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**Diagnosis and evaluation of gastric cancer with positron emission tomography**

WuC *et al.* PET imaging of gastric cancer

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**Abstract**

Gastric cancer is the second leading cause of cancer mortality worldwide. The diagnosis of gastric cancer has been significantly improved with the broadly available of gastrointestinal endoscopy. Effective technologies for accurate staging and quantitative evaluation are still in demand to merit reasonable treatment and better prognosis for the patients presented with advanced disease. Preoperative staging using conventional imaging tools, such as computed tomography (CT) and endoscopic ultrasonography, are inadequate. Positron emission tomography (PET), using 18F-fluorodeoxyglucose (FDG) as a tracer and integrating CT for anatomic localization, holds a promise to detect unsuspected metastasis and has been extensively used in a variety of malignancies. However, the value of FDG PET/CT in diagnosis and evaluation of gastric cancer is still controversial. This article reviewed the current literature in diagnosis, staging, response evaluation, and relapse monitoring of gastric cancer, and discussed the current understanding, improvement, and future prospects in this area.

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**Key words:** Gastric cancer; Positron emission tomography/computed tomography; 18F-fluorodeoxyglucose

**Core tip:** This systematic review summarized and discussed various aspects regarding Positron emission tomography (PET), and PET/ computed tomography application in gastric cancer, including diagnosis and its influencing factors, therapy evaluation, recurrent detection, current limitations and improvement and so on**.**

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**INTRODUCTION**

Gastric cancer, a common malignancy with a poor prognosis, is listed as the second leading cause of cancer mortality worldwide[[1](#_ENREF_1)]. To date, a curative therapy for gastric cancer mainly relies on the complete resection of the tumor; thus, early diagnosis and accurate evaluation are important for decision-making regarding treatment and for the prognosis. The broad availability of gastrointestinal endoscopy has significantly improved the diagnosis of gastric cancer. Effective methods for the accurate staging and quantitative evaluation of gastric cancer are in demand to develop a reasonable selection of treatments for most patients presented with advanced gastric cancer. Accurate staging of the disease, including the full disclosure of the local invasion extent, lymph node involvement, and distant metastasis, is important for patient management and surgical planning. Conventional imaging tools for preoperative staging, including computed tomography (CT) and endoscopic ultrasonography (EUS), have so far been found inadequate due to their technical limitations[[2](#_ENREF_2)].

In recent decades, positron emission tomography (PET) using 18F-fluorodeoxyglucose (FDG) as a tracer has proven useful in the diagnosis and evaluation of a variety of malignancies by providing metabolic information about tumors. In particular, most PET scanners have now been integrated with CT into a single system, significantly increasing diagnostic accuracy by combining metabolic and anatomic images. FDG PET/CT has shown great advantages in staging, therapeutic evaluation, and recurrence surveillance in various malignancies[[3](#_ENREF_3)]. As for gastric cancer, several clinical guidelines, including those of the National Comprehensive Cancer Network (NCCN), indicate that PET/CT is recommended in patients if metastatic cancer is not evident and is useful in demonstrating occult metastatic disease[[4](#_ENREF_4)]. The European Society for Medical Oncology (ESMO) guidelines for gastric cancer also suggest that PET imaging may improve staging through an increased detection of the involved lymph nodes or metastatic disease[[5](#_ENREF_5)]. However, the overall sensitivity of PET and PET/CT in the detection of gastric cancer is relatively low compared to that of most other malignancies. Due to such reasons as the physical FDG uptake and involuntary movements of the gastric wall, some types of gastric malignancies will affect the detection ability of FDG PET for gastric cancers. Thus, the value of FDG PET/CT to the diagnosis and evaluation of gastric cancer is still controversial[[6](#_ENREF_6),[7](#_ENREF_7)].

This article broadly reviews the current literature on FDG PET and PET/CT for the diagnosis, staging, therapeutic evaluation, and relapse monitoring of gastric cancer. An up-to-date understanding, recent improvements, and future prospects in this area are also discussed.

**DETECTION AND EVALUATION OF PRIMARY GASTRIC CANCER**

The detectability and diagnostic accuracy of FDG PET or FDG PET/CT in gastric cancer may be influenced by many factors, such as the tumor size, histological type, and location as well as the physiological FDG uptake by the gastric wall.

***Influence from tumor size***

Tumor size is one of the major factors influencing the FDG PET detection of primary gastric cancer. For small lesions, PET detection is always a challenge due to its limited spatial resolution. A study showed that FDG PET had a sensitivity of 76.7% for the detection of gastric cancer > 30 mm but only 16.8% for those less than 30 mm[[8](#_ENREF_8)]. Recent studies have indicated that tumor size was a major factor influencing the standardized uptake value (SUV) of gastric cancer on FDG PET[[9](#_ENREF_9),[10](#_ENREF_10)]. In another study, tumor invasion depth was found to be an independent factor for the FDG uptake in gastric lesions[[11](#_ENREF_11)]. Because late-stage tumors are usually larger in size with deeper invasion, advanced gastric cancers (AGC), in general, tend to yield a higher sensitivity in FDG PET imaging than early stage gastric cancers (EGC). Dassen and colleagues summarized the sensitivity of FDG PET as ranging from 26% to 63% for EGC and from 93% to 98% for AGC [[7](#_ENREF_7)].

***Influence from histological type***

FDG PET may also have different sensitivity for the detection of different types of gastric malignancies. The biological characteristics vary among different types of gastric malignancies, which may significantly influence the uptake of FDG. Most studies reported that FDG PET had significantly lower sensitivities in detecting diffuse type, mucinous adenocarcinoma (MAC) or signet-ring cell carcinoma (SRC) than intestinal type or tubular adenocarcinoma (TAC) gastric adenocarcinoma[[8](#_ENREF_8),[12-15](#_ENREF_12)], although some studies using different patient groups obtained different results [[9](#_ENREF_9),[10](#_ENREF_10),[16](#_ENREF_16)].

The potentially lower FDG uptake in diffuse type gastric adenocarcinoma or MAC/SRC may be influenced by several factors, including the low-density diffuse infiltration of adenocarcinoma cells, existence of extracellular or intracellular metabolic inert mucus content, and low expression level of glucose transporter 1 (GLUT-1)[[12](#_ENREF_12),[13](#_ENREF_13),[17](#_ENREF_17)]. These factors thus cause the low sensitivity of FDG PET in these types of gastric cancers.

***Influence from tumor location***

The stomach regions can be divided into the gastro-esophageal junction (GEJ) and the upper (or proximal), middle, and lower (or distal) parts. FDG PET detection of GEJ tumors was reported to be more sensitive than that of gastric adenocarcinomas at other stomach parts, possibly due to the higher incidence of intestinal types within GEJ cancers[[18](#_ENREF_18)]. Although some researchers reported that FDG PET had a similar detectability to that of gastric cancers located at the upper, middle, and lower parts of the stomach[[8](#_ENREF_8),[19](#_ENREF_19)], some others argued that gastric cancers located at the upper or proximal part were more readily detected than those at the lower or distal part of the stomach[[13](#_ENREF_13)].

***Influence from the physiological uptake of the gastric wall***

The physiological uptake can also influence PET detection of gastric cancers. Physiological accumulation is a common issue for the detection of malignancy using FDG PET or FDG PET/CT imaging. Under empty-stomach states, approximately 38.0% and 59.5% of normal gastric walls show moderate and intensive FDG uptake[[20](#_ENREF_20)], and the specificity was reported to be as low as 50%[[21](#_ENREF_21)] using FDG PET for gastric cancers due to the high incidence of normal gastric wall uptakes. Previously, it was reported that there were significant differences in the physiological FDG uptake among the three parts of the gastric wall (upper > middle > lower); thus, this technique may be more confidently used to diagnose a gastric malignancy at the distal part of the stomach[[22](#_ENREF_22)]. Recently, many studies have focused on methods to increase the sensitivity and specificity of FDG PET or PET/CT by reducing the physiological uptake in the gastric wall through methods such as gastric distention[[20](#_ENREF_20),[21](#_ENREF_21),[23-27](#_ENREF_23)] or through medicines to inhibit gastric movement[[28](#_ENREF_28),29], as will be discussed in the following sections.

***Influence of tumor biology***

For gastric cancers, one of the most frequently studied genes associated with FDG uptake is GLUT-1. Several studies have reported that tumorous GLUT-1 expression was positively associated with the FDG SUV of gastric cancers[[12](#_ENREF_12),[13](#_ENREF_13),[17](#_ENREF_17)]. Most recently, some hypoxia-related gene expressions, such as hypoxia-inducible factor 1 (HIF-1) in gastric cancer cells, were also found to contribute to FDG uptake in gastric tumors[[10](#_ENREF_10)]. Actually, GLUT-1 and HIF-1 gene transcriptions are interrelated with one another, and they both play key roles in tumor cell metabolic changes[[30](#_ENREF_30)].

**EVALUATION OF LYMPH NODE INVOLVEMENT**

For N staging in gastric malignancies, one meta-analysis reported that the sensitivity and specificity of FDG PET or PET/CT ranged from 33.3 – 64.6% and 85.7%-97.0%, respectively, although there was no significant diagnostic difference compared to AUS, CT or MRI[[31](#_ENREF_31)]. Other individual studies reported that FDG PET or PET/CT was less sensitive but more specific compared to commonly used CT and magnetic resonance imaging (MRI)[[16](#_ENREF_16),[32](#_ENREF_32),[33](#_ENREF_33)]. There are many reasons for the low sensitivity of FDG PET in detecting lymph node metastases. The first is the histological type of the primary tumor. As summarized before, the diffuse type or MAC/SRC was usually less or non FDG-avid. Therefore, metastases of the same cell types in lymph nodes were less likely to be detectable by FDG PET[[16](#_ENREF_16),[33](#_ENREF_33)]. Additionally, many studies have found that the SUVmax of the primary tumor was associated with the SUVmax of the lymph nodes[[33](#_ENREF_33),[34](#_ENREF_34)]. In a report, 60%-70% of lymph node metastases were not detected in patients with non FDG-avid primary tumors[[35](#_ENREF_35)]. The second reason is the size of metastatic lymph node. Some metastatic lymph nodes in gastric cancer could be as small as 3 mm[[36](#_ENREF_36)], which is beyond the detectability of most PET scanners. The PET scanners have a spatial resolution of 4 -6 mm. Some small lymph nodes are even more difficult to discriminate because of the radioactive volume effect generated by the nearby primary tumor. Even with PET/CT, many lymph node metastases remain ambiguous[[34](#_ENREF_34)]. Other factors, such as the high physiological uptake background from the normal gastric wall, would also compromise the sensitivity of PET for N staging.

In spite of the low sensitivity, FDG PET or PET/CT usually showed a higher specificity than most other imaging modalities, including CT and MRI, in the N-staging of gastric cancers. Because FDG PET and FDG PET/CT diagnose lymph node metastasis using glucose metabolism rather than the size change, it is very useful to distinguish the enlarged lymph nodes due to inflammation from cancer cell metastasis. Additionally, the different criteria for lymph node enlargement in CT and MRI images can also decrease the specificity of these modalities in the N-staging of gastric cancers.

**EVALUATION OF DISTANT METASTASIS**

In general, the conventional tools for detecting distant metastasis are CT and histological confirmation. Among the many metastatic sites for gastric cancer, peritoneal metastasis is considered an operative contraindication and represents the most difficult type for treatment[[37](#_ENREF_37)]. Compared to CT, FDG PET usually showed a lower sensitivity for the diagnosis of peritoneal seeding[[14](#_ENREF_14),[34](#_ENREF_34),[38](#_ENREF_38),[39](#_ENREF_39)]. Reasons explaining these results include the following: (1) the small and diffuse growing patterns of metastasis seeding and (2) the diffuse histological type of gastric cancers, which is more likely to spread into the peritoneal cavity[[40](#_ENREF_40)]. Therefore, many studies suggest high quality CT as the preferred modality of choice for the diagnosis of peritoneal metastasis[[38](#_ENREF_38)]. Although the sensitivity is lower, FDG PET or PET/CT could still be useful for detecting peritoneal metastasis, especially when the CT results are equivocal. FDG imaging of peritoneal metastasis may also help to avoid unnecessary laparotomy in a considerable portion of patients. Just as in the recently published work by Smyth *et al*[[14](#_ENREF_14)], although FDG PET/CT does not add benefit to high-quality contrast CT for identifying gastric cancer peritoneal metastases, the use of FDG-PET/CT in addition to CT, EUS and laparoscopy can avoid futile gastrectomy in almost 10% of patients, saving more than $10,000 per patient. The authors recommend its use in staging all potentially operable gastric cancer patients.

The frequently targeted distant solid organs include the liver, lungs and bones. In a study reported by Chung *et al*[[41](#_ENREF_41)], FDG PET/CT imaging was able to detect solid organ metastasis (lungs, liver, bone, or adrenal gland) with a sensitivity of 95.2% and a specificity of 100%. In another study, FDG PET detections of the liver, lung and bone metastases were found to be satisfactory and accurate[[42](#_ENREF_42)]. Specifically, for liver metastasis, a study reported that FDG PET was sensitive for the detection of liver metastasis from gastric cancers[[43](#_ENREF_43)], although a meta-analysis reviewing CT, US, EUS, and FDG PET, FDG PET showed only a moderate ability in this aspect[[38](#_ENREF_38)]. For bone metastasis, whole-body bone scanning is a frequently used modality to evaluate the status of bone metastasis. In a study, the authors compared the value of FDG PET and whole-body bone scintigraphy for the detection of bone metastasis in gastric cancer patients. They found that both modalities had a similar sensitivity and accuracy for detecting bone metastasis in gastric cancer, but FDG PET was superior for detecting synchronous bone metastasis[[44](#_ENREF_44)], with a sensitivity of 93.5%. However, Yoshioka *et al*[[42](#_ENREF_42)] reported that FDG PET did not seem to be useful for the detection of bone metastasis, with a sensitivity of only 30%.

**RESPONSE EVALUATION AND RELAPSE MONITORING**

Currently, the only curative treatment for gastric cancer is the surgical removal of gastric tumors with lymph node dissection. Recently, some treatment combinations, such as chemotherapy or radiotherapy, have been used in addition to surgical removal for gastric cancer patients. The evaluation of the therapy outcomes is, therefore, of great importance in managing patients, guiding future therapy improvements, and directing personalized treatments. Currently, FDG PET or PET/CT is emerging as an effective tool for therapeutic evaluation in many types of cancers, including gastric cancers. The following sections will discuss tumor response evaluation and tumor recurrence prediction using FDG PET or PET/CT in gastric cancer.

***Tumor response evaluation or prediction***

Although curative surgery remains the mainstay of gastric cancer treatment, the 5-year survival in these patients is only approximately 25%[[45](#_ENREF_45)]. To improve the relapse-free and overall survival in these patients, perioperative chemotherapy or radiochemotherapy has been gaining increasing interest in recent years for gastric cancers[[46-48](#_ENREF_46)]. For preoperative or so-called neoadjuvant chemotherapy, there has been accumulating evidence that it might improve the survival in responding patients with locally advanced gastric cancers[[49](#_ENREF_49),[50](#_ENREF_50)]. However, for non-responders, the high amount of complications following neoadjuvant chemotherapy and surgery as well as the minimal benefit from this additional therapy have to be considered[[51](#_ENREF_51)]. Depending on the different therapy regimes and evaluation methods, it has been reported that approximately 30%-60% of patients receiving preoperative chemotherapy were histological responders, including both total and partial responders[[46](#_ENREF_46),[52](#_ENREF_52)]. Therefore, it is important to distinguish those non-responding patients at an early phase of chemotherapies to prevent further ineffective and potentially harmful interventions.

In recent years, evidence suggested that FDG PET or FDG PET/CT seems to be an effective noninvasive tool for response assessment in gastric cancer[[12](#_ENREF_12),[53-55](#_ENREF_53)]. Metabolic reduction early after the initial of neoadjuvant chemotherapy can be used to discriminate non-responders from responders for further therapeutic adjustments (Figure 1). FDG uptake changes in tumor sites seemed to be associated with subsequent histological tumor regression as well as with patient survival. In a phase II trial reported by Fabio *et al*[[53](#_ENREF_53)] using response evaluation criteria in solid tumors (RECIST) by CT as a standard response evaluation tool, they discovered that the sensitivity and specificity of FDG PET was satisfactory (83% and 75%, respectively) in evaluating gastric cancer responses to neoadjuvant chemotherapy. In correlation with the prognosis, metabolic responders had a preferable prognosis compared to metabolic non-responders, and FDG PET evaluation was found to be even better than RECIST evaluation by CT in predicting the median time to disease progression (TTP) and overall survival (OS). However, due to the low FDG uptake in some types of gastric cancers, it is sometimes still difficult or inaccurate to evaluate tumor responses based on SUV change in these cases. Therefore, in the retrospective study of Ott *et al*[[55](#_ENREF_55)], the authors specifically described the FDG non–avid patients as a third metabolic group, aside from metabolic responders and non-responders. They suggested that the FDG non–avid group had a poor response rate and unfavorable prognosis similar to that of metabolic non-responders, indicating that neoadjuvant chemotherapy may not be useful in patients with low FDG uptakes at baseline PET imaging. In that study, they also found that FDG PET imaging analysis was in good accordance with the pathological analysis for tumor response and that metabolic responders (34.7%) also tended to have a more favorable prognosis compared to metabolic non-responders (65.3%) and FDG non–avid patients. In both of the studies described above, the PET evaluation of tumor response resulted in patient treatment strategy changes, during which non-responders either stopped previous chemotherapy plans and underwent earlier surgical removals or changed to other chemotherapy regimes.

***Tumor recurrence prediction and surveillance***

In many other types of malignancies, FDG PET/CT has been widely used for both preoperative prediction and post-surgery/treatment surveillance for tumor recurrence[[56-59](#_ENREF_56)]. For gastric cancer, the conventionally used recurrence prediction parameters include the stage of gastric cancer, depth of tumor invasion, and extent of lymph node metastasis[[60](#_ENREF_60),[61](#_ENREF_61)]. However, these factors are sometimes difficult to evaluate before surgery for gastric cancer; therefore, FDG PET/CT, as a noninvasive evaluation method, has been used to provide additional information to predict recurrence after an operation or treatment. Most studies found that FDG uptake in gastric cancer was an independent, significant prognostic factor for predicting cancer recurrence after curative surgical resection[[19](#_ENREF_19),[62](#_ENREF_62),[63](#_ENREF_63)]. In these studies, patients with lower uptakes of FDG in the gastric lesions before surgery had significant lower incidences of tumor recurrence and better recurrence-free survival after the operations, especially those with intestinal type or TAC. In FDG non-avid diffuse type or MAC/SRC, a better prognostic tendency preferring lower FDG uptake was also discovered, but no exact conclusion was made[[62](#_ENREF_62)]. In addition, preoperative FDG PET/CT was reported as a predictor for the curability of gastric cancer. In a retrospective study by Hur *et al*[[64](#_ENREF_64)] high FDG uptake in the primary tumor and positive FDG uptake in local lymph nodes at PET/CT were significantly associated with non-curative resection, suggesting these patients should be subjected to neoadjuvant chemotherapy or laparoscopic staging to avoid unnecessary laparotomy. However, a conflicting report suggested that the survival rate showed no significant difference between the patients with and without tumor FDG uptakes[[13](#_ENREF_13)], but this may due to the effects of adjuvant chemotherapy after surgery, which was not performed in other studies.

For post-surgery surveillance, contrast-enhanced CT is the most commonly used imaging tool for gastric cancer, but it cannot always detect the presence and viability of tumor precisely, such as when differentiating recurrent tumors from post-surgical changes. With the increasing clinical use of PET/CT, some studies reported that FDG PET/CT was superior to contrast-enhanced CT in the detection of recurrent gastric cancer after initial surgery[[65](#_ENREF_65)], whereas others reported that these two imaging modalities shared a similar performance in the detection of gastric recurrence after surgery[[66](#_ENREF_66)]. Based on two recent meta-analyses, the sensitivity and specificity of FDG PET/CT in detecting gastric cancer recurrence after surgical removal were 78%, 86%, 82% and 88%, respectively[[67](#_ENREF_67),[68](#_ENREF_68)], and the results of PET imaging may have impacted patient management to different degrees, either by avoiding previously planned therapeutic procedures or by using previously unplanned treatment procedures[[65](#_ENREF_65),[69](#_ENREF_69)]. However, whether FDG PET/CT should be added in addition to CT examination for post-surgery gastric cancer recurrence surveillance is still debatable, as there was quite a large amount of evidence suggesting that the benefits from PET/CT imaging were not sufficient to overweigh its high cost compared to CT examination alone. In the study reported by Sim *et al*[[66](#_ENREF_66)] the additional PET/CT on contrast CT did not increase diagnostic accuracy in the detection of recurred gastric cancer in general, and contrast-enhanced CT was even more sensitive than PET/CT for detecting peritoneal seeding. An earlier study using FDG PET suggested that PET was not suited for the follow-up of gastric cancer after treatment [[70](#_ENREF_70)], but that might be due to the lower image quality at that time and the lack of image fusion, especially the anatomic localization by CT.

**FDG PET IN OTHER TYPES OF GASTRIC NEOPLASMS**

***Gastric lymphoma***

Primary gastric lymphoma (PGL) is the most frequent non-Hodgkin's lymphoma (NHL) of extranodal origin, and it accounts for 3%-5% of all of the malignant tumors of the stomach[[71](#_ENREF_71)]. Histologically, PGL can be divided into diffuse large B-cell lymphoma (DLBCL) of the stomach and mucosa-associated lymphoid tissue (MALT) gastric lymphoma. The role of PET in PGL has been reported recently, and many studies have supported the usefulness of PET as a tool for response evaluation in PGL[[72-75](#_ENREF_72)]. One study used both CT and FDG PET/CT for the staging of patients with PGL and found that PET/CT correctly up-graded 22% and down-graded 14% of the patients, suggesting that PET/CT was more accurate in staging PGL. In addition, the study found that FDG SUVmax was significantly associated with Lugano stage, indicating that PET imaging could reflect the aggressiveness of disease[[72](#_ENREF_72)], which was also supported by another study[[74](#_ENREF_74)]. In the study reported by Sharma *et al*[[73](#_ENREF_73)], 18F-FDG PET/CT used in follow-ups seemed to be very accurate for the detection of relapse after treatment.

For the major two histological types of PGL, the FDG PET/CT detection rate was higher in the DLBCL subtype than the MALT lymphoma, with sensitivities of 97%-100% and 39%-80%, respectively[[72](#_ENREF_72),[75](#_ENREF_75),[76](#_ENREF_76)]. Therefore, FDG PET or PET/CT has its limitations in detecting MALT lymphoma compared to other subtypes. Such limitations were reported by Yi *et al*[[72](#_ENREF_72)] in the same study, showing that treatment-related ulcerative or mucosal lesions caused a high rate of false positive uptake, especially in patients with MALT lymphoma, indicating that PET/CT scans alone may not be enough to assess the response of PGL.

***Gastrointestinal stromal tumors***

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract, representing 1%-3% of gastrointestinal malignancies. Approximately 70% of GIST occurs in the stomach, 20% in the small intestine, and less than 10% in the esophagus[[77](#_ENREF_77)]. GIST derives from interstitial Cajal cells, and almost 100% of patients with GIST express c-kit receptor tyrosine kinase. Therefore, tyrosine kinase inhibitors, such as imatinib mesylate, now represent the standard treatment for patients with inoperable GIST[[78](#_ENREF_78)]. The major application of FDG PET or PET/CT imaging to GIST is for therapeutic evaluation to provide early tumor response information, and a vast majority of studies have confirmed the value of FDG PET and PET/CT over morphological-based imaging modalities in this aspect[[79-85](#_ENREF_79)]. In some of these studies, the PET criteria correlate well with progression-free survival, while CT evaluation did not. Therefore, 18F-FDG PET has become the gold standard for the early assessment of tumor response to imatinib as well as other c-kit inhibitors in response in GIST. In addition to the therapeutic evaluation, FDG PET and PET/CT have also been used to analyze the prognostic value of FDG SUVmax in GIST patients[[86](#_ENREF_86),[87](#_ENREF_87)], to differentiate GIST with abdominal lymphoma by studying the metabolic heterogeneity differences[[88](#_ENREF_88)] and to study FDG kinetics and gene expression in GIST[[89](#_ENREF_89)].

***Gastric schwannomas***

Schwannomas are tumors originating from nerves with a Schwann cell sheath. The stomach is the most common site of gastrointestinal schwannomas, accounting for 0.2% of all gastric neoplasms[[90](#_ENREF_90)]. There were several case reports of gastric schwannomas with FDG PET scans, and all of these cases showed high FDG uptakes, with SUVmax ranging from 5.8 to 7.1[[91-93](#_ENREF_91)]. Therefore, these studies indicated the necessity of differentiating between gastric schwannomas and GIST, both of which will show up as intensive FDG accumulations on PET images.

**IMPROVEMENTS IN THE DIAGNOSIS OF GASTRIC CANCER USING PET OR PET/CT**

As previously stated, the overall sensitivity and specificity of PET and PET/CT in the detection of gastric cancer is relatively lower than those of some other malignancies. The physiological uptake of FDG in the normal gastric wall and the existence of non FDG-avid histological types of gastric cancer may all contribute to this result. To improve the diagnosis and evaluation of gastric cancers using PET or PET/CT, several improvements have been applied in different aspects, either by decreasing the physiological uptake of the normal gastric wall, applying different time-point of imaging, or using more specific radio-tracers. In this section, therefore, we will mainly discuss improvements in the following three aspects.

***Gastric distension***

Because FDG is not a tumor-specific tracer, many benign lesions in the stomach, such as gastritis, leiomyoma, polyps, and even normal gastric walls, can have moderate to intense FDG uptakes. Therefore, when a positive uptake is observed in the stomach, the interpretation of the images should be carefully conducted, especially for post-treatment evaluation. To decrease the physiological uptake, gastric distention has been studied recently as a modified PET imaging protocol for patients with questionable stomach lesions that resulted in increased specificity and accuracy for the detection of gastric malignancies. Gastric distention can be achieved by the consumption of water, milk, food, or foaming agents before PET scanning[[20](#_ENREF_20),[21](#_ENREF_21),[23-27](#_ENREF_23)] (Table 1). After distention, the physiological uptake of the normal gastric wall was relatively decreased, thus increasing the tumor/background ratio, even for small size tumors (Figure 2). In addition, with water or milk as a negative contrast agent in the stomach, tumors could be more easily delineated. Some local lymph node metastases can also be detected with a lower gastric wall uptake background, improving the accuracy of staging[[23](#_ENREF_23)].

***Dual-time point imaging***

Another potential method for differentiating benign lesions in the stomach from malignancies is dual time-point PET scanning, which visualizes the trends of the FDG uptake changes. It is well recognized that for a malignant lesion, FDG uptake at late time-point (usually 2-3 h after FDG injection) PET scanning will be increased compared to the early time-point imaging result (45 min to 1 h after tracer injection). However, for physiological uptake or other non-malignant lesions, this value will most likely decrease or remain the same[[94](#_ENREF_94)]. This method has proven useful in the detection, staging and differentiation of various types of cancer, including breast cancer[[95](#_ENREF_95)], lung cancer[[96](#_ENREF_96)], and colorectal cancer[[97](#_ENREF_97)]. For gastric cancers, limited studies have been reported. In the only report by Lan *et al*[[98](#_ENREF_98)] involving five gastric malignant tumors and three cases of gastritis, the SUVmax in the late time-point (2.5-3 h after FDG injection) increased by 4%-45% in all 5 malignant lesions, whereas two cases of gastritis had decreased uptakes, with the remaining one remaining at the same SUV level. The late time-point was especially useful when the early time-point SUV was equivocal. In the future, the exact value of dual time-point scanning for gastric cancer imaging awaits further proof.

***Non-FDG tracers in the evaluation of gastric cancer***

Targeting cell glucose metabolism using FDG is extensively used in PET oncologic imaging. However, due to the unsatisfactory imaging results of FDG PET or PET/CT in FDG non-avid gastric cancers, new PET imaging tracers are needed for the better detection of gastric cancer with higher sensitivity and specificity. Therefore, a new type of PET imaging tracer, 18F-FLT, has been developed and used to target cell proliferation in many *in vivo* imaging studies. The mechanism for the cell proliferating imaging using 18F-FLT proceeds in the following manner. After being taken up by the cell via both passive diffusion and facilitated transport by Na+-dependent carriers, 18F-FLT will be phosphorylated by thymidine kinase 1 (TK1) into 18F-FLT-monophosphate, which is trapped in the cell. However, because the enzymatic activity of TK1 is different in quiescent cells and proliferating cells, the accumulation of 18F-FLT-monophosphate will be higher in proliferating cells, such as malignant cancer cells, normal hepatocytes, and bone marrow cells[[99](#_ENREF_99)]. Recently, 18F-FLT PET and PET/CT imaging has been used in many types of cancers, such as colorectal cancer[[100](#_ENREF_100)], lung cancer[[101](#_ENREF_101)], brain tumors[[102](#_ENREF_102)] and gastrointestinal tumors[[103](#_ENREF_103)].

In gastric cancer, the use of 18F-FLT was reported to increase the detection rate of gastric cancers, especially for FDG non-avid histological types. In the study reported by Herrmann and Ott *et al*[[104](#_ENREF_104)], 18F-FLT in the preoperative detection of gastric cancer had a sensitivity of 100%, while FDG showed only a 69% sensitivity in the same population. In another study, 18F-FLT showed a slight increase in the detection rate of primary gastric cancers, with a similar sensitivity to FDG (95.2% and 95.0%, respectively)[[105](#_ENREF_105)]. Importantly, in both studies, FLT was able to delineate gastric lesions that were negative in FDG images, most of which were nonintestinal or diffuse types upon histology. Based on this advantage, Ott *et al*[[106](#_ENREF_106)] further investigated the value of 18F-FLT PET imaging in predicting gastric cancer responses to neoadjuvant chemotherapy and patient prognosis. In that study, the SUVmeanof 18F-FLT but not the FDG two weeks after chemotherapy was the only independent prognostic factor for gastric cancer patients. The unchanged high uptake of 18F-FLT after treatment might indicate the failure of treatment because this suggested a constant proliferation at the tumor site. However, recently, another study came to the opposite conclusion, suggesting that 18F-FLT PET had no added value in the preoperative staging of gastric cancer, especially for liver and bone metastasis, which had much lower sensitivity than FDG PET [[107](#_ENREF_107)]. Indeed, the high physiological uptake of FLT in the liver and bone marrow can hamper the detection of some primary gastric tumors and bone metastasis sites, rendering FLT not suitable for M-staging (Table 2). In the future, the exact value of 18F-FLT in the diagnosis and evaluation of gastric cancer needs further investigation.

**LIMITATIONS AND FUTURE PROSPECTS**

In summary, the limitations of FDG PET and PET/CT in the diagnosis and evaluation of gastric cancers mainly come from three aspects: (1) the variety of histological differences in gastric cancer, (2) the physiological properties of the stomach, and (3) the spatial resolution of PET. Many FDG non-avid histological types greatly decrease the sensitivity of FDG PET and PET/CT in gastric cancer detection, and new imaging tracers, including FLT, are currently under evaluation as alternatives. For the second limitation, gastric distention by different methods seems to be effective in decreasing background uptake. Furthermore, pharmaceutical interventions, including muscle relaxants and proton pump inhibitors, are also under further investigation for this purpose. As to the third limitation, currently the highest achievable spatial resolution of PET is 2.36 mm for clinical purposes and 0.83 mm for pre-clinical uses[[108](#_ENREF_108)]. The observation of many early stage gastric cancer and metastatic lymph nodes similar or below this range therefore remains difficult to achieve from PET images. In combination with CT, PET/CT appears to improve the accuracy of many diseases, including gastric cancers, but N-staging in gastric cancer is still not satisfactory under current conditions. In the future, the spatial resolution of PET can be improved by optimizing the camera design within the physical fundamental limitations. In addition, the new generation of multimodality imaging equipment, such as PET/MR and PET/CT/MR, will hopefully provide complementary advantages in the diagnosis and evaluation of various diseases, including gastric cancers.

**CONCLUSION**

PET and PET/CT technology provides a useful tool in the diagnosis and evaluation of gastric cancers. These modalities can detect lymph node metastases and distant metastatic sites in other organs using one single image, can identify early tumor responses that may not be apparent using other modalities, and may have prognostic value that can change patient management. Although many problems remain, PET and PET/CT imaging remains promising, and with current and further improvements, PET and PET/CT imaging may make the diagnosis and evaluation of gastric cancer more standardized and accurate.

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**Figure 1** **18F-fluorodeoxyglucose positron emission tomography /computed tomography for the response evaluation of neoadjuvant chemotherapy.** 18F-fluorodeoxyglucose (FDG) Tomography/Computed Tomography (PET/CT) imaging of a responder patient before (A) and after three cycles of chemotherapy (B); After therapy, the patient showed significant tumor SUV reduction (A: SUVmax = 4.1, B: SUVmax = 2.1, %△SUV = 37.3%), corresponding to his histological response (Grade 2b) according to the JRSGC (Japanese Research Society for Gastric Carcinoma) criteria; FDG PET/CT imaging of a non-responder patient before (C) and after three cycles of chemotherapy (D); The tumor SUV was the same after therapy (C: SUVmax = 9.2, B: SUVmax = 9.7, %△SUV = -5.4%), corresponding to his histological response (Grade 0) according to the JRSGC criteria. SUV: Standardized uptake value.

**Figure 2** **8F-fluorodeoxyglucose positron emission tomography imaging of gastric cancer under gastric distention.** A small size gastric tumor (arrow, 1.5 cm × 1.2 cm, high differentiated gastric adenocarcinoma) was clearly observed with low background gastric wall uptake due to gastric distention.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Patients** | **Number** | **Imaging modality** | **Distention methods** | **Sensitivity** | **Specificity** |
| Before distention | After distention | Before distention | After distention |
| Tian *et al*[[27](#_ENREF_27)] (2004)  | With suspected gastric tumors | 38 | FDG PET | Oral intake of vesicant (2-3g) with 40-60 mL water |  | 83% |  | 88% |
| Yun *et al*[[26](#_ENREF_26)] (2005)  | After gastrectomy for gastric cancer | 30 | FDG PET | Drinking at least 300 mL water | 94% | 88% | 69% | 92% |
| Zhu *et al*[[25](#_ENREF_25)] (2007)  | With proven primary gastric carcinomas | 3 | FDG PET | Intake of 100 gbread and 400 mL cow milk |  |  |  |  |
| Zhu *et al*[[20](#_ENREF_20)] (2008)  | With proven gastric tumors | 24 | FDG PET | Intake of 300-400 mL cow milk |  | 96% |  |  |
| Kamimura *et al* [[21](#_ENREF_21)](2009)  | With gastric carcinomas | 16 | FDG PET | Intake 400 mL water | 100% | 88% | 50% | 100% |
| Lee *et al*[[23](#_ENREF_23)] (2013)  | With proven gastric tumors | 44 | FDG PET/CT | Intake 500 mL water | 50% | 75% |  |  |
| Ma *et al*[[24](#_ENREF_24)] (2013)  | With suspected gastric tumors | 68 | FDG PET/CT | Intake milk with Diatrizoate Meglumine | 93% | 91% | 75% | 92% |

**Table 1 Gastric distention methods in 18F-fluorodeoxyglucose positron emission tomography and positron emission tomography/computed tomography imaging of gastric cancers**

FDG: 18F-fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography.

**Table 2 Comparison of 18F-FLT and 18F-fluorodeoxyglucose positron emission tomography or positron emission tomography/computed tomography imaging for detection of gastric cancers**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Study purpose** | **Imaging modality** | **SUV** | **Sensitivity for detection of primary tumor** | **Sensitivity for detection of metastasis** | **Prognostic factor** |
| **18F-FLT** | **18F-FDG** | **18F-FLT** | **18F-FDG** | **18F-FLT** | **18F-FDG** |
| Herrmann *et al*[[104](#_ENREF_104)] (2009)  | Preoperative evaluation | PET | Mean: 6.0 | Mean: 8.4 | 100% | 69% |  |  |  |
| Kameyama *et al*[[105](#_ENREF_105)] (2009)  | Preoperative evaluation | PET | Mean: 7.0 | 9.4 | 95% | 95% |  |  |  |
| Kameyama *et al*[[103](#_ENREF_103)] (2011)  | Preoperative evaluation | PET | Mean: 2.1 – 8.0 |  | 90% |  |  |  |  |
| Ott *et al*[[106](#_ENREF_106)] (2011)  | Neoadjuvant chemotherapy evaluation | PET | Before treatment: 6.1After treatment: 5.3 | Before treatment: 8.4After treatment: 5.2 |  |  |  |  | FLT uptake at 2-wk after treatment |
| Zhou *et al*[[107](#_ENREF_107)] (2013)  | Preoperative evaluation | PET/CT | Max: 5.5 | Max: 8.4 | 92% | 95% | Liver: 30%Bone: 20%Other organs: 90%-97% | Liver: 100%Bone: 100%Other organs: 91%-95% |  |

FDG: 18F-fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; SUV: Standardized uptake value.