

## Multiple primary malignant tumors of upper gastrointestinal tract: A novel role of $^{18}\text{F}$ -FDG PET/CT

Long Sun, Ying Wan, Qin Lin, Yong-Hong Sun, Long Zhao, Zuo-Ming Luo, Hua Wu

Long Sun, Yong-Hong Sun, Long Zhao, Zuo-Ming Luo, Hua Wu, Minnan PET Center, the First Affiliated Hospital of Xiamen University, Xiamen 361003, Fujian Province, China  
Ying Wan, College of Life Science and Technology, Huazhong University of Science and Technology, Wuhan 430074, Hubei Province, China

Qin Lin, Department of Radiation, the First Affiliated Hospital of Xiamen University, Xiamen 316003, Fujian Province, China  
Author contributions: Sun L wrote the paper; Lin Q, Sun YH, Zhao L and Luo ZM completed patient follow-ups and data collection; Wan Y and Wu H supervised the writing and organization process.

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Correspondence to: Hua Wu, MD, Minnan PET Center, the First Affiliated Hospital of Xiamen University, Xiamen 361003, Fujian Province, China. wuhua1025@163.com

Telephone: +86-592-2139527 Fax: +86-592-2139527

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**RESULTS:**  $^{18}\text{F}$ -FDG PET/CT scan was positive in 32 suspicious lesions, 30/32 were true positive primary lesions, and 2/32 were false positive. In 15 suspicious lesions with negative  $^{18}\text{F}$ -FDG PET/CT scan, 12/15 were true negative and 3/15 were false negative. Among the 15 patients, 12 patients had 29 primary synchronous tumors confirmed by pathology, including 8 cases of esophageal cancers accompanied with gastric cancer and 4 of hypopharynx cancers with esophageal cancer. The other 3 patients had 4 new primary metachronous tumors, which were multiple primary esophageal cancers. PET/CT imaging detected local lymph node metastases in 11 patients. Both local lymph node metastases and distant metastases were detected in 4 patients. On a per-primary lesion basis, the sensitivity, specificity, accuracy, negative predictive value and positive predictive value of  $^{18}\text{F}$ -FDG PET/CT for detecting multiple primary cancer of UGI tract were 90.9%, 85.7%, 89.4%, 80% and 93.7%, respectively.

**CONCLUSION:** The whole body  $^{18}\text{F}$ -FDG PET/CT may play an important role in evaluating the multiple primary malignant tumors of UGI tract cancer.

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### Abstract

**AIM:** To evaluate the capacity of  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography/computed tomography ( $^{18}\text{F}$ -FDG PET/CT) for detecting multiple primary cancer of upper gastrointestinal (UGI) tract.

**METHODS:** Fifteen patients (12 without cancer histories and 3 with histories of upper GI tract cancer) were investigated due to the suspicion of primary cancer of UGI tract on X-ray barium meal and CT scan. Subsequent whole body  $^{18}\text{F}$ -FDG PET/CT scan was carried out for initial staging or restaging. All the patients were finally confirmed by endoscopic biopsy or surgery. The detection rate of multiple primary malignant cancers was calculated based on  $^{18}\text{F}$ -FDG PET/CT and endoscopic examinations.

**Key words:** Upper gastrointestinal tract cancer; Esophageal cancer; Gastric cancer; Positron emission tomography/computed tomography;  $^{18}\text{F}$ -fluorodeoxyglucose

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## INTRODUCTION

Metachronous or synchronous esophageal cancer has been identified in patients with head and neck cancer, gastric cancer or colon cancer<sup>[1]</sup>. Alcohol drinking and tobacco smoking are the major risk factors for upper aerodigestive tract cancers, accounting for a large proportion of cases in developed countries<sup>[2,3]</sup>. The occurrence of multiple primary cancers in the aerodigestive tract has been explained by the concept of field carcinogenesis. Combined exposure to alcohol and tobacco has a multiplicative effect on carcinogenesis of upper aerodigestive tract<sup>[4,5]</sup>.

X-ray barium meal examination, endoscopic examination, computed tomography (CT) are the main techniques used for the staging and follow-up of upper gastrointestinal (UGI) tract cancer<sup>[6,7]</sup>. However, the reported increase in sensitivity of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) over CT has been attributed to the capacity of <sup>18</sup>F-FDG PET/CT to detect metabolic abnormalities that precede the morphological changes seen by CT. This study was undertaken to further define the value of <sup>18</sup>F-FDG PET/CT in evaluating multiple primary metachronous or synchronous cancer of UGI.

## MATERIALS AND METHODS

### Patients

Fifteen patients with multiple UGI tract cancer (13 males and 2 female, aged 49-78 years with a mean age of 61 years) were selected for a retrospective review from our electronic database, who were imaged by <sup>18</sup>F-FDG PET/CT between January 2007 and January 2010 because of the suspicious findings for multiple UGI tract cancer by the X-ray barium meal and endoscopic examinations. All the patients were finally confirmed by endoscopic biopsy or surgery.

### <sup>18</sup>F-FDG PET/CT technique

The patients were asked to fast for at least 4 h before undergoing <sup>18</sup>F-FDG PET/CT. Their blood glucose level should be within the normal range (70-120 mg/dL) prior to intravenous injection of <sup>18</sup>F-FDG. The patients received an intravenous injection of 370-666 MBq (10-18 mCi) of <sup>18</sup>F-FDG. Data acquisition by an integrated PET/CT system (Discovery STE; GE Medical Systems, Milwaukee, WI, USA) was performed within 60 min after injection. The procedure of data acquisition was as follows: CT scanning was performed first, from the head to the pelvic floor, with 110 kV, 110 mA, a tube rotation time of 0.5 s, a 3.3-mm section thickness, which was matched to the PET section thickness. Immediately after CT scanning, a PET emission scan covering the identical transverse field of view was obtained. Acquisition time was 3 min per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation.

### PET/CT image interpretation

The <sup>18</sup>F-FDG PET/CT images were prospectively interpreted by two experienced nuclear physicians. One had 21 years of experience in both nuclear medicine and radiology, and the other had six years of experience in both nuclear medicine and radiology, who read the <sup>18</sup>F-FDG PET/CT images on a high-resolution computer screen, and reached a consensus in cases of discrepancy.

Based the knowledge of the normal biodistribution of <sup>18</sup>F-FDG, lesions were identified as foci with increased tracer accumulation relative to that in comparable normal contralateral structures and surrounding soft tissues. The lesions were qualitatively graded as definitely or probably abnormal (categorized as representing a tumor) if the accumulation of <sup>18</sup>F-FDG was markedly to moderately increased. Diffuse and mildly increased activity or no increased activity (in the case of an abnormality identified on CT, but no corresponding abnormality was present on PET) was considered to be a normal or benign disease.

### Statistical analysis

The results of PET/CT were quantified using the following definitions: accuracy [(true positive) + (true negative)/(total patients)], sensitivity [(true positive)/(true positive + false negative)], specificity [(true negative)/(true negative + false positive)], positive predictive value [(true positive)/(true positive + false positive)], and negative predictive value [(true negative)/(true negative + false negative)].

## RESULTS

### Clinical presentation

At the time of multiple primary lesions of suspected UGI cancer, the mean age of the patients was 61 years with a predominant tendency in men. Twelve men and one woman had heavy tobacco and alcohol consumption histories in this group of patients.

PET/CT is able to demonstrate the entire UGI tract in almost all patients, even following incomplete endoscopic examination due to obstructing upper esophageal tumors in 4 patients (Figure 1). PET/CT imaging is helpful to guide accurately localization of lower esophageal lesions in the remaining patients.

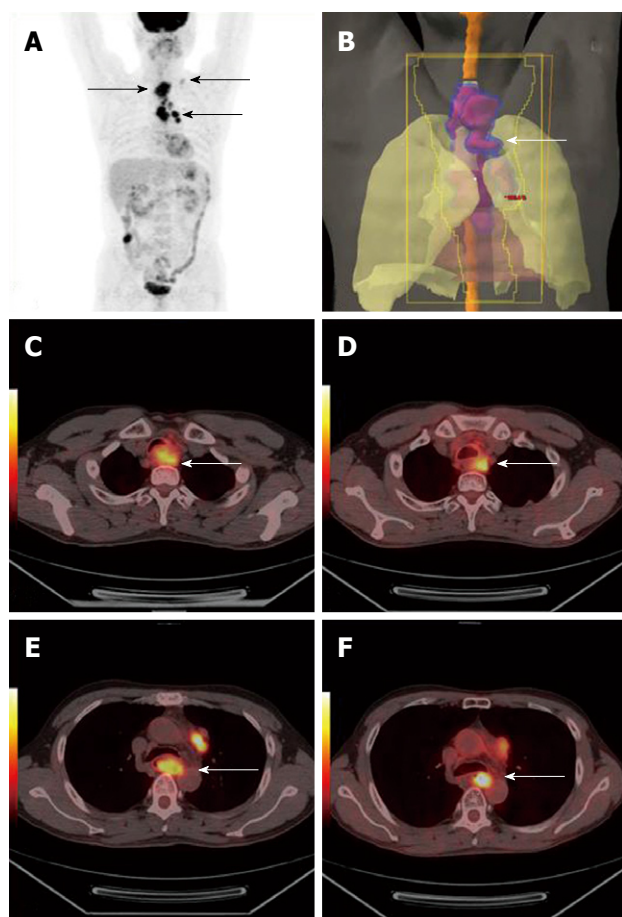
### PET/CT diagnosis

<sup>18</sup>F-FDG PET/CT scan was positive in 32 suspicious lesions, of which 30 were true positive primary lesions and 2 were false positive. Among 15 suspicious lesions with negative <sup>18</sup>F-FDG PET/CT scan, 12 were true negative and 3 were false negative.

On a per-primary lesion basis, sensitivity, specificity, accuracy, negative predictive value and positive predictive value of <sup>18</sup>F-FDG PET/CT in detecting multiple primary cancer of UGI tract were 90.9%, 85.7%, 89.4%, 80% and 93.7%, respectively.

### Primary tumor, local lymph node metastases and distant metastases

Of the 15 patients, 12 patients had 29 primary synchro-



**Figure 1** A 52-year-old man with synchronous multiple esophageal cancers. The first positron emission tomography/computed tomography (PET/CT) images revealed multiple hypermetabolic esophageal lesions and hypermetabolic supraclavicular, mediastinal lymph nodes (arrows in A, C, E). PET/CT imaging guided radiation plan (arrows in B). The second PET/CT images after 50Gy radiation treatment demonstrated shrinkage of lesions and decrease of fluorodeoxyglucose uptake (arrows D, F).

nous tumors confirmed by pathology (Table 1), including 8 cases of esophageal cancer combined with gastric cancer and 4 had hypopharynx cancer combined with esophageal cancer. The other 3 patients had 4 new primary metachronous tumors (Table 2 and Figure 2).

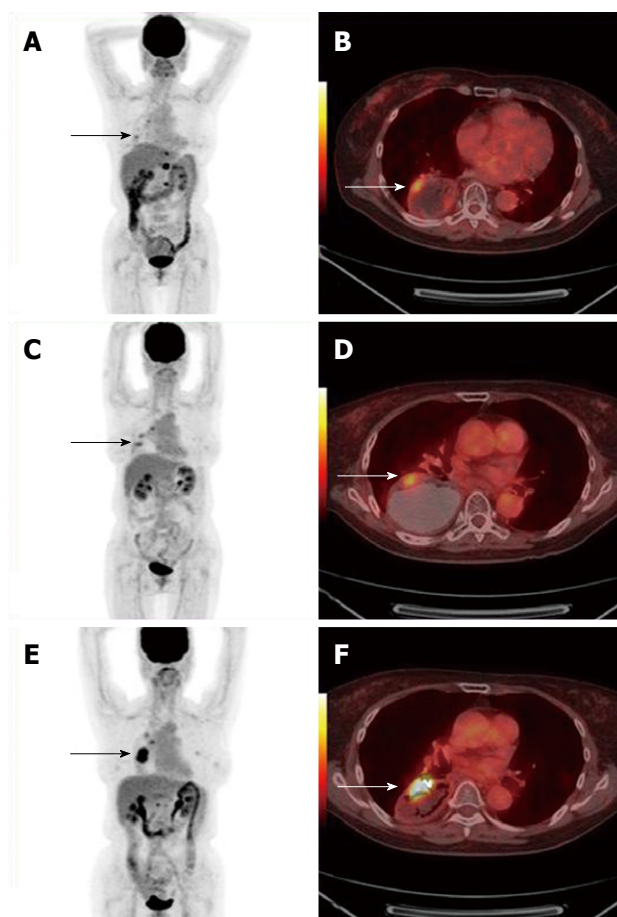
PET/CT imaging detected local lymph node metastases in 11 patients (Figure 3). Both local lymph node metastases and distant metastases were detected in 4 patients.

### Impact on clinical management

Clinical treatment plans were changed in 11 (73.3%) patients after PET/CT examination.  $^{18}$ F-FDG PET/CT imaging-guided radiotherapy was performed in 11 patients.

## DISCUSSION

Synchronous cancers were predominantly located in the aerodigestive tract, primarily in the lung, head and neck and esophagus<sup>[8]</sup>. Kumagai *et al*<sup>[9]</sup> reported half of the patients with multiple upper aerodigestive tract squamous cell carcinomas are initially seen with synchronous



**Figure 2** A 56-year-old woman with metachronous gastric cancer after esophageal cancer resection 5 years ago. Positron emission tomography/computed tomography (PET/CT) displayed multi-retroperitoneal lymph node recurrence (arrow in A), which was later verified as esophageal cancer metastasis (squamous cell carcinoma). PET revealed a small lesion at gastric tube, but endoscopy was negative (arrows in A, B, C, D). Third PET/CT showed an enlarged gastric lesion, and endoscopic biopsy verified gastric tube cancer (adenocarcinoma) (arrows in E, F).

tumors. It is also believed that these second primary cancers arise independently following exposure to a common carcinogen by a process that has been called field cancerization<sup>[10]</sup>. At least 75% of head and neck cancers are attributable to a combination of cigarette smoking and alcohol drinking<sup>[11]</sup>. In our cases, 13 patients (86.7%) had heavy tobacco and alcohol consumption histories. Synchronous tumors of UGI tract were detected in 12 patients. Esophageal cancers combined with gastric cancer (53.3%) were most frequently seen in our study.

Patients with primary head and neck malignancies have a 3%-7% yearly incidence of second primary cancers. Most metachronous squamous cell carcinomas become manifest within 3 years<sup>[12]</sup>. Detection of second primaries has an important impact on therapy. For the patients treated for advanced squamous cell carcinoma in the oral cavity or oropharynx during the first year after completion of their curative treatment, routine surveillance for detecting early locoregional recurrence, distant metastases, and second metachronous primary tumors is very important<sup>[13,14]</sup>. Due to the poor prognosis of head



Table 1 Characteristics of synchronous tumor in 12 patients

Sex/age (yr)	PET/CT findings				Endoscopic results
	T	T	N	M	
F/61	EPC (lower)	Cardiac	Gastrohepatic		EPC (lower), cardiac
M/60	Hypopharynx	EPC (mid, lower)	Mediastinal		Hypopharynx
M/62	EPC (upper)	EPC (lower)	Supraclavicular		EPC (upper)
M/59	EPC (lower)	Cardiac	Mediastinal, gastrohepatic		EPC (lower), cardiac
M/61	Hypopharynx	EPC (mid)	Right cervical		Hypopharynx
M/62	EPC (mid)	Cardiac	Gastrohepatic		EPC (mid), cardiac
M/78	EPC (lower)	Pylorus	Mediastinal, gastrohepatic	Lung	EPC (lower), pylorus
M/57	EPC (mid, lower)	Cardiac	Mediastinal, gastrohepatic	Lung	EPC (mid, lower)
M/52	EPC (upper)	EPC (mid, lower)	Mediastinal, supraclavicular		EPC (upper, mid)
M/62	EPC (mid, lower)	Cardiac	Mediastinal, gastrohepatic	Liver	EPC (mid, lower)
M/53	Hypopharynx	EPC (mid, lower)	Cervical, mediastinal, retroperitoneal		Hypopharynx
M/60	EPC (upper)	EPC (mid)	Supraclavicular, mediastinal		EPC (upper, mid)

PET/CT: Positron emission tomography/computed tomography; EPC: Esophageal cancer.

Table 2 Characteristics of metachronous tumor in 3 patients

Sex/age (yr)	PET/CT findings				Endoscopic results
	Primary	Secondary	N	M	
M/68	EPC resection 10 yr ago	Hypopharynx	Cervical		Hypopharynx
M/49	GC resection 25 yr ago	EPC (lower), Cardiac	Supraclavicular	Lung	EPC (lower), cardiac
F/63	EPC resection 5 yr ago	Gastric tube cancer	Retroperitoneal		Gastric tube cancer

PET/CT: Positron emission tomography/computed tomography; EPC: Esophageal cancer; GC: Gastric cancer.

and neck cancer, the data of metachronous cancer of UGI tract were limited. In this study, 3 patients had 4 primary metachronous tumors. The interval from first tumor to second tumor ranged from 5 to 10 years.

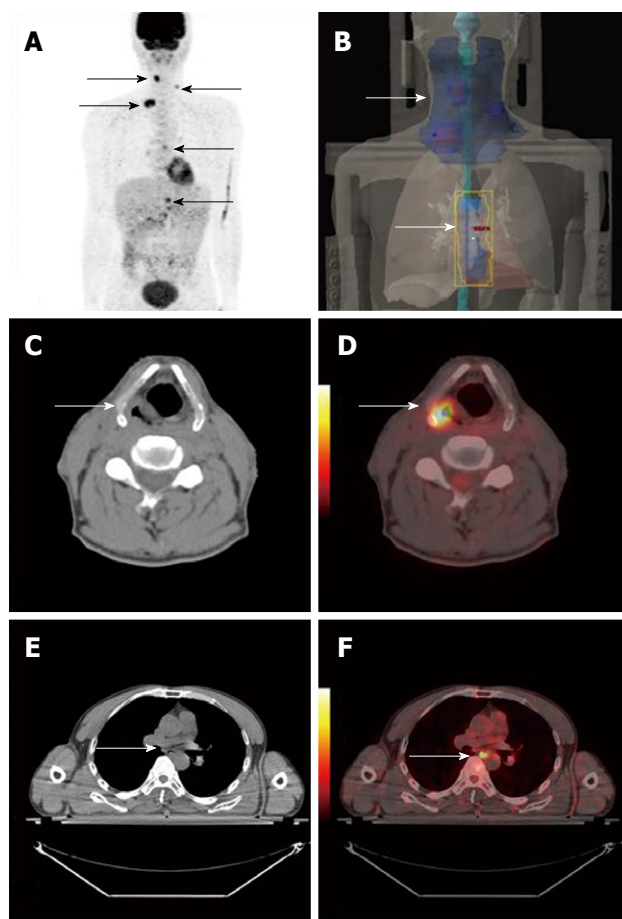
In the majority of follow-up protocols, radiologic and endoscopic evaluation has been proven to be useful in the early detection of metachronous and recurrent neoplasms in the follow-up of patients with previously treated carcinomas of the ear, nose, and throat. Adequate staging of UGI cancer including CT and endoscopic ultrasonography has been considered to be helpful for avoiding useless surgery<sup>[15,16]</sup>. However, more than 30% of the distant metastases have been reported to be radiographically occult with conventional diagnostic strategy and surgery. It has been still performed in a considerable number of patients with distant metastases. Moreover, the overall survival after curative resection does not exceed 25%, with an overall median disease-free survival of only 12 mo.

Conventional staging methods consisting of both CT and EUS evaluate local unresectability or metastatic diseases based on the anatomic alterations. Their low sensitivity and low specificity were related to the low accuracy in determining a curative surgery, indicating the demand for a different approach<sup>[17,18]</sup>. In contrast to conventional anatomic imaging, PET can reveal metabolic alterations in tumor tissues. Most malignant tumors present a high uptake of <sup>18</sup>F-FDG due to an increased anaerobic glycolysis<sup>[19]</sup>. In our previous studies, <sup>18</sup>F-FDG PET/CT was found to be valuable in detecting previously unknown

metastases in esophageal cancer. Routinely performed <sup>18</sup>F-FDG PET/CT in the preoperative work-up of these tumors may therefore reduce the number of unnecessary surgical procedures<sup>[20]</sup>.

There have been several investigations into the utility of <sup>18</sup>F-FDG PET or PET/CT in relation to multiple primary cancers detection. Major advantages of the whole body <sup>18</sup>F-FDG PET/CT are the capability to perform full-body scan with the potential to detect local and distant metastases in one single examination and the possibility of distinguishing new active disease from scar or necrotic tissues<sup>[21,22]</sup> since tumors with increased <sup>18</sup>F-FDG uptake are more metabolically active and biologically aggressive<sup>[23,24]</sup>.

The accurate staging of multiple primary cancer of UGI tract is essential to select appropriate treatment and to anticipate disease progression. Conventional imaging methods that rely on detection of the structural changes caused by tumors usually have limitations in determining the extent of UGI, especially lymph node metastasis<sup>[25,26]</sup>. PET/CT is a fundamentally different imaging technique that identifies focal areas of increased metabolism associated with malignancies. PET/CT is more sensitive than regular CT scan in determining regional and distant lymph node involvement in the squamous cell carcinoma as well as adenocarcinoma of the esophagus. PET can play an important role in evaluating the pretreatment staging of esophageal cancer<sup>[27,28]</sup>. A noteworthy finding in the present study is the high incidence of 100% (13/13) of local lymph node metastases and distant metastases



**Figure 3** A 53-year-old woman with synchronous hypopharynx cancer combined with esophageal cancer. Positron emission tomography/computed tomography (PET/CT) images revealed hypermetabolic hypopharynx and esophageal lesions, and multiple hypermetabolic supraclavicular, mediastinal lymph nodes (arrows in A). PET/CT imaging guided radiation plan (arrows in B). CT and PET/CT fused images showed hypermetabolic hypopharynx and esophageal lesions (arrows in C, D, E, F).

detected by  $^{18}\text{F}$ -FDG PET/CT. Furthermore, clinical decisions of treatment were changed in 11 patients after PET/CT examinations.

There are several limitations in this study. First, due to the retrospective feature of the study, we did not get all of the medical details for some of the patients. There are also some disadvantages associated with PET/CT imaging. For example, small tumors might be undetected because partial-volume effects result in a falsely low measurement of true  $^{18}\text{F}$ -FDG activity<sup>[29]</sup>. Another drawback of PET/CT is that  $^{18}\text{F}$ -FDG frequently accumulates in areas of inflammation. Variable physiologic FDG uptake patterns and benign pathological causes of  $^{18}\text{F}$ -FDG uptake can be specifically recognized and properly categorized in other instances<sup>[30]</sup>.

The choice of diagnostic techniques must be based on the site and histologic characteristics of the synchronous tumors. Although  $^{18}\text{F}$ -FDG PET/CT may be the preferred technique for staging UGI cancer, it can not replace other techniques, such as Lugol chromoendoscopy, for detecting synchronous UGI cancer in high-risk populations<sup>[31]</sup>.

Our results suggested that  $^{18}\text{F}$ -FDG PET/CT may

be useful in evaluating the multiple primary malignant tumors of UGI cancer. It may play an important role in the initial staging of multiple synchronous or metachronous UGI tract cancers.

## COMMENTS

### Background

Multiple primary malignancies in a single patient are relatively rare but have increased in frequency in recent decades. Metachronous or synchronous esophageal cancer has been identified in patients with head and neck cancer, gastric cancer or colon cancer. Alcohol drinking and tobacco smoking are the major risk factors for upper aerodigestive tract cancers, accounting for a large proportion of cases in developed countries. The occurrence of multiple primary cancers in the aerodigestive tract also has been explained by the concept of field carcinogenesis. Combined exposure to alcohol and tobacco has a multiplicative effect on carcinogenesis of upper aerodigestive tract.

### Research frontiers

Positron emission tomography/computed tomography (PET/CT) provides anatomic landmarks for better characterization of increased  $^{18}\text{F}$ -fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) uptake. PET/CT is a widely accepted imaging method in the management of a wide variety of cancers. The reported increase in sensitivity of PET/CT over conventional techniques has been attributed to the ability of PET/CT to detect metabolic abnormalities that precede the morphologic changes seen by CT. However, the usefulness and limitations of  $^{18}\text{F}$ -FDG PET/CT in evaluating multiple primary malignant tumors of upper gastrointestinal tract still need further clinical evaluations.

### Innovations and breakthroughs

The early detection of multiple primary malignant tumors of upper gastrointestinal (UGI) cancer will enable prompt management and will increase the cure rate of the disease. Whole body  $^{18}\text{F}$ -FDG PET/CT scan could provide valuable information for early detection and might guide salvage treatment for multiple primary malignant tumors of UGI cancer.

### Applications

$^{18}\text{F}$ -FDG PET/CT may be useful in evaluating the multiple primary malignant tumors of UGI cancer. It may play an important role in the initial staging of multiple synchronous or metachronous UGI tract cancers.

### Peer review

The manuscript is very well written and should be accepted for publication.

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