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18F-fluorodeoxyglucose positron emission tomography-computed tomography scan after gastric endoscopy in those who present with non-specific symptoms, is it necessary or not?

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Abstract

Background and Aims: Retrospectively analyze the sensitivity of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) in the diagnosis of gastric malignancy compared with gastric endoscopy in persons with nonspecific symptoms and evaluate the necessity of 18F-FDG PET-CT scan before surgery. **Materials and Methods:** A total of 53 patients with gastric malignancy proven by surgery and pathology were enrolled in the study. All the patients underwent gastric endoscopy and PET-CT scan before surgery. And the PET-CT images were interpreted by the observers who were blinded to the results of the gastric endoscopy. The sensitivity of gastric endoscopy, 18F-FDG PET-CT, and serum tumor markers in the diagnosis of gastric malignancy were calculated ultimately. **Results:** Of 53 gastric malignancy patients, five cases were proven to be false-negative detected by gastric endoscopy, and the sensitivity of which was 90.57%. The sensitivity of PET scan alone was 86.79%, which was observed no significant difference to that of gastric endoscopy diagnosis, $P = 0.54$. While all of the patients had been detected positive on PET-CT images, the sensitivity of which was significantly higher than that of the gastric endoscopy diagnosis or that of the serum tumor markers, $P < 0.001$. And the FDG uptake was positively correlated with the depth of the cancer invasion into the gastric wall ($P < 0.0001$) and the degree of lymph nodes infiltration ($P = 0.02$). It also various from different differentiation degree significantly, $P = 0.04$. **Conclusions:** 18F-fluorodeoxyglucose PET-CT could detect gastric carcinoma in persons with nonspecific symptoms which showed negative in gastric endoscopy. And it is necessary to be aware of the possibility of gastric malignancy when the result of PET-CT scan is positive.

Key words: 18F-fluorodeoxyglucose, gastric endoscopy, gastric malignancy positron emission tomography-computed tomography

Introduction

Gastric cancer remains one of the most common cancers worldwide. More than two-third of new cases have occurred in developing countries. It is a disease with a high death rate (700,000/year) making it the second most common cause of cancer death worldwide after lung cancer. With advanced disease at the time of diagnosis, many gastric cancer patients have a poor prognosis. Therefore, it is essential for early diagnosis and pretreatment assessment. Unfortunately, to the best of our knowledge, no complete and unified preoperative standards of gastric cancer diagnosis and staging have been applied clinically.[1] The diagnosis is usually established by endoscopy and subsequent histological examination of tumor biopsies. However, studies[2] have shown that gastroscopy may not detect gastric cancer accurately for its false negative, which may mislead the patients and delay treatment.

18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) is a powerful modality for evaluating various tumors. The potential of FDG-PET for early detection of cancer has been investigated because the test enables scanning of the whole body simultaneously and noninvasively. And integrated 18F-FDG and computed tomography (18F-FDG PET-CT) combines anatomic and metabolic information, which has increased sensitivity and specificity in comparison to PET or CT as a single modality. Shoda *et al.*[3] investigated the sensitivity of FDG PET compared with gastroscopy in gastric cancer screening for asymptomatic individuals. They concluded that 18F-FDG PET was poorly sensitive (10%) for detection of gastric cancer in the early stages. Other reports proved that the FDG PET-CT had the potential in the detection of locally advanced or recurrent gastric cancer, but not in finding early-stage gastric cancer.[4,5] Therefore, thinking of the possibility of false-negative cases were found during gastric endoscopy, we retrospectively analyzed the role of 18F-FDG PET-CT in detecting gastric cancer in present study comparing with the gastric endoscopy, and evaluated the necessity of 18F-FDG PET-CT scan before surgery in patients with gastric cancer as well.

Materials and Methods

Patients

The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation. All the data were analyzed anonymously in our study. The patient information was anonymized and de-identified prior to analysis. The selection criterion of this retrospective study was as follows: (1) The patients were diagnosed malignant gastric tumor by pathology diagnosis of the surgical materials. (2) They had presented with nonspecific symptoms such as abdominal distention, pain, nausea, vomiting, and gastric discomfort before gastric endoscopy performed. (3) The gastric endoscopy was performed <2 weeks before they underwent PET-CT scan. (4) The pathologic results of the endoscopy were with three statuses when PET-CT performed, one was not acquired, another was malignant result, and the other was benign result. (5) Patients undergone gastric resection after PET-CT imaging. From June 2012 to January 2014, 53 consecutive patients (32 men and 21 women, age range 25–74 years, mean age 53 ± 12 years) were enrolled in our study. And 18F-FDG PET-CT scan was performed along with serum tumor marker detected.

Positron emission tomography-computed tomography scan

All of the patients fasted for at least 6 h before PET-CT scan except water intake. The blood glucose concentration of each patient was controlled under the level of 7.4 mmol/L before FDG (0.12–0.15 mCi/kg) was injected intravenously. 45–60 min

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later, the FDG PET-CT scans were performed with a GE Discovery STE[16] integrated PET-CT scanner combining the ability to acquire CT images and PET data of the same patient in one session. In order to better distend the gastric wall for the evaluation of gastric cancer before PET-CT scan, each patient was asked to drink as much water as possible (more than 500 ml) just before PET-CT scan. The whole-body CT data were acquired first by a continuous spiral technique on a 16-slice helical CT, with the following parameters: Gantry rotation speed, 0.8 s per rotation; 140 KV; 17.5 mm per rotation table speed. All CT scans were obtained with 3.75 mm thick axial sections and the axial field of view was 15.6 cm. Subsequently, a positron emission scan was performed from the thigh to the head at a 3 min/bed position speed. Combined with CT data, the attenuation corrected PET images were reconstructed by an ordered subset expectation maximization algorithm and then normalized by both injected dose and patients' body weight.

Image analysis

All reports of whole-body ^{18}F-FDG PET-CT imaging of these patients were reviewed. These clinical reports were originally generated this way: All the PET-CT images were interpreted by two independent observers blinded to the clinical data and results of gastric endoscopy. The standardized uptake value (SUV) was calculated as, SUV = (activity in region of interest in mCi/mL)/(injected dose in mCi/weight in kg), and the maximum SUV (SUVmax) was measured on the GE XELERIS workstation. We interpreted the PET-CT images combined increased FDG uptake with the structure information from CT data. Areas with increased FDG uptake compared with surrounding tissue were read as PET positive. And the main CT signs for diagnosing gastric cancer were thickening of the gastric wall or mass in the premise of good gastric filling. The PET-CT result was classified as positive when the positive PET images were consistent with the abnormal structures on CT images. Moreover, a senior radiologist would review the CT images as well as help in diagnosing gastric malignancies, especially when the malignancy without an intense FDG uptake (signet ring cell cancer for example), which would be considered as "PET-CT positive." We assessed the diagnostic accuracy of gastric endoscopy, serum tumor markers, ^{18}F-FDG PET-CT, PET alone in the detection of gastric cancer preoperatively.

TNM classification and histopathological classification

Fifty-three patients underwent surgery after the ^{18}F-FDG PET-CT scan performed. Gastrectomy and regional lymph node dissection were carried out for malignant tumors. The final pathological diagnosis was confirmed from specimens resected surgically. The depth of cancer invasion and the extent of lymph node metastasis were also documented. The histopathological subtype of gastric cancer in our study was determined according to the following classification:[6] Tubular/papillary carcinomas, Signet ring cell carcinoma, Mucinous carcinomas, and Solid/other carcinomas. The gastric cancer TNM staging was referred to the sixth edition of UICC TNM classification of malignant tumors.

Serum tumor markers

The serum tumor markers including carcinoembryonic antigen (CEA), CA72-4, CA50, CA12-5, and CA19-9 were detected <1-week before or after PET/CT scan. We got the results of these tumor markers in forty patients with gastric carcinoma. All the patients fasted for at least 6 h before venous blood collection.

Statistical analysis

With the surgical pathology diagnosis as the golden standard, the sensitivity of PET-CT, PET alone, gastric endoscopy, and serum tumor markers were calculated. Statistical analysis was assessed by Chi-square Test and Fisher's Exact Test for comparing the constituent ratio, Kruskal–Wallis Test for SUVmax comparison of different T stage, N stage, and differentiation in patients with gastric carcinoma.

Results

Primary tumor assessment by gastric endoscopy and serum tumor markers

Of 53 patients with malignant tumor proven by surgery and pathology, false-negative endoscopic results were obtained from five patients, which included one gastric body ulcer, two gastric cardia ulcer, one chronic gastritis with moderate atypical hyperplasia and one intraepithelial neoplasia detected by gastric endoscopy. The characteristics of these patients were showed in the Table 1. And the sensitivity of gastric endoscopy in this study was 90.57%.

We got the results of serum tumor markers levels in 40 patients with gastric carcinoma in our study. Increased CEA levels were detected in five patients, increased CA72-4 levels in two patients, increased CA50 levels in three patients, increased CA19-9 levels in four patients, and increased CA12-5 levels in seven patients. Then the sensitivity of these serum tumor markers were 12.5%, 5%, 7.5%, 10%, and 17.5%, respectively, much lower than ^{18}F-FDG PET/CT scan, $P < 0.05$.

Primary tumor assessment by ^{18}F-fluorodeoxyglucose-positron emission tomography/computed tomography

All the ^{18}F-FDG PET-CT imaging reports of these patients were reviewed. The characteristics of patients enrolled in this study are shown in Table 2. All of the patients, who were diagnosed malignant of the lesions, had been detected positive on PET-CT images. Then the sensitivity of detecting gastric malignant tumor in symptomatic person according to the ^{18}F-FDG PET-CT results is 100% in our study, which was significantly higher than that of the gastric endoscopy diagnosis or that of the serum tumor markers, $P < 0.001$. There were 46 patients with positive FDG accumulation, but seven not. The sensitivity of PET scan alone was 86.79%, which was observed no significant difference to that of gastric endoscopy diagnosis, $P = 0.54$. The highest SUVmax was 14, while the median of which was 4.3 (0.46–14).

Of the 53 patients with gastric carcinoma, the SUVmax various from different differentiation degree significantly, $P = 0.04$. The most increased FDG uptake was demonstrated in moderately differentiated carcinoma. The FDG uptake was positively correlated with the depth of the cancer invasion into the gastric wall ($P < 0.0001$) and the degree of lymph nodes infiltration ($P = 0.02$).

In those patients with false-negative endoscopic results, all the ^{18}F-FDG PET-CT images showed positive and four of them showed increased FDG uptake obviously. The median SUVmax of them was 3.05 (1.8–3.8), which did not show statistical difference to that of other patients with gastric carcinoma, $P = 0.14$ [Figures 1 and 2].

Table 1: The characteristics of patients with false-negative gastroscopic result

	Patient No.l	Patient No. 2	Patient No. 3	Patient No. 4	Patient No. 5
Gentler	Female	Female	Female	Male	Male
Age	57	53	34	72	61
Location	gastric antrum	gastric body	gastric cardia	gastric body	gastric cardia
Pathology (gastroscopy)	moderate atypical hyperplasia	ulcer	ulcer	intraepithelial neoplasia	ulcer
SUV_{max}	3.05	3.4	2.3	1.8	3.8
Pathology (surgery)	adenocarcinoma	adenocarcinoma	adenocarcinoma including partly signet ring cell carcinoma	adenocarcinoma	adenocarcinoma
Depth of cancer invasion	submucosa	subserosa	serosal invasion	mucosa	submucosa
Differentiation	moderate	moderate	poor	high	high
Lymph node involvement	-	-	+	-	-
Tumor marker	-	-	CA125+	-	-

Table 2: The characteristics of patients in our study

Gastric malignancy	N	Median SUV_{max}	P
Location			
Gastric fundus	1	1.5	
Gastric cardia	11	4.6 (0.8~14)	0.23
Gastric body	16	5.45(1~12.6)	
Gastric antrum	25	3.2 (0.46~10)	
Pathology			
Gastric carcinoma			
Tubular/papillary carcinomas	32	4.45 (0.46~14)	
Signet ring cell carcinoma†	11	2.9 (1~12.6)	
Mucinous carcinomas	2	7,35 (6.5~8.2)	0.59
Other carcinomas‡	2	5.25 (4.7~5,8)	
Gastric lymphoma	6	3.65 (2~7.1)	
Differentiation (gastric carcinoma)	47	4.5 (0.46~14)	
Poorly difleremiated	26	3.75 (1~12.6)	0.04*
Moderately differentiated	19	8 (0.46~14)	
well differentiated	2	1.35 (1~1.7)	
Depth of cancer invasion			
Tl stage	8	1.1 (0.8~3.05)	
T2 stage	10	2.8 (0.46~12)	<0.001
T3 stage	16	6.15 (1.8~14)	
T4 slage	13	5.8 (2.9~12.6)	
Lymph node involvement			
No	18	2.8 (0.46-14)	
Nl	22	4.75 (1.2~11.2)	0.02*
N2	7	5.8(3.1~12/6)	

STS=Soft tissue sarcomas, IMFT=Inflammaory myofibrobalstic tumour, RMS=Rhabdomyosarcoma, GIST=GastroIntestinal stromal tumour

Discussion

Gastric carcinoma is still the most common cause of death due to cancer despite the improved prognosis resulting from early diagnosis, radical operations, and the development of chemotherapy. Pretreatment assessment is essential for the management of gastric carcinoma. The standard staging modalities are CT and endoscopic ultrasound, which depend on structural characteristics for diagnosis. In our study, we have shown the high sensitivity of PET-CT in detecting early gastric carcinoma and verified the necessity to receive PET-CT imaging after gastroscopy in those, who with symptoms of stomach discomfort.

Possible reasons for the high detection rate in gastric carcinomas by 18F-fluorodeoxyglucose positron emission tomography-computed tomography

There are a few issues to be addressed, which might have influenced the sensitivity calculated in this study. First, integrated 18F-FDG PET and CT combines anatomic and metabolic information, which has increased both sensitivity and specificity compared with PET or CT as a single modality. Although 18F-FDG PET now is not an appropriate first-line diagnostic procedure in the detection of stomach cancer and may play a valuable role in the detection of distant metastases, such as those of the liver, lungs, adrenal glands, and so on. The high sensitivity of PET in detecting the primary adenocarcinoma of the stomach was confirmed in this prospective study, which is consistent with several other reports.[7]

Second, CT scanning plays an important role in our study, it showed the following: (1) Polypoidal mass with or without ulceration, (2) focal wall thickening with mucosal irregularity or ulceration, (3) wall thickening with the absence of normal mucosal folds (infiltrative lesions), (4) focal infiltration of the gastric wall, (5) mucinous carcinomas, which have low FDG uptake. The third is, CT scanning may have several pitfalls when FDG PET is needed. For example, a pseudomass as a result of a normal gastroesophageal junction may be seen, underdistention of the stomach may simulate wall thickening, and perigastric nodes may not be observed if the stomach is not well distended.

Furthermore, thinking of the majority of people receiving gastric endoscopy only when they feel abdominal discomfort, we establish the selection criterion in our study that the subjects were those who presented with nonspecific symptoms rather than an asymptomatic population, which may have improved the sensitivity. Cause the screening sensitivity of 18F-FDG PET in an asymptomatic population is much lower.

The low detection rate of tumor markers in early gastric carcinomas

The tumor markers routinely used in gastric cancer are CEA and CA19-9. In our study, CA12-5 seemed to be the tumor marker with better sensitivity of 12.5%, but no significant difference was shown among these markers. Tumor markers have been demonstrated to be of no use in mass screening for the diagnosis of gastric cancer, due to the insufficient specificity of most of them, and to their poor sensitivity, mainly in the early stages.

Comparison 18F-fluorodeoxyglucose positron emission tomography-computed tomography with upper gastric endoscopic test

Most of the published studies had focused on recurrent gastric cancer or locally advanced diseases.[8,9] However,
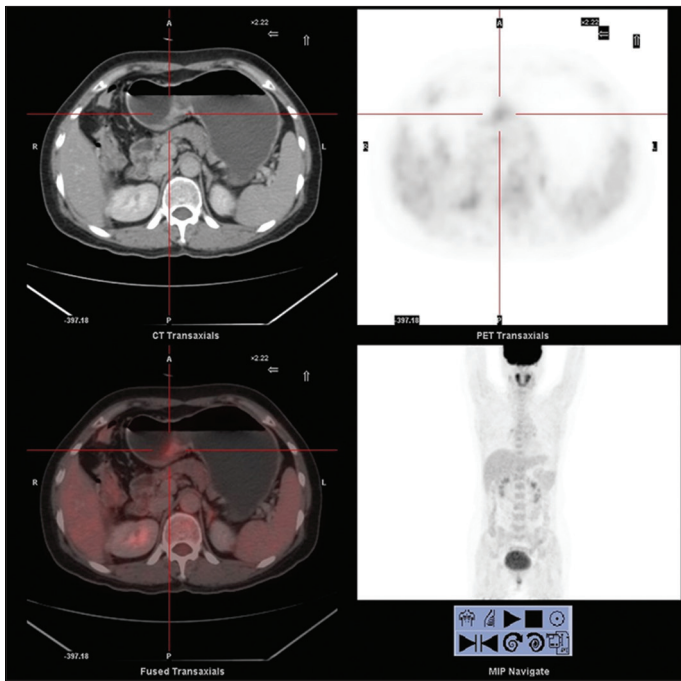
Figure 1: A female patient, 57 years old, the pathologic result of gastric endoscopy was moderate atypical hyperplasia, but the pathologic result after surgery was adenocarcinoma. The computed tomography (CT) (upper left), 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) (upper right), and fused 18F-FDG PET-CT (lower left) images as follows: Transaxial images: The abdomen CT image showed thickening gastric wall in gastric antrum, and elevated FDG uptake lesions in the abdominal cavity detected by PET imaging, maximum standardized uptake value was 3.05. The fused PET-CT image revealed that the high-FDG uptake lesion was located in the gastric antrum. Coronal image (lower right): The whole-body PET image of the patient showed high-FDG uptake mass located in the abdomen
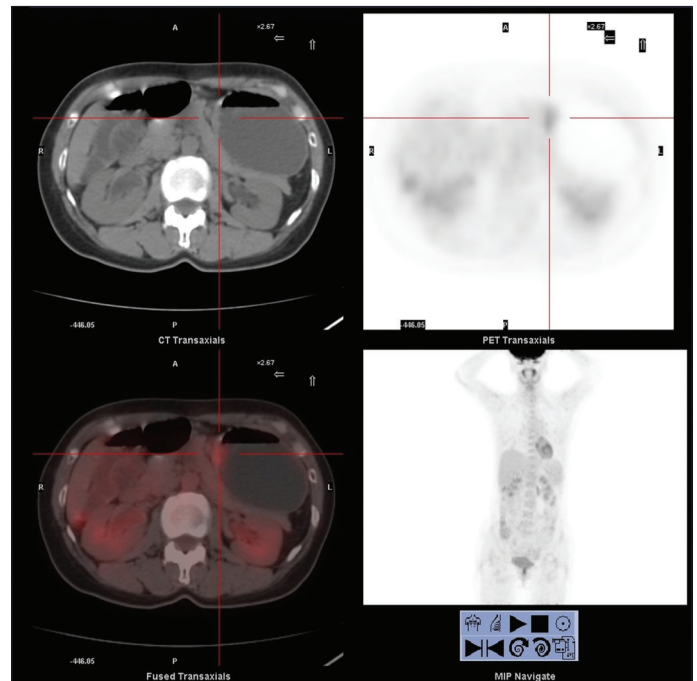

Figure 2: A female patient, 53 years old, the pathologic result of gastric endoscopy was gastric ulcer, but the pathologic result after surgery was adenocarcinoma. The computed tomography (CT) (upper left), 18F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) (upper right) and fused 18F-FDG PET-CT (lower left) images as follows: Transaxial images: The abdomen CT image showed thickening gastric wall in gastric body, and elevated FDG uptake lesions in the abdominal cavity detected by PET imaging, maximum standardized uptake value was 3.4. The fused PET-CT image revealed that the high-FDG uptake lesion was located in the gastric body. Coronal image (lower right): The whole-body PET image of the patient showed high-FDG uptake mass located in the abdomen

few of them focused on the early gastric carcinoma. They found a poor sensitivity and low negative predictive value in screening recurrence, or locally advanced disease, with figures around 70%. While regular endoscopy with multiple biopsies has been recommended as the most optimal method for early detection of gastric cancer.[10] However, the five false-negative cases in our study decreased its diagnostic efficiency.

We think the reason of false negatives were as follows. Gastric biopsy is generally considered easier to get a positive result in polypoidal tumor, but not in ulcerative lesions like the false-negative cases in our study. Another reason is that the tumor infiltrated to the muscle and serosa where was too deep for the biopsy forceps to get the suitable specimen easily. The third reason may be that it was difficult to identify the cancer cell structure cause of the mixture with serious inflammation, bleeding, and tissue necrosis or the cancer cell structure was damaged. Other reasons including the preparation of the biopsy specimen and the diagnostic criteria for pathology, etc.

The false positive results in FDG PET-CT scan was still a problem that should be payed attention to. The water gastric distention method was used in our study, so that the physiological gastric FDG uptake was reduced.

Based on the above, for those who with a negative result in gastric endoscopic test and positive result in PET-CT scan, it is necessary to be aware of the possibility of gastric malignancy.

To increase the frequency of follow-up or to receive the gastric endoscopic test again is essential.

Conclusion

18F-fluorodeoxyglucose PET-CT could detect gastric carcinoma, which showed negative in gastric endoscopy. In those who presented with nonspecific abdominal discomfort, receiving PET-CT scan is a good choice when the gastric endoscopic test has no positive finding. And it is necessary to be aware of the possibility of gastric malignancy when the result of PET-CT scan is positive. To increase the frequency of follow-up or to receive the gastric endoscopic test again is essential.

Conflicts of interest
There are no conflicts of interest.

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