results were correlated with histopathologically. The poorly cohesive type according to the WHO classification, diffuse type according to the Lauren classification and infiltrative type according to the Ming classification had low FDG uptake in these patients. Therefore, the correlation between FDG uptake and histopathologic characteristics might be useful for FDG PET/CT imaging in GC patients [7].

Diagnostic accuracy of whole-body [¹⁸F]FDG PET/CT and regional [¹⁸F]FDG PET/CT after water gastric inflation was assessed in preoperative GC patients (n = 44). The sensitivity of whole-body PET/CT (50%) was augmented by regional PET/CT (75%) for primary tumour detection. Furthermore, the sensitivity of whole-body PET/CT (24.6%) for LN metastasis was significantly increased by regional PET/CT (36.1%). Regional PET/CT can be used to improve FDG uptake in GC patients [8].

The utility of [¹⁸F]FDG PET/CT was evaluated for progression-free survival (PFS) before therapy in GC patients (n = 321). The Low SUVmax group (\leq 5.74) had a longer mean PFS than that of the high SUVmax group (> 5.74). Stage, depth of tumour invasion, presence of LN metastasis and SUVmax (> 5.74 vs \leq 5.74) were associated with recurrence. High SUVmax (> 5.74) and high metabolic tumour volume (MTV) (> 16.42) were poor prognostic factors for PFS [9].

The prognostic role of baseline and interim [¹⁸F]FDG PET/CT during chemotherapy was examined in patients (n = 44) with recurrent/metastatic advanced gastric cancer (AGC). Initial and change of metabolic parameters (MP)-MTV, tumour lesion glycolysis (TLG) and SUVmax and SUVmean were measured. Decreased percentage of SUVmax and SUVmean on interim PET/CT and initial values of volumetric parameters (MTV and TLG) were significant predicting factors for chemotherapy response. Furthermore, the decreased percentage values of metabolic parameters as well as maximum and mean SUV were important prognostic factors for overall survival (OS) and PFS [10].

The prediction of prognosis was investigated SUVmax of metastatic LNs using [18 F]FDG PET/CT in preoperative GC patients (n = 151). Results were confirmed histologically. Nodal SUVmax was an independent prognostic factor for recurrence-free survival (RFS) and OS [11].

The metabolic affinity of primary tumours or metastatic LNs on [¹⁸F]FDG PET/CT was studied for the prediction of survival in patients (n = 168) with AGC. [¹⁸F]FDG PET/CT had 73.8% sensitivity for the detection of advanced pT \geq 3 stages. Furthermore, [¹⁸F]FDG PET/CT had 92.2% specificity for the detection of the advanced pN (\geq 2) stage. Data showed that the [¹⁸F]FDG affinity of LNs was an independent prognostic factor for RFS [12].

TNM Staging

Imaging of LN metastasis and accurate staging is needed for effective therapy before surgery. However, accurate staging with conventional diagnostic imaging modalities such as CT is not enough due to its low sensitivity and low specificity. Therefore, nuclear medicine imaging methods with high specificity such as [18F]FDG PET/CT are necessary to detect metastasis [13].

In a comparative retrospective study, the effect of FDG-PET for the staging of Gastric adenocarcinoma (GA) was analysed in 608 patients who had biopsy-proven GA and 207 patients who had both CT and FDG-PET. FDG-PET identified primary tumour (PT) (125 vs 120) more than CT alone. Furthermore, FDG detected distant lymph node disease (DLN) (41 vs 25) more than CT alone. In addition, FDG-PET up-staged 31 patients and down-staged 17 patients. PET/CT was more helpful than CT for the staging of GA [14].

In another comparative study, FDG PET/CT was researched in 97 histologically proven GC patients. It was reported that FDG uptake in both tumour and LN were related to poor OS. In contrast to FDG PET/CT, lymphadenomegaly was not related to OS on CT. FDG PET/CT had more prognostic importance than CT for staging [15].

A study (n = 90) reported that FDG PET/CT had 78.9% sensitivity for detecting primary GC. It was noted that T3/T4 disease had higher SUVmax than T1/T2 disease (9.0 vs 3.8) on PET/CT imaging. The SUVmax of the primary tumour was associated with tumour size. FDG-PET/CT had 64.5% sensitivity, 85.7% specificity, 71.1% accuracy, 90.9% PPV, and 52.2 % NPV for evaluation of local LN metastasis [16].

[¹⁸F]FDG PET/CT was examined in non-junctional GC patients (n = 279). 80.6% of the primary tumour was FDG-avid. PET/CT detected 7% of patients that could not be shown with other imaging methods. For metastatic disease, PET/CT had 49.3% sensitivity, 97.1% specificity, 85.0% PPV, 85.4% NPV. This recent study reported that PET/CT should be used for staging and it should have a place in guidelines [17].

[¹⁸F]FDG PET/CT was analysed to image metabolically positive lymph nodes (MPLN) in patients (n = 50) with locally AGC. The numbers of MPLN were associated with the numbers of histologically positive LNs . The numbers of MPLN, PET/CT positive LN, SUVmax of LN (> 2.8), TNM stage were correlated with OS. Therefore, the number of MPLN is an important parameter for predicting the prognosis of locally AGC [18].

The relationship between FDG uptake in the primary tumour/LNs and clinicopathological factors, especially pStage III/IV were evaluated in AGC patients (n = 117). FDG uptake in primary tumour and LNs were related with pStage III/IV. FDG PET/CT had 22.7% sensitivity, 90.5% specificity for LN metastasis. FDG PET/CT had 80.4% sensitivity for the detection of pStage III/IV disease. As a result, PET/CT was a helpful modality for the evaluation of pStage III/IV [13].

In a retrospective study (n = 45), the role of F-FDG PET/CT for staging GC was compared with contrast-enhanced computed tomography (CECT). There was no significant statistical difference found between PET parameters and histotype, grading, and site of the gastric lesion. FDG PET/CT had higher specificity for both LN and distant metastasis [19].

In another retrospective study, clinicopathologic parameters that were related to [¹⁸F]FDG avidity was examined. Large tumour size, non-signet ring cell carcinoma type, and glucose transporter 1-positive expression on immunohistochemistry were strong predictive factors about [¹⁸F]FDG avidity. PET scoring system which was developed from these parameters detected [¹⁸F] FDG-avid cancer and it had 85% sensitivity and 71% specificity [20]. [¹⁸F]FDG PET/CT was compared with CECT in 45 GC patients for staging. While CECT had 92.11% sensitivity, 57.14% specificity; [¹⁸F]FDG PET/CT had 81.58% sensitivity, 85.71% specificity for detection of GC. Whereas CECT had 70.83% sensitivity, 61.90% specificity; [¹⁸F]FDG PET/CT had 58.33% sensitivity, 95.24% specificity for LN involvement. While CECT had 80% sensitivity, 62.86% specificity; [¹⁸F]FDG PET/CT had 60% sensitivity, 88.57% specificity for distant metastases. The authors stated that [¹⁸F]FDG PET/CT was helpful for the assessment of GC for the detection of the primary tumour, LN and distant metastasis [19].

[¹⁸F]FDG PET/CT was compared with CECT for staging in locally AGC patients (n=106). The combination of [¹⁸F]FDG PET/CT on CECT provided better diagnostic accuracy for imaging of both distant LN metastasis and bone metastasis [21].

Curability

The utility of FDG PET/CT was evaluated for predicting the curability of endoscopic submucosal dissection (ESD) for early GC in a first research study. EGCs (n = 210) of 199 patients were included. The detection rate of early GC with FDG PET/CT was 37.1%. In contrast to that, the detection of early GC which were not curable by ESD had 79% sensitivity, 91% specificity. It was concluded that FDG PET/CT might be a useful method secondary to endoscopy for this purpose [22].

Detection of recurrent tumours

Diagnostic performance of FDG PET/CT for surveillance was investigated in asymptomatic 190 GC patients (early GC patients: n = 115; AGC patients: n = 75) after surgery. FDG PET/CT had good diagnostic performance with 84.2% sensitivity and 87.7% specificity [23].

In another study, the diagnostic performance of [¹⁸F]FDG PET/CT was evaluated in AGC patients (n = 46) who were asymptomatic and negative on conventional imaging. Final verification was performed using clinical follow-up, tumour markers, CT, endoscopy and with/without a histopathologic diagnosis. [¹⁸F]FDG PET/CT had 100% sensitivity, 88.1% specificity, 44.4 % PPV and 100 % NPV in the patient-based analysis irrespective of the recurrence site [24].

FDG PET/CT was retrospectively compared with CECT to detect gastric carcinoma recurrence. The recurrence group (60 patients) and control group were (60 patients) were included. There was no significant difference found between these two methods for the detection of patient-based overall recurrence. On the other hand, CECT had higher sensitivity (96%) than PET/CT (50%) for imaging peritoneal carcinomatosis. Furthermore, on pathology-based analysis CECT had higher sensitivity (98%) than PET/CT (80%). Therefore, CECT might be a primary method for the detection of tumour recurrence [25].

Diagnostic performance of PET/CT was investigated in [18 F]FDG-avid AGC patients (n = 368) for detection of recurrence. PET had higher sensitivity (81.0%) for [18 F]FDG-avid tumours than both non-avid tumours and nonanastomosis site recurrences (52.4%). PET had high specificity (97.1% and 97.5%) in both groups [26].

In a meta-analysis study (828 patients in 14 studies) diagnostic accuracy of [18F]FDG PET for detection of GC recurrence was examined. On a per-patient basis analysis, [18F]FDG PET had 85% sensitivity. On per-lesion basis analysis, [18F]FDG PET had 75% sensitivity [27].

The diagnostic utility of FDG PET/CT was evaluated in 279 patients. The primary tumour was FDG-avid in 80% of patients. PET/CT detected unsuspected metastases in 7% of patients. In addition, these metastases could not be detected by conventional staging without PET/CT in 5% of patients. Patients with FDG-avid nodes had an incurable disease. This retrospective study suggested that PET/CT should be considered in international recommendations [17].

Therapeutic response evaluation

Investigators evaluated the importance of PET imaging using [¹⁸F]FDG and [¹⁸F]fluoro-3'-deoxy-3'-Lfluorothymidine (FLT) for early metabolic response in AGC patients (n = 64) who were treated with chemotherapy. PET imaging was performed at baseline and 14 days after therapy beginning. FDG PET had 70% sensitivity and 83% specificity for predicting clinical response. FDG PET had 58% sensitivity and 100% specificity for predicting disease control status using with total uptake value reduction percentage (d-SUV) value. In contrast to FDG, the d-SUV value of FLT-PET was not useful for both predicting clinical response and disease control status. Decreased FDG uptake in liver metastasis helped predict both clinical response and disease control status [28].

The accuracy of FDG PET/CT to predict early pathologic response after neoadjuvant chemotherapy was analysed in 44 patients with locally advanced GC or esophagogastric junction II/III. PET/CT had 90.9% sensitivity, 47.3% specificity, and 63.3% accuracy for prediction of response [29].

Diffusion-weighted MRI (DW-MRI) and [18 F]FDG PET/CT were compared for therapy response in patients with locally advanced GA (n = 17). Apparent diffusion coefficient (ADC) value and SUVmean corrected for partial volume effect were evaluated and compared with histopathological tumour regression grade. It was concluded that DW-MRI was more helpful than FDG-PET/CT for the evaluation of therapy response [30].

In a prospective study, therapy response in AGC patients (n = 74) who had lesions (n = 620) with > 1 cm on CT were included and each lesion was also assessed with [¹⁸F]FDG PET. Poorly cohesive carcinomas exhibited lower SUVmax than adenocarcinomas. Human epidermal growth factor receptor 2 (HER2)-positive tumours had higher SUVmax in comparison with HER2-negative tumours. The changes in SUVmax and total lesion glycolysis (TLG) owing to chemotherapy were associated with the changes in tumour size. Patients with a decrease in both tumour size and SUVmax had a better prognosis than patients who had only a decrease in tumour size or SUVmax [31].

Prediction of HER2 status

Surgery is often a part of the treatment of GC. However, surgery is not efficient especially for inoperable or metastatic GC patients. As a result of this, other therapy options are required for these patients [32]. Well or moderately differentiated GA, express HER2 more than poorly differentiated GA [33]. This is important to predict HER2 status for HER2-targeted molecular therapy.

PET/CT plays a leading role in predicting the therapy response of various cancers [32].

Association between [¹⁸F]FDG uptake and HER2 expression was evaluated in 64 GC patients. SUVmax and tumour differentiation was correlated with HER2 expression. When a SUVmax = 6.2 as a cut off value was used, [¹⁸F]FDG PET/CT had 64.4% accuracy for predicting the HER2 expression. [¹⁸F]FDG PET/CT also might help predict HER-2 targeted therapy response. However, further prospective studies are still needed to understand its potential [32].

In a research study, it was found that (n = 124) HER2-positive GCs had higher SUVmax (median = 12.1) than HER2-negative (median = 7.4) GCs. FDG PET/CT volume-based parameters can play a role in both HER2-positive GCs and HER2-negative cancers for predicting the prognosis of AGC [34]. However, in another study (n = 31), that firstly compared SUVmax and HER2 status in agematched and sex-matched patients with GC and gastroesophageal junction adenocarcinomas (GEJC), SUVmax was not correlated with HER2 status of both cancer types. High SUVmax was correlated with decreased OS. Nonetheless, larger cohort studies are still needed to validate this result [35].

Conclusions

GC still has high mortality and is responsible for cancer-related deaths worldwide. Patients are asymptomatic at an early stage of GC. Early screening tests have vital importance for cancer patients. Unfortunately, there is no routine screening test for GC in daily clinical practice. On the other hand, new various screening biomarkers in the blood are still in progress and these studies are could not be applied to patients. Therefore, most of the cases diagnosed at the late stage which patients had an incurable disease. Even though diagnostic imaging modalities improved with current technology in this century, early and accurate detection of GC is still challenging for clinicians. Accurate staging and assessment of treatment response are important for a patient's lifetime. PET/CT is a noninvasive imaging modality that is important for TNM staging especially for detection of distant metastasis, evaluation of therapy response, curability, detection of recurrent tumours. However, some pathological types of gastric tumours are not FDG avid and these tumours may not be detectable on PET/CT images. Although this disadvantage, PET/CT hybrid imaging method has a great contribution to the management of these patients.

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