

WJG 20th Anniversary Special Issues (8): Gastric cancer

Diagnosis and evaluation of gastric cancer by positron emission tomography

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Received: October 29, 2013 Revised: December 18, 2013

Accepted: January 14, 2014

Published online: April 28, 2014

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

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

Wu CX, Zhu ZH. Diagnosis and evaluation of gastric cancer by positron emission tomography. *World J Gastroenterol* 2014; 20(16): 4574-4585 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i16/4574.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i16.4574>

Abstract

Gastric cancer is the second leading cause of cancer mortality worldwide. The diagnosis of gastric cancer has been significantly improved with the broad availability 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, is 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 reviews the current literature in diagnosis, staging, response evaluation, and relapse monitoring of gastric cancer, and discusses the current understanding, improvement, and future prospects in this area.

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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]. 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].

In recent decades, positron emission tomography (PET) using ^{18}F -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]. 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]. 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]. However, the overall sensitivities of PET and PET/CT in the detection of gastric cancer are relatively low compared to those in 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 cancer. Thus, the value of FDG PET/CT in the diagnosis and evaluation of gastric cancer is still controversial^[6,7].

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 of 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]. Recent studies have indicated that tumor size was a major factor influencing the standardized uptake value (SUV) of gastric cancer on FDG PET^[9,10]. In another study, tumor invasion depth was found to be an independent factor for the FDG uptake in gastric lesions^[11]. Because late-stage tumors are usually larger in size with deeper invasion, advanced gastric cancer (AGC), in general, tend to yield a higher sensitivity in FDG PET imaging than early stage gastric cancer (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].

Influence of histological type

FDG PET may also have different sensitivities 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 the intestinal-type gastric adenocarcinoma or tubular adenocarcinoma (TAC)^[8,12-15], although some studies using different patient groups obtained different results^[9,10,16].

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 metabolically inert mucus content, and low expression level of glucose transporter 1 (GLUT-1)^[12,13,17]. These factors cause the low sensitivity of FDG PET in these types of gastric cancer.

Influence of tumor location

The stomach regions can be divided into the gastroesophageal 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]. Although some researchers reported that FDG PET had a similar detectability for gastric cancers located at the upper, middle, and lower parts of the stomach^[8,19], 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].

Influence of the physiological uptake of the gastric wall

The physiological uptake can also influence PET detection of gastric cancer. 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], and the specificity was reported to be as low as 50%^[21] using FDG PET for gastric cancer 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]. 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^[20,21,23-27] or through medicines to inhibit gastric movement^[28,29], as will be discussed in the following sections.

Influence of tumor biology

For gastric cancer, 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 cancer^[12,13,17]. Most recently, the expression of some hypoxia-related genes, such as hypoxia-inducible factor 1 (HIF-1) in gastric cancer cells, was also found to contribute to FDG uptake in gastric tumors^[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].

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 between 33.3%-64.6% and 85.7%-97.0%, respectively, although there was no significant diagnostic difference compared to AUS, CT or magnetic resonance imaging (MRI)^[31]. Other individual studies reported that FDG PET or PET/CT was less sensitive but more specific compared to commonly used CT and MRI^[16,32,33]. 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^[16,33]. Additionally, many studies have found that the SUV_{max} of the primary tumor was associated with the SUV_{max} of the lymph nodes^[33,34]. In a report, 60%-70% of lymph node metastases were not detected in patients with non FDG-avid primary tumors^[35]. The second reason is the size of metastatic lymph nodes. Some metastatic lymph nodes in gastric cancer could be as small as 3 mm^[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 by PET/CT, many lymph node metastases remain ambiguous^[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 cancer. Because FDG PET and FDG PET/CT diagnose lymph node metastasis using glucose metabolism rather than the size change, it is very useful to dis-

tinguish 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 cancer.

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]. Compared to CT, FDG PET usually showed a lower sensitivity for the diagnosis of peritoneal seeding^[14,34,38,39]. 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 cancer, which is more likely to spread into the peritoneal cavity^[40]. Therefore, many studies suggest high quality CT as the preferred modality of choice for the diagnosis of peritoneal metastasis^[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], 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 \$10000 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], 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 detection of the liver, lung and bone metastases was found to be satisfactory and accurate^[42]. Specifically, a study reported that FDG PET was sensitive for the detection of liver metastasis from gastric cancer^[43], although a meta-analysis reviewing CT, US, EUS, and FDG PET, FDG PET showed only a moderate ability in this aspect^[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 the two 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], with a sensitivity of 93.5%. However, Yoshioka *et al.*^[42] reported that FDG PET did not seem to be useful for the detection of bone metastasis, with a sensitivity of only 30%.

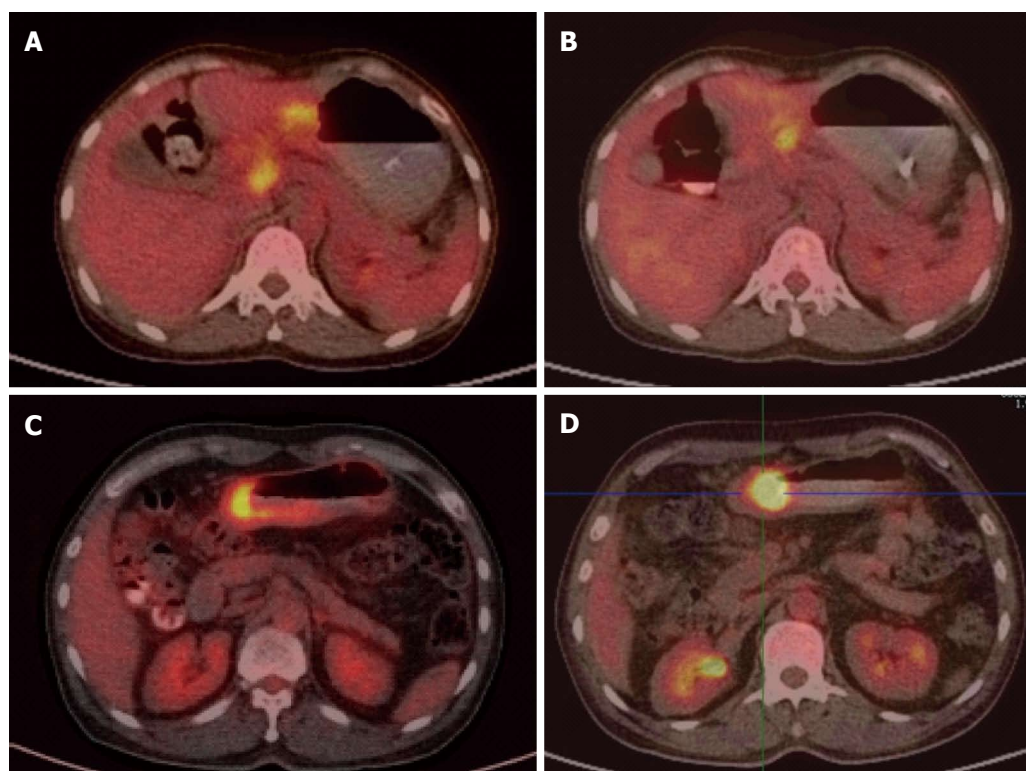


Figure 1 ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography for evaluation of response to neoadjuvant chemotherapy. ^{18}F -fluorodeoxyglucose (FDG) tomography/computed tomography (PET/CT) imaging of a responder patient before (A) and after three cycles of chemotherapy (B); After therapy, the patient showed significant tumor SUV reduction (A: $\text{SUV}_{\text{max}} = 4.1$, B: $\text{SUV}_{\text{max}} = 2.1$, $\% \Delta \text{SUV} = 37.3\%$), corresponding to his histological response (Grade 2b) according to the JRS GC (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: $\text{SUV}_{\text{max}} = 9.2$, D: $\text{SUV}_{\text{max}} = 9.7$, $\% \Delta \text{SUV} = -5.4\%$), corresponding to his histological response (Grade 0) according to the JRS GC criteria. SUV: Standardized uptake value.

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 cancer. 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]. 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 cancer^[46-48]. 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 cancer^[49,50]. However, for non-responders, a considerable number of complications following neoadjuvant chemotherapy and surgery as well as the minimal benefit from this additional therapy have to be considered^[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^[46,52]. 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 has suggested that FDG PET or FDG PET/CT seems to be an effective noninvasive tool for response assessment in gastric cancer^[12,53-55]. 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 Di Fabio *et al*^[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 were 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. However, due to the low FDG uptake in some types of gastric cancer, it is sometimes still difficult or inaccurate to evaluate tumor responses based on SUV change in these cases. Therefore, in a retrospective study of Ott *et al.*^[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 regimens.

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]. 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^[60,61]. 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^[19,62,63]. In these studies, patients with lower uptakes of FDG in the gastric lesions before surgery had significantly lower incidences of tumor recurrence and better recurrence-free survival after the operation, 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]. In addition, preoperative FDG PET/CT was reported as a predictor of the curability of gastric cancer. In a retrospective study by Hur *et al.*^[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 that 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], but this may due to the effects of adjuvant chemotherapy before 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], whereas others reported that these two imaging modalities shared a similar performance in the detection of gastric recurrence after surgery^[66]. Based on two recent meta-analyses, the sensitivity of FDG PET/CT in detecting gastric cancer recurrence after surgical removal was 78%-86%, whereas the specificity was 82%-88%^[67,68], and the results of PET imaging impacted patient management to different degrees, either by avoiding previously planned therapeutic procedures or by using previously unplanned treatment procedures^[65,69]. 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 outweigh its high cost compared to CT examination alone. In the study reported by Sim *et al.*^[66] the additional PET/CT on contrast CT did not increase diagnostic accuracy in the detection of recurrent 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], 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 of extranodal origin, and it accounts for 3%-5% of all of the malignant tumors of the stomach^[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]. 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 SUV_{max} was significantly associated with Lugano stage, indicating that PET imaging could reflect the aggressiveness of disease^[72], which was also supported by another study^[74]. In the study reported by Sharma *et al.*^[73], ¹⁸F-FDG PET/CT used in follow-ups seemed to be very accurate for the detection of relapse after treatment.

For the two major histological types of PGL, the FDG PET/CT detection rate was higher in the DLBCL subtype than in the MALT lymphoma, with sensitivities of 97%-100% and 39%-80%, respectively^[72,75,76]. 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] 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 GISTs occurs in the stomach, 20% in the small intestine, and less than 10% in the esophagus^[77]. GISTs derive 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 GISTs^[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]. 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 GISTs. In addition to the therapeutic evaluation, FDG PET and PET/CT have also been used to analyze the prognostic value of FDG SUV_{max} in GIST patients^[86,87], to differentiate GISTs from abdominal lymphoma by studying the metabolic heterogeneity differences^[88] and to study FDG kinetics and gene expression in GISTs^[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]. There were several case reports of gastric schwannomas with FDG PET scans, and all of these cases showed high FDG uptakes, with SUV_{max} ranging from 5.8 to 7.1^[91-93]. Therefore, these studies indicated the necessity of differentiating between gastric schwannomas and GISTs, 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 are relatively lower than those in 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 cancer 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 distension 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 distension can be achieved by the consumption of water, milk, food, or foaming agents before PET scanning^[20,21,23-27] (Table 1). After distension, 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].

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]. This method has proven useful in the detection, staging and differentiation of various types of cancers, including breast cancer^[95],

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

Ref.	Patients	n	Imaging modality	Distention methods	Sensitivity		Specificity	
					Before distention	After distention	Before distention	After distention
Tian <i>et al</i> ^[27]	With suspected gastric tumors	38	FDG PET	Oral intake of vesicant (2-3 g) with 40-60 mL water		83%		88%
Yun <i>et al</i> ^[26]	After gastrectomy for gastric cancer	30	FDG PET	Drinking at least 300 mL water	94%	88%	69%	92%
Zhu <i>et al</i> ^[25]	With proven primary gastric carcinomas	3	FDG PET	Intake of 100 g bread and 400 mL cow milk				
Zhu <i>et al</i> ^[20]	With proven gastric tumors	24	FDG PET	Intake of 300-400 mL cow milk		96%		
Kamimura <i>et al</i> ^[21]	With gastric carcinomas	16	FDG PET	Intake 400 mL water	100%	88%	50%	100%
Lee <i>et al</i> ^[23]	With proven gastric tumors	44	FDG PET/CT	Intake 500 mL water	50%	75%		
Ma <i>et al</i> ^[24]	With suspected gastric tumors	68	FDG PET/CT	Intake milk with diatrizoate meglumine	93%	91%	75%	92%

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

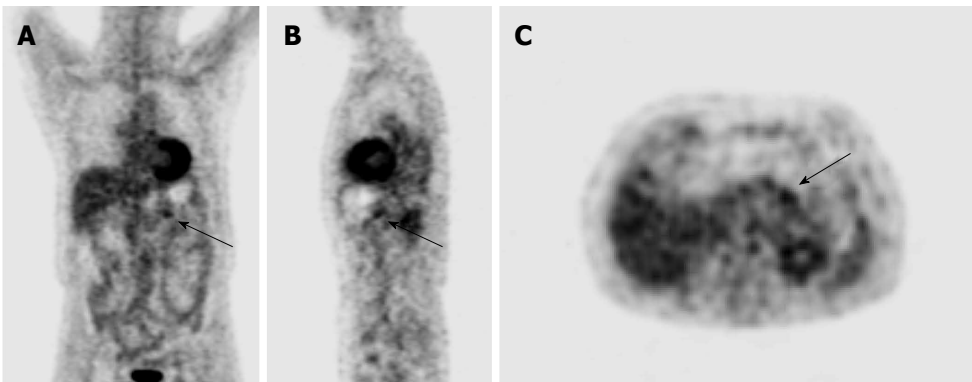


Figure 2 ¹⁸F-fluorodeoxyglucose positron emission tomography imaging of gastric cancer under gastric distention. A small size gastric tumor (arrow, 1.5 cm × 1.2 cm, highly differentiated gastric adenocarcinoma) was clearly observed with low background gastric wall uptake due to gastric distention (A-C).

lung cancer^[96], and colorectal cancer^[97]. For gastric cancer, limited studies have been reported. In the only report by Lan *et al*^[98] involving five gastric malignant tumors and three cases of gastritis, the SUV_{max} 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 cancer, 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 devel-

oped 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]. Recently, ¹⁸F-FLT PET and PET/CT imaging has been used in many types of cancers, such as colorectal cancer^[100], lung cancer^[101], brain tumors^[102] and gastrointestinal tumors^[103].

In gastric cancer, the use of ¹⁸F-FLT was reported to increase the detection rate, especially for FDG non-avid histological types. In a study reported by Herrmann and Herrmann *et al*^[104], ¹⁸F-FLT in the preoperative detection of gastric cancer had a sensitivity of 100%, while FDG

Table 2 Comparison of ^{18}F -FLT and ^{18}F -fluorodeoxyglucose positron emission tomography or positron emission tomography/computed tomography imaging for detection of gastric cancer

Ref.	Study purpose	Imaging modality	SUV		Sensitivity for detection of primary tumor		Sensitivity for detection of metastasis		Prognostic factor
			^{18}F -FLT	^{18}F -FDG	^{18}F -FLT	^{18}F -FDG	^{18}F -FLT	^{18}F -FDG	
Herrmann <i>et al</i> ^[104]	Preoperative evaluation	PET	Mean: 6.0	Mean: 8.4	100%	69%			
Kameyama <i>et al</i> ^[105]	Preoperative evaluation	PET	Mean: 7.0	9.4	95%	95%			
Kameyama <i>et al</i> ^[103]	Preoperative evaluation	PET	Mean: 2.1-8.0		90%				
Ott <i>et al</i> ^[106]	Neoadjuvant chemotherapy evaluation	PET	Before treatment: 6.1 After treatment: 5.3	Before treatment: 8.4 After treatment: 5.2					FLT uptake at 2-wk after treatment
Zhou <i>et al</i> ^[107]	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: ^{18}F -fluorodeoxyglucose; PET/CT: Positron emission tomography/computed tomography; SUV: Standardized uptake value.

showed only a 69% sensitivity in the same population. In another study, ^{18}F -FLT showed a slight increase in the detection rate of primary gastric cancer, with a similar sensitivity to FDG (95.2% and 95.0%, respectively)^[105]. Importantly, in both studies, FLT was able to delineate gastric lesions that were negative in FDG images, most of which were non intestinal or diffuse types upon histology. Based on this advantage, Ott *et al*^[106] further investigated the value of ^{18}F -FLT PET imaging in predicting gastric cancer responses to neoadjuvant chemotherapy and patient prognosis. In that study, the SUV_{mean} of ^{18}F -FLT but not the FDG two weeks after chemotherapy was the only independent prognostic factor for gastric cancer patients. The unchanged high uptake of ^{18}F -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 ^{18}F -FLT PET had no added value in the preoperative staging of gastric cancer, especially for liver and bone metastasis, which had a much lower sensitivity than FDG PET^[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 ^{18}F -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 cancer 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]. The observation of early stage gastric cancer and metastatic lymph nodes similar to 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 cancer, 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 cancer.

CONCLUSION

PET and PET/CT technology provides a useful tool for the diagnosis and evaluation of gastric cancer. 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.

REFERENCES

- Jemal A**, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011; **61**: 69-90 [PMID: 21296855 DOI: 10.3322/caac.20107]
- Kiff RS**, Taylor BA. Comparison of computed tomography, endosonography, and intraoperative assessment in TN staging of gastric carcinoma. *Gut* 1994; **35**: 287-288 [PMID: 8166822]
- Bar-Shalom R**, Yefremov N, Guralnik L, Gaitini D, Frenkel A, Kuten A, Altman H, Keidar Z, Israel O. Clinical performance of PET/CT in evaluation of cancer: additional value for diagnostic imaging and patient management. *J Nucl Med* 2003; **44**: 1200-1209 [PMID: 12902408]
- NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Gastric Cancer. 2013. Available from: URL: http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
- Waddell T**, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013; **24** Suppl 6: vi57-vi63 [PMID: 24078663 DOI: 10.1093/annonc/mdt344]
- Shimada H**, Okazumi S, Koyama M, Murakami K. Japanese Gastric Cancer Association Task Force for Research Promotion: clinical utility of 18F-fluoro-2-deoxyglucose positron emission tomography in gastric cancer. A systematic review of the literature. *Gastric Cancer* 2011; **14**: 13-21 [PMID: 21331531 DOI: 10.1007/s10120-011-0017-5]
- 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**: 449-455 [PMID: 19147324 DOI: 10.1016/j.ejso.2008.11.010]
- 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**: 192-196 [PMID: 16952037 DOI: 10.1007/s10120-006-0374-7]
- Namikawa T**, Okabayashi T, Nogami M, Ogawa Y, Kobayashi M, Hanazaki K. Assessment of (18)F-fluorodeoxyglucose positron emission tomography combined with computed tomography in the preoperative management of patients with gastric cancer. *Int J Clin Oncol* 2013; Epub ahead of print [PMID: 23877653 DOI: 10.1007/s10147-013-0598-6]
- Takebayashi R**, Izuishi K, Yamamoto Y, Kameyama R, Mori H, Masaki T, Suzuki Y. [18F]Fluorodeoxyglucose accumulation as a biological marker of hypoxic status but not glucose transport ability in gastric cancer. *J Exp Clin Cancer Res* 2013; **32**: 34 [PMID: 23718763 DOI: 10.1186/1756-9966-32-34]
- 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 [PMID: 17294670]
- Ott K**, Fink U, Becker K, Stahl A, Dittler HJ, Busch R, Stein H, Lordick F, Link T, Schwaiger M, Siewert JR, Weber WA. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. *J Clin Oncol* 2003; **21**: 4604-4610 [PMID: 14673049 DOI: 10.1200/JCO.2003.06.574]
- Stahl A**, Ott K, Weber WA, Becker K, Link T, Siewert JR, Schwaiger M, Fink U. FDG PET imaging of locally advanced gastric carcinomas: correlation with endoscopic and histopathological findings. *Eur J Nucl Med Mol Imaging* 2003; **30**: 288-295 [PMID: 12552348 DOI: 10.1007/s00259-002-1029-5]
- Smyth E**, Schöder H, Strong VE, Capanu M, Kelsen DP, Coit DG, Shah MA. A prospective evaluation of the utility of 2-deoxy-2-[(18)F]fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer. *Cancer* 2012; **118**: 5481-5488 [PMID: 22549558 DOI: 10.1002/cncr.27550]
- Youn SH**, Seo KW, Lee SH, Shin YM, Yoon KY. 18F-2-Deoxy-2-Fluoro-D-Glucose Positron Emission Tomography: Computed Tomography for Preoperative Staging in Gastric Cancer Patients. *J Gastric Cancer* 2012; **12**: 179-186 [PMID: 23094230 DOI: 10.5230/jgc.2012.12.3.179]
- Kim SK**, Kang KW, Lee JS, Kim HK, Chang HJ, Choi JY, Lee JH, Ryu KW, Kim YW, Bae JM. Assessment of lymph node metastases using 18F-FDG PET in patients with advanced gastric cancer. *Eur J Nucl Med Mol Imaging* 2006; **33**: 148-155 [PMID: 16228236 DOI: 10.1007/s00259-005-1887-8]
- Kawamura T**, Kusakabe T, Sugino T, Watanabe K, Fukuda T, Nashimoto A, Honma K, Suzuki T. Expression of glucose transporter-1 in human gastric carcinoma: association with tumor aggressiveness, metastasis, and patient survival. *Cancer* 2001; **92**: 634-641 [PMID: 11505409]
- Wu AJ**, Goodman KA. Positron emission tomography imaging for gastroesophageal junction tumors. *Semin Radiat Oncol* 2013; **23**: 10-15 [PMID: 23207042 DOI: 10.1016/j.semradi.2012.09.001]
- 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**: 247-253 [PMID: 14961197 DOI: 10.1007/s00268-003-7191-5]
- 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**: 25-29 [PMID: 18287193 DOI: 10.2967/jnmt.107.044081]
- Kamimura K**, Nagamachi S, Wakamatsu H, Fujita S, Nishii R, Umemura Y, Ogita M, Komada N, Sakurai T, Inoue T, Fujimoto T, Nakajo M. 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**: 431-439 [PMID: 19352209 DOI: 10.1097/MNM.0b013e3283299a2f]
- Koga H**, Sasaki M, Kuwabara Y, Hiraka K, Nakagawa M, Abe K, Kaneko K, Hayashi K, Honda H. An analysis of the physiological FDG uptake pattern in the stomach. *Ann Nucl Med* 2003; **17**: 733-738 [PMID: 14971621]
- Lee SJ**, Lee WW, Yoon HJ, Lee HY, Lee KH, Kim YH, Park do J, Kim HH, So Y, Kim SE. Regional PET/CT after water gastric inflation for evaluating loco-regional disease of gastric cancer. *Eur J Radiol* 2013; **82**: 935-942 [PMID: 23410909 DOI: 10.1016/j.ejrad.2013.01.014]
- Ma Q**, Xin J, Zhao Z, Guo Q, Yu S, Xu W, Liu C, Zhai W. Value of 18F-FDG PET/CT in the diagnosis of primary gastric cancer via stomach distension. *Eur J Radiol* 2013; **82**: e302-e306 [PMID: 23434453 DOI: 10.1016/j.ejrad.2013.01.021]
- Zhu Z**, Li F, Zhuang H. Gastric distension by ingesting food is useful in the evaluation of primary gastric cancer by FDG PET. *Clin Nucl Med* 2007; **32**: 106-109 [PMID: 17242562 DOI: 10.1097/01.rlu.0000252181.76139.5e]
- 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**: 953-957 [PMID: 15937305]
- Tian J**, Chen L, Wei B, Shao M, Ding Y, Yin D, Yao S. The value of vesicant 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) in gastric malignancies. *Nucl Med Commun* 2004; **25**: 825-831 [PMID: 15266178]
- Emmott J**, Sanghera B, Chambers J, Wong WL. The effects of N-butylscopolamine on bowel uptake: an 18F-FDG PET study. *Nucl Med Commun* 2008; **29**: 11-16 [PMID: 18049092 DOI: 10.1097/MNM.0b013e3282f1d706]
- Domeki Y**, Yamazaki E, Matsuura A, Kitajima K, Murakami K, Kato H. Effects of a proton pump inhibitor on the physiological accumulation of fluoro-2-deoxy-D-glucose (FDG) in FDG-positron emission tomography. *Surg Today* 2012; **42**: 927-933 [PMID: 22825654 DOI: 10.1007/s00595-012-0265-y]

- 30 **Semenza GL.** HIF-1: upstream and downstream of cancer metabolism. *Curr Opin Genet Dev* 2010; **20**: 51-56 [PMID: 19942427 DOI: 10.1016/j.gde.2009.10.009]
- 31 **Kwee RM, Kwee TC.** Imaging in assessing lymph node status in gastric cancer. *Gastric Cancer* 2009; **12**: 6-22 [PMID: 19390927 DOI: 10.1007/s10120-008-0492-5]
- 32 **Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, Law C, Paszat L, Coburn N.** How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. *Gastric Cancer* 2012; **15** Suppl 1: S3-18 [PMID: 21837458 DOI: 10.1007/s10120-011-0069-6]
- 33 **Ha TK, Choi YY, Song SY, Kwon SJ.** F18-fluorodeoxyglucose-positron emission tomography and computed tomography is not accurate in preoperative staging of gastric cancer. *J Korean Surg Soc* 2011; **81**: 104-110 [PMID: 22066108 DOI: 10.4174/jkss.2011.81.2.104]
- 34 **Chen J, Cheong JH, Yun MJ, Kim J, Lim JS, Hyung WJ, Noh SH.** Improvement in preoperative staging of gastric adenocarcinoma with positron emission tomography. *Cancer* 2005; **103**: 2383-2390 [PMID: 15856477 DOI: 10.1002/cncr.21074]
- 35 **Kim EY, Lee WJ, Choi D, Lee SJ, Choi JY, Kim BT, Kim HS.** The value of PET/CT for preoperative staging of advanced gastric cancer: comparison with contrast-enhanced CT. *Eur J Radiol* 2011; **79**: 183-188 [PMID: 20226612 DOI: 10.1016/j.ejrad.2010.02.005]
- 36 **Mönig SP, Zirbes TK, Schröder W, Baldus SE, Lindemann DG, Dienes HP, Hölscher AH.** Staging of gastric cancer: correlation of lymph node size and metastatic infiltration. *AJR Am J Roentgenol* 1999; **173**: 365-367 [PMID: 10430138 DOI: 10.2214/ajr.173.2.10430138]
- 37 **Sadeghi B, Arvieux C, Glehen O, Beaujard AC, Rivoire M, Baulieux J, Fontaumar E, Brachet A, Caillot JL, Faure JL, Porcheron J, Peix JL, François Y, Vignal J, Gilly FN.** Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. *Cancer* 2000; **88**: 358-363 [PMID: 10640968]
- 38 **Wang Z, Chen JQ.** Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. *BMC Gastroenterol* 2011; **11**: 19 [PMID: 21385469 DOI: 10.1186/1471-230X-11-19]
- 39 **Lim JS, Kim MJ, Yun MJ, Oh YT, Kim JH, Hwang HS, Park MS, Cha SW, Lee JD, Noh SH, Yoo HS, Kim KW.** Comparison of CT and 18F-FDG PET for detecting peritoneal metastasis on the preoperative evaluation for gastric carcinoma. *Korean J Radiol* 2006; **7**: 249-256 [PMID: 17143028]
- 40 **Duarte I, Llanos O.** Patterns of metastases in intestinal and diffuse types of carcinoma of the stomach. *Hum Pathol* 1981; **12**: 237-242 [PMID: 7228019]
- 41 **Chung HW, Lee EJ, Cho YH, Yoon SY, So Y, Kim SY, Lee MH, Kim JH, Lee SY, Sung IK, Park HS, Yoo MW, Lee KY.** High FDG uptake in PET/CT predicts worse prognosis in patients with metastatic gastric adenocarcinoma. *J Cancer Res Clin Oncol* 2010; **136**: 1929-1935 [PMID: 20306088 DOI: 10.1007/s00432-010-0852-5]
- 42 **Yoshioka T, Yamaguchi K, Kubota K, Saginoya T, Yamazaki T, Ido T, Yamaura G, Takahashi H, Fukuda H, Kanamaru R.** Evaluation of 18F-FDG PET in patients with advanced, metastatic, or recurrent gastric cancer. *J Nucl Med* 2003; **44**: 690-699 [PMID: 12732669]
- 43 **Yeung HW, Macapinlac H, Karpeh M, Finn RD, Larson SM.** Accuracy of FDG-PET in Gastric Cancer. Preliminary Experience. *Clin Positron Imaging* 1998; **1**: 213-221 [PMID: 14516555]
- 44 **Ma DW, Kim JH, Jeon TJ, Lee YC, Yun M, Youn YH, Park H, Lee SI.** 18F-fluorodeoxyglucose positron emission tomography-computed tomography for the evaluation of bone metastasis in patients with gastric cancer. *Dig Liver Dis* 2013; **45**: 769-775 [PMID: 23831128 DOI: 10.1016/j.dld.2013.02.009]
- 45 **Siewert JR, Böttcher K, Stein HJ, Roder JD.** Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. *Ann Surg* 1998; **228**: 449-461 [PMID: 9790335]
- 46 **Biffi R, Fazio N, Luca F, Chiappa A, Andreoni B, Zampino MG, Roth A, Schuller JC, Fiori G, Orsi F, Bonomo G, Crosta C, Huber O.** Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer. *World J Gastroenterol* 2010; **16**: 868-874 [PMID: 20143466]
- 47 **Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, Pignon JP, Rougier P, Sakamoto J, Sargent D, Sasako M, Van Cutsem E, Buyse M.** Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *JAMA* 2010; **303**: 1729-1737 [PMID: 20442389 DOI: 10.1001/jama.2010.534]
- 48 **Wildiers H, Neven P, Christiaens MR, Squifflet P, Amant F, Weltens C, Smeets A, van Limbergen E, Debrock G, Renard V, Van Eenoo L, Wynendaele W, Paridaens R.** Neoadjuvant capecitabine and docetaxel (plus trastuzumab): an effective non-anthracycline-based chemotherapy regimen for patients with locally advanced breast cancer. *Ann Oncol* 2011; **22**: 588-594 [PMID: 20709813 DOI: 10.1093/annonc/mdq406]
- 49 **Mezhir JJ, Tang LH, Coit DG.** Neoadjuvant therapy of locally advanced gastric cancer. *J Surg Oncol* 2010; **101**: 305-314 [PMID: 20187070 DOI: 10.1002/jso.21483]
- 50 **Knight G, Earle CC, Cosby R, Coburn N, Youssef Y, Malthaner R, Wong RK.** Neoadjuvant or adjuvant therapy for resectable gastric cancer: a systematic review and practice guideline for North America. *Gastric Cancer* 2013; **16**: 28-40 [PMID: 22467061 DOI: 10.1007/s10120-012-0148-3]
- 51 **An JY, Kim KM, Kim YM, Cheong JH, Hyung WJ, Noh SH.** Surgical complications in gastric cancer patients preoperatively treated with chemotherapy: their risk factors and clinical relevance. *Ann Surg Oncol* 2012; **19**: 2452-2458 [PMID: 22395984 DOI: 10.1245/s10434-012-2267-9]
- 52 **Ott K, Sendler A, Becker K, Dittler HJ, Helmberger H, Busch R, Kollmannsberger C, Siewert JR, Fink U.** Neoadjuvant chemotherapy with cisplatin, 5-FU, and leucovorin (PLF) in locally advanced gastric cancer: a prospective phase II study. *Gastric Cancer* 2003; **6**: 159-167 [PMID: 14520529 DOI: 10.1007/s10120-003-0245-4]
- 53 **Di Fabio F, Pinto C, Rojas Llimpe FL, Fanti S, Castellucci P, Longobardi C, Mutri V, Funaioli C, Sperandi F, Giaquinta S, Martoni AA.** The predictive value of 18F-FDG-PET early evaluation in patients with metastatic gastric adenocarcinoma treated with chemotherapy plus cetuximab. *Gastric Cancer* 2007; **10**: 221-227 [PMID: 18095077 DOI: 10.1007/s10120-007-0438-3]
- 54 **Couper GW, McAteer D, Wallis F, Norton M, Welch A, Nicolson M, Park KG.** Detection of response to chemotherapy using positron emission tomography in patients with oesophageal and gastric cancer. *Br J Surg* 1998; **85**: 1403-1406 [PMID: 9782025 DOI: 10.1046/j.1365-2168.1998.00963.x]
- 55 **Ott K, Herrmann K, Lordick F, Wiedner H, Weber WA, Becker K, Buck AK, Dobritz M, Fink U, Ulm K, Schuster T, Schwaiger M, Siewert JR, Krause BJ.** 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**: 2012-2018 [PMID: 18381939 DOI: 10.1158/1078-0432.CCR-07-0934]
- 56 **Jiménez-Bonilla JF, Quirce R, Martínez-Rodríguez I, Banzo I, Rubio-Vassallo AS, Del Castillo-Matos R, Ortega-Nava F, Martínez-Amador N, Ibáñez-Bravo S, Carril JM.** Diagnosis of recurrence and assessment of post-recurrence survival in patients with extracranial non-small cell lung cancer evaluated by 18F-FDG PET/CT. *Lung Cancer* 2013; **81**: 71-76 [PMID: 23597930 DOI: 10.1016/j.lungcan.2013.03.015]
- 57 **Chung HH, Kwon HW, Kang KW, Kim JW, Park NH, Song YS, Kang SB.** Preoperative [F]FDG PET/CT predicts recurrence in patients with epithelial ovarian cancer. *J Gynecol Oncol* 2012; **23**: 28-34 [PMID: 22355464 DOI: 10.3802/jgo.2012.23.1.28]

- 58 **Israel O**, Kuten A. Early detection of cancer recurrence: 18F-FDG PET/CT can make a difference in diagnosis and patient care. *J Nucl Med* 2007; **48** Suppl 1: 28S-35S [PMID: 17204718]
- 59 **Pan L**, Han Y, Sun X, Liu J, Gang H. FDG-PET and other imaging modalities for the evaluation of breast cancer recurrence and metastases: a meta-analysis. *J Cancer Res Clin Oncol* 2010; **136**: 1007-1022 [PMID: 20091186 DOI: 10.1007/s00432-009-0746-6]
- 60 **Wu B**, Wu D, Wang M, Wang G. Recurrence in patients following curative resection of early gastric carcinoma. *J Surg Oncol* 2008; **98**: 411-414 [PMID: 18767119 DOI: 10.1002/jso.21133]
- 61 **Shiraishi N**, Inomata M, Osawa N, Yasuda K, Adachi Y, Kitano S. Early and late recurrence after gastrectomy for gastric carcinoma. Univariate and multivariate analyses. *Cancer* 2000; **89**: 255-261 [PMID: 10918153]
- 62 **Lee JW**, Lee SM, Lee MS, Shin HC. Role of 18F-FDG PET/CT in the prediction of gastric cancer recurrence after curative surgical resection. *Eur J Nucl Med Mol Imaging* 2012; **39**: 1425-1434 [PMID: 22673973 DOI: 10.1007/s00259-012-2164-2]
- 63 **Graziosi L**, Bugiantella W, Cavazzoni E, Cantarella F, Porcari M, Baffa N, Donini A. Role of FDG-PET/CT in follow-up of patients treated with resective gastric surgery for tumour. *Ann Ital Chir* 2011; **82**: 125-129 [PMID: 21682102]
- 64 **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 [PMID: 20932345 DOI: 10.1186/1477-7819-8-86]
- 65 **Bilici A**, Ustaalioglu BB, Seker M, Kefeli U, Canpolat N, Tekinsoy B, Ozugur S, Gumus M. The role of 18F-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* 2011; **38**: 64-73 [PMID: 20838995 DOI: 10.1007/s00259-010-1611-1]
- 66 **Sim SH**, Kim YJ, Oh DY, Lee SH, Kim DW, Kang WJ, Im SA, Kim TY, Kim WH, Heo DS, Bang YJ. The role of PET/CT in detection of gastric cancer recurrence. *BMC Cancer* 2009; **9**: 73 [PMID: 19250554 DOI: 10.1186/1471-2407-9-73]
- 67 **Zou H**, Zhao Y. 18FDG PET-CT for detecting gastric cancer recurrence after surgical resection: a meta-analysis. *Surg Oncol* 2013; **22**: 162-166 [PMID: 23747134 DOI: 10.1016/j.suronc.2013.05.001]
- 68 **Wu LM**, Hu JN, Hua J, Gu HY, Zhu J, Xu JR. 18 F-fluorodeoxyglucose positron emission tomography to evaluate recurrent gastric cancer: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2012; **27**: 472-480 [PMID: 21916986 DOI: 10.1111/j.1440-1746.2011.06919.x]
- 69 **Sun L**, Su XH, Guan YS, Pan WM, Luo ZM, Wei JH, Wu H. 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**: 4627-4632 [PMID: 18698676]
- 70 **De Potter T**, Flamen P, Van Cutsem E, Penninckx F, Filez L, Bormans G, Maes A, Mortelmans L. Whole-body PET with FDG for the diagnosis of recurrent gastric cancer. *Eur J Nucl Med Mol Imaging* 2002; **29**: 525-529 [PMID: 11914891 DOI: 10.1007/s00259-001-0743-8]
- 71 **Ferrucci PF**, Zucca E. Primary gastric lymphoma pathogenesis and treatment: what has changed over the past 10 years? *Br J Haematol* 2007; **136**: 521-538 [PMID: 17156403 DOI: 10.1111/j.1365-2141.2006.06444.x]
- 72 **Yi JH**, Kim SJ, Choi JY, Ko YH, Kim BT, Kim WS. 18F-FDG uptake and its clinical relevance in primary gastric lymphoma. *Hematol Oncol* 2010; **28**: 57-61 [PMID: 19593742 DOI: 10.1002/hon.905]
- 73 **Sharma P**, Suman SK, Singh H, Sharma A, Bal C, Malhotra A, Kumar R. Primary gastric lymphoma: utility of 18F-fluorodeoxyglucose positron emission tomography-computed tomography for detecting relapse after treatment. *Leuk Lymphoma* 2013; **54**: 951-958 [PMID: 23043310 DOI: 10.3109/10428194.2012.717694]
- 74 **Watanabe Y**, Suefuji H, Hirose Y, Kaida H, Suzuki G, Uozumi J, Ogo E, Miura M, Takasu K, Miyazaki K, Nakahara K, Ishibashi M, Okamura T, Ohshima K, Hayabuchi N. 18F-FDG uptake in primary gastric malignant lymphoma correlates with glucose transporter 1 expression and histologic malignant potential. *Int J Hematol* 2013; **97**: 43-49 [PMID: 23212465 DOI: 10.1007/s12185-012-1225-4]
- 75 **Radan L**, Fischer D, Bar-Shalom R, Dann EJ, Epelbaum R, Haim N, Gaitini D, Israel O. FDG avidity and PET/CT patterns in primary gastric lymphoma. *Eur J Nucl Med Mol Imaging* 2008; **35**: 1424-1430 [PMID: 18418594 DOI: 10.1007/s00259-008-0771-8]
- 76 **Perry C**, Herishanu Y, Metzger U, Bairey O, Ruchlemer R, Trejo L, Naparstek E, Sapir EE, Polliack A. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. *Eur J Haematol* 2007; **79**: 205-209 [PMID: 17662066 DOI: 10.1111/j.1600-0609.2007.00895.x]
- 77 **Miettinen M**, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. *Arch Pathol Lab Med* 2006; **130**: 1466-1478 [PMID: 17090188 DOI: 10.1043/1543-2165(2006)130[1466:]
- 78 **van Oosterom AT**, Judson I, Verweij J, Stroobants S, Donato di Paola E, Dimitrijevic S, Martens M, Webb A, Sciort R, Van Glabbeke M, Silberman S, Nielsen OS. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. *Lancet* 2001; **358**: 1421-1423 [PMID: 11705489]
- 79 **Antoch G**, Kanja J, Bauer S, Kuehl H, Renzing-Koehler K, Schuette J, Bockisch A, Debatin JF, Freudenberg LS. Comparison of PET, CT, and dual-modality PET/CT imaging for monitoring of imatinib (STI571) therapy in patients with gastrointestinal stromal tumors. *J Nucl Med* 2004; **45**: 357-365 [PMID: 15001674]
- 80 **Stefanelli A**, Treglia G, Mirk P, Muoio B, Giordano A. F-FDG PET Imaging in the Evaluation of Treatment Response to New Chemotherapies beyond Imatinib for Patients with Gastrointestinal Stromal Tumors. *ISRN Gastroenterol* 2011; **2011**: 824892 [PMID: 21991530 DOI: 10.5402/2011/824892]
- 81 **Goerres GW**, Stupp R, Barghout G, Hany TF, Pestalozzi B, Dizendorf E, Schnyder P, Luthi F, von Schulthess GK, Leyvraz S. The value of PET, CT and in-line PET/CT in patients with gastrointestinal stromal tumours: long-term outcome of treatment with imatinib mesylate. *Eur J Nucl Med Mol Imaging* 2005; **32**: 153-162 [PMID: 15690223 DOI: 10.1007/s00259-004-1633-7]
- 82 **Gayed I**, Vu T, Iyer R, Johnson M, Macapinlac H, Swanston N, Podoloff D. The role of 18F-FDG PET in staging and early prediction of response to therapy of recurrent gastrointestinal stromal tumors. *J Nucl Med* 2004; **45**: 17-21 [PMID: 14734662]
- 83 **McAuliffe JC**, Hunt KK, Lazar AJ, Choi H, Qiao W, Thall P, Pollock RE, Benjamin RS, Trent JC. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. *Ann Surg Oncol* 2009; **16**: 910-919 [PMID: 18953611 DOI: 10.1245/s10434-008-0177-7]
- 84 **Maurel J**, Martins AS, Poveda A, López-Guerrero JA, Cubedo R, Casado A, Martínez-Trufero J, Ramón Ayuso J, Lopez-Pousa A, Garcia-Albeniz X, García del Muro X, de Alava E. Imatinib plus low-dose doxorubicin in patients with advanced gastrointestinal stromal tumors refractory to high-dose imatinib: a phase I-II study by the Spanish Group for Research on Sarcomas. *Cancer* 2010; **116**: 3692-3701 [PMID: 20564079 DOI: 10.1002/cncr.25111]
- 85 **Fuster D**, Ayuso JR, Poveda A, Cubedo R, Casado A, Martínez-Trufero J, López-Pousa A, Del Muro XG, Lomeña F, Maurel J, Pons F. Value of FDG-PET for monitoring treatment

- response in patients with advanced GIST refractory to high-dose imatinib. A multicenter GEIS study. *Q J Nucl Med Mol Imaging* 2011; **55**: 680-687 [PMID: 21150863]
- 86 **Park JW**, Cho CH, Jeong DS, Chae HD. Role of F-fluoro-2-deoxyglucose Positron Emission Tomography in Gastric GIST: Predicting Malignant Potential Pre-operatively. *J Gastric Cancer* 2011; **11**: 173-179 [PMID: 22076223 DOI: 10.5230/jgc.2011.11.3.173]
 - 87 **Otomi Y**, Otsuka H, Morita N, Terazawa K, Furutani K, Harada M, Nishitani H. Relationship between FDG uptake and the pathological risk category in gastrointestinal stromal tumors. *J Med Invest* 2010; **57**: 270-274 [PMID: 20847527]
 - 88 **Watabe T**, Tatsumi M, Watabe H, Isohashi K, Kato H, Yanagawa M, Shimosegawa E, Hatazawa J. Intratumoral heterogeneity of F-18 FDG uptake differentiates between gastrointestinal stromal tumors and abdominal malignant lymphomas on PET/CT. *Ann Nucl Med* 2012; **26**: 222-227 [PMID: 22187313 DOI: 10.1007/s12149-011-0562-3]
 - 89 **Strauss LG**, Dimitrakopoulou-Strauss A, Koczan D, Pan L, Hohenberger P. Correlation of dynamic PET and gene array data in patients with gastrointestinal stromal tumors. *ScientificWorldJournal* 2012; **2012**: 721313 [PMID: 22701369 DOI: 10.1100/2012/721313]
 - 90 **Melvin WS**, Wilkinson MG. Gastric schwannoma. Clinical and pathologic considerations. *Am Surg* 1993; **59**: 293-296 [PMID: 8489097]
 - 91 **Komatsu D**, Koide N, Hiraga R, Furuya N, Akamatsu T, Uehara T, Miyagawa S. Gastric schwannoma exhibiting increased fluorodeoxyglucose uptake. *Gastric Cancer* 2009; **12**: 225-228 [PMID: 20047128 DOI: 10.1007/s10120-009-0526-7]
 - 92 **Takeda M**, Amano Y, Machida T, Kato S, Naito Z, Kumita S. CT, MRI, and PET findings of gastric schwannoma. *Jpn J Radiol* 2012; **30**: 602-605 [PMID: 22660866 DOI: 10.1007/s11604-012-0093-4]
 - 93 **Ohno T**, Ogata K, Kogure N, Ando H, Aihara R, Mochiki E, Zai H, Sano A, Kato T, Sakurai S, Oyama T, Asao T, Kuwano H. Gastric schwannomas show an obviously increased fluorodeoxyglucose uptake in positron emission tomography: report of two cases. *Surg Today* 2011; **41**: 1133-1137 [PMID: 21773906 DOI: 10.1007/s00595-010-4401-2]
 - 94 **Zhuang H**, Pourdehnad M, Lambright ES, Yamamoto AJ, Lanuti M, Li P, Mozley PD, Rossman MD, Albelda SM, Alavi A. Dual time point 18F-FDG PET imaging for differentiating malignant from inflammatory processes. *J Nucl Med* 2001; **42**: 1412-1417 [PMID: 11535734]
 - 95 **Hahn S**, Hecktor J, Grabellus F, Hartung V, Pöppel T, Kimmig R, Forsting M, Antoch G, Heusner TA. Diagnostic accuracy of dual-time-point 18F-FDG PET/CT for the detection of axillary lymph node metastases in breast cancer patients. *Acta Radiol* 2012; **53**: 518-523 [PMID: 22547387 DOI: 10.1258/ar.2012.110420]
 - 96 **Lin YY**, Chen JH, Ding HJ, Liang JA, Yeh JJ, Kao CH. Potential value of dual-time-point 18F-FDG PET compared with initial single-time-point imaging in differentiating malignant from benign pulmonary nodules: a systematic review and meta-analysis. *Nucl Med Commun* 2012; **33**: 1011-1018 [PMID: 22825038 DOI: 10.1097/MNM.0b013e32835710d6]
 - 97 **Filippi L**, D'Arienzo M, Scopinaro F, Salvatori R, Bagni O. Usefulness of dual-time point imaging after carbonated water for the fluorodeoxyglucose positron emission imaging of peritoneal carcinomatosis in colon cancer. *Cancer Biother Radiopharm* 2013; **28**: 29-33 [PMID: 23134220 DOI: 10.1089/cbr.2012.1179]
 - 98 **Lan XL**, Zhang YX, Wu ZJ, Jia Q, Wei H, Gao ZR. The value of dual time point (18F)-FDG PET imaging for the differentiation between malignant and benign lesions. *Clin Radiol* 2008; **63**: 756-764 [PMID: 18555033 DOI: 10.1016/j.crad.2008.01.003]
 - 99 **Been LB**, Suurmeijer AJ, Cobben DC, Jager PL, Hoekstra HJ, Elsinga PH. [18F]FLT-PET in oncology: current status and opportunities. *Eur J Nucl Med Mol Imaging* 2004; **31**: 1659-1672 [PMID: 15565331 DOI: 10.1007/s00259-004-1687-6]
 - 100 **Muijs CT**, Beukema JC, Widder J, van den Bergh AC, Havenga K, Pruim J, Langendijk JA. 18F-FLT-PET for detection of rectal cancer. *Radiother Oncol* 2011; **98**: 357-359 [PMID: 21295872 DOI: 10.1016/j.radonc.2010.12.008]
 - 101 **Yang W**, Zhang Y, Fu Z, Yu J, Sun X, Mu D, Han A. Imaging of proliferation with 18F-FLT PET/CT versus 18F-FDG PET/CT in non-small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2010; **37**: 1291-1299 [PMID: 20309686 DOI: 10.1007/s00259-010-1412-6]
 - 102 **Backes H**, Ullrich R, Neumaier B, Kracht L, Wienhard K, Jacobs AH. Noninvasive quantification of 18F-FLT human brain PET for the assessment of tumour proliferation in patients with high-grade glioma. *Eur J Nucl Med Mol Imaging* 2009; **36**: 1960-1967 [PMID: 19672593 DOI: 10.1007/s00259-009-1244-4]
 - 103 **Kameyama R**, Yamamoto Y, Izuishi K, Sano T, Nishiyama Y. Correlation of 18F-FLT uptake with equilibrative nucleoside transporter-1 and thymidine kinase-1 expressions in gastrointestinal cancer. *Nucl Med Commun* 2011; **32**: 460-465 [PMID: 21423062 DOI: 10.1097/MNM.0b013e32834209b5]
 - 104 **Herrmann K**, Ott K, Buck AK, Lordick F, Wilhelm D, Souvatzoglou M, Becker K, Schuster T, Wester HJ, Siewert JR, Schwaiger M, Krause BJ. Imaging gastric cancer with PET and the radiotracers 18F-FLT and 18F-FDG: a comparative analysis. *J Nucl Med* 2007; **48**: 1945-1950 [PMID: 18006614 DOI: 10.2967/jnumed.107.044867]
 - 105 **Kameyama R**, Yamamoto Y, Izuishi K, Takebayashi R, Hagiike M, Murota M, Kaji M, Haba R, Nishiyama Y. Detection of gastric cancer using 18F-FLT PET: comparison with 18F-FDG PET. *Eur J Nucl Med Mol Imaging* 2009; **36**: 382-388 [PMID: 18985344 DOI: 10.1007/s00259-008-0970-3]
 - 106 **Ott K**, Herrmann K, Schuster T, Langer R, Becker K, Wieder HA, Wester HJ, Siewert JR, zum Büschenfelde CM, Buck AK, Wilhelm D, Ebert MP, Peschel C, Schwaiger M, Lordick F, Krause BJ. Molecular imaging of proliferation and glucose utilization: utility for monitoring response and prognosis after neoadjuvant therapy in locally advanced gastric cancer. *Ann Surg Oncol* 2011; **18**: 3316-3323 [PMID: 21537865 DOI: 10.1245/s10434-011-1743-y]
 - 107 **Zhou M**, Wang C, Hu S, Zhang Y, Yao Z, Li J, Guo W, Zhang Y. 18F-FLT PET/CT imaging is not competent for the pretreatment evaluation of metastatic gastric cancer: a comparison with 18F-FDG PET/CT imaging. *Nucl Med Commun* 2013; **34**: 694-700 [PMID: 23604223 DOI: 10.1097/MNM.0b013e328361663a]
 - 108 **Moses WW**. Fundamental Limits of Spatial Resolution in PET. *Nucl Instrum Methods Phys Res A* 2011; **648** Supplement 1: S236-S240 [PMID: 21804677 DOI: 10.1016/j.nima.2010.11.092]

P- Reviewers: Petersen LJ, Xiao Q S- Editor: Qi Y

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ISSN 1007-9327



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