Nineteen cases with synchronous multiple primary cancers studied by ^{18}F-FDG PET/CT

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Keywords: Positron emission tomography/computed tomography (PET/CT)
- ^{18}F-fuoro-2-deoxyglucose (^{18}F-FDG)
- Synchronous primary cancers

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Received:
11 December 2016
Accepted revised :
20 December 2016

Abstract

Objective: To evaluate fluorine-18-fuoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in diagnosing synchronous multiple primary cancers (SMPC). **Methods:** Nineteen patients with pathologically-confirmed SMPC were collected. Clinical and ^{18}F-FDG PET/CT characteristics of these patients were reviewed and analyzed. Maximum standardized uptake value, (SUVmax) of all lesions was measured and difference (Δ)SUVmax between the SUV of two primary tumors in each patient was calculated as: [(the larger SUVmax - the smaller SUVmax)/ the larger SUVmax]×100%. **Results:** A total of 38 lesions were identified, which were most frequently located in gastrointestinal tract (n=16), followed by lung (n=10), breast (n=4), kidney (n=4), liver (n=2), pancreas (n=1) and thyroid (n=1). Pathologies of these 38 lesions were 18 adenocarcinomas, 8 squamous cell carcinomas, 4 breast invasive ductal carcinomas, 4 renal cell carcinomas, 2 hepatocellular carcinomas, 1 pancreatic ductal adenocarci-noma and 1 papillary thyroid carcinoma. The mean SUVmax of all lesions was 8.5±6.9, most of them being more than 2.5 (n=30). The mean ΔSUVmax was 57.3%±24.6%, indicating different metabolism of the pri-mary cancers in each patient. **Conclusion:** In our center, SMPC most commonly involved the gastrointes-tinal tract and adenocarcinomas were the most common pathology type. ^{18}F-FDG PET/CT was useful in the diagnosis of SMPC and the ΔSUV max indicates different pathological origins of the synchronous cancers.

Hell J Nucl Med 2017; 20(1): 36-40 *Epub ahead of print: 20 March 2017* *Published online: 20 April 2017*

Introduction

Multiple primary cancers (MPC) are relatively rare, accounting for 0.7%-11.7% of all cases with cancer [1-3]. The prevalence of MPC showed an increasing trend in recent decades [4]. According to Cunliffe et al (1984) [5], MPC can be generally classified into two categories: synchronous and metachronous, depending on whether the cancers occurred within 6 months or later.

Timely identification of synchronous MPC (SMPC) may alter treatment plan. The conventional imaging modalities including ultrasound (US), CT and magnetic resonance imaging (MRI) have limitations in detecting SMPC because of their commonly regional imaging pattern. In recent years, hybrid fluorine-18-fuoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has emerged as a promising imaging modality in the evaluation of malignant tumors [6-7]. Moreover, it has been reported that the introduction of ^{18}F-FDG PET/CT imaging to assess malignant tumors has resulted in increased detection of SMPC [8-10].

In this study, we retrospectively studied 19 patients with SMPC that were histopathologically confirmed. Clinical and ^{18}F-FDG PET/CT characteristics of these patients were reviewed and analyzed.

Subjects and Methods

Patients

The study was approved by our Institutional Review Board. Patients' informed consent was waived because of the retrospective nature of this study. All 19 patients had received ^{18}F-FDG PET/CT examinations for their primary staging of a known or suspected primary

malignancy from June 2010 to November 2013.

The mean age of these 19 patients was 64.1 years, ranging from 32 to 80 years. Seven patients were female while 12 patients were male.

Data acquisition and reconstruction of ^{18}F-FDG PET/CT

Fluorine-18-FDG PET/CT scans were obtained with a PET/CT scanner (Discovery VCT, GE Healthcare, Milwaukee, Wisconsin, USA). All patients fasted for at least 6 hours before examination. The serum glucose just before PET/CT scanning was less than 10 mmol/dL. Patients were scanned at 50-60 minutes after the intravenous (i.v.) injection of ^{18}F-FDG (4.44MBq/kg), typically, patients were scanned from the base of the skull to the mid-thigh. Computed tomography was performed first with: tuber voltage 140 kV, tuber current 200mA, gantry rotation time 0.5s, pitch 0.516, matrix 512×512, and thickness 3.75mm. Then, PET acquisition was obtained with patients in the same position. Acquisition time was 2min per table position in 3D mode. Image data sets for PET were reconstructed iteratively by applying the CT data for attenuation correction, and co-registered images displayed on a workstation.

Image interpretation and statistical analysis

Whole-body ^{18}F-FDG PET/CT of these patients were retrieved and reviewed by two nuclear medicine physicians, who served for 14 and 7 years in both nuclear medicine and radiology departments. Locations of lesions were recorded and the maximal standardized uptake values (SUVmax) of the lesions were measured. On PET/CT, the ^{18}F-FDG avid lesions were considered synchronous primary cancers if the following conditions were met: a) More than 2 hypermetabolic lesions had SUVmax $\geqslant$ 2.5, b) Lesions appearance or location or growing pattern were not suggestive of metastases [11]. If lesions presented any signs of malignancy on CT, they were also considered malignant, even if were hypometabolic on PET (SUVmax<2.5). SUVmax of all lesions were measured and ΔSUVmax between the two SUVmax was calculated as [(the larger SUVmax – the smaller SUVmax)/the larger SUVmax]×100%.

The final diagnosis was obtained from pathology either by biopsy or by surgery. Categorical variables were expressed as frequencies or percentages while numerical variables were expressed as mean ± standard deviation (SD).

Results

Patient clinical and baseline information

A total of 38 SMPC were identified. Baseline and clinical information of patients are summarized in Table 1. Obviously, SMPC most commonly involved the gastrointestinal tract with a total of 16 (42.1%) lesions identified, including 6 in esophagus, 5 in stomach, 3 in colon and 2 in rectum. Other organs involved comprised lung (n=10), breast (n=4), kidney (n=4), liver (n=2), pancreas (n=1) and thyroid (n=1).

Pathologically, these 38 lesions were most commonly adenocarcinomas, while there were 8 squamous cell carcinomas, 4 breast invasive ductal carcinomas and 4 renal cell carcinomas, 2 hepatocellular carcinomas, 1 pancreatic ductal adenocarcinoma and 1 papillary thyroid carcinoma. Local lymph node metastases were confirmed in 7 patients (Table 2).

Table 1. *Clinical and demographic information of patients included*

Items	Count (%)/Mean (SD)
Gender (n=19)	
Male	12
Female	7
Age	64.1±11.4
Location of malignances (n=38 in 19 patients)	
Gastrointestinal tract	16 (42.1)
Lung	10 (26.3)
Breast	4 (10.5)
Kidney	4 (10.5)
Liver	2 (5.3)
Pancreas	1 (2.6)
Thyroid	1 (2.6)
SUVmax (n=38 in 19 patients)	8.5±6.9

Clinical-PET correlation

The detected by ^{18}F-FDG PET/CT SMPC are shown in Table 1 and Table 2.

The mean value of SUVmax of all lesions was 8.5±6.9. Most of the synchronous lesions (30/38) showed hyper-metabolism on PET imaging with SUVmax being higher than 2.5. However, 8 (8/38) lesions showed limited ^{18}F-FDG uptake with SUVmax being less than 2.5. Representative cases are shown in Figure 1 and Figure 2. These 8 lesions were predominantly located in the lung (4) and in the kidneys (4). The histopathology of the hypometabolic lung lesions was moderately differentiated adenocarcinoma. The kidney lesions were all clear cell carcinoma. A typical case is shown in Figure 3.

The mean value of ΔSUVmax of all lesions was 57.3%± 24.6% (18.9% to 94.8%), while 14 (73.7%) cases exhibited a ΔSUVmax above 41%, which was considered the optimal cut-off point for early distinguishing SMPC from metastases [12]. The great ΔSUVmax between two of the cancers in each patient indicated their different pathological origins [12].

Table 2. *Characteristics of ^{18}F-FDG PET/CT, detected synchronous primary cancers with histopathologic findings in 19 patients*

	Lesions (SUVmax) on PET/CT				Histopathology		
	1	2	ΔSUV_{max}	M	1	2	M
1	Colon (8.9)	Kidney (1.6)	82.0%	Non	ACA	CCRC	Non
2	Esophagus (11.7)	Lung (2.8)	76.1%	>>	ESCC	LA	Non
3	Esophagus (14.0)	Lung (8.1)	42.1%	LN	ESCC	LA	WS
4	Lung (10.6)	Lung (5.4)	49.1%	>>	LA	LSCC	WS
5	Colon (11.8)	Kidney (1.8)	84.8%	>>	CA	CCRC	LN
6	Rectum (21.5)	Kidney (1.6)	92.6%	Non	RA	CCRC	Non
7	Liver (5.3)	Gastric (4.3)	18.9%	>>	HCC	GA	Non
8	Liver (12.4)	Gastric (3.9)	68.6%	>>	HCC	GA	Non
9	Breast (6.7)	Lung (0.9)	86.6%	LN	BIDC	LA	LN
10	Breast (7.4)	Lung (1.5)	79.7%	>>	BIDC	LA	LN
11	Esophagus (19.1)	Rectum (10.8)	43.5%	>>	ESCC	RA	WS
12	Colon (30.9)	Kidney (1.6)	94.8%	Non	CA	CCRC	LN
13	Thyroid (17.5)	Breast (9.9)	43.4%	LN	PTC	BIDC	LN
14	Esophagus (12.2)	Gastric (7.6)	37.7%	Non	ESCC	GA	Non
15	Esophagus (9.4)	Gastric (21.5)	56.3%	LN	ESCC	GA	WS
16	Lung (1.1)	Lung (0.8)	27.3%	Non	LSCC	LA	Non
17	Breast (4.9)	Lung (2.8)	42.9%	>>	BIDC	LA	LN
18	Gastric (2.5)	Pancreas (3.6)	30.6%	>>	GA	PDA	Non
19	Esophagus (14.0)	Lung (9.5)	32.1%	>>	ESCC	LA	LN

Note: BIDC, breast invasive ductal carcinoma; CA, colon adenocarcinoma; CCRC, clear cell renal carcinoma; ESCC, esophageal squamous cell carcinoma; GA, gastric adenocarcinoma; HCC, hepatocellular carcinoma; LA, lung adenocarcinoma; LN, lymph node; LSCC, lung squamous cell carcinoma; M, metastasis; PDA, pancreatic ductal adenocarcinoma; PTC, papillary thyroid carcinoma; RA, rectal adenocarcinoma; SUVmax, the maximum of standardized uptake value; WS, without surgery.

Synchronous primary malignancies that were ^{18}F-FDG avid were identified incidentally in all 19 patients by PET/CT. This resulted in directing of treatment plan in these patients as operation was recommended for patient with SMPC not having metastases. Local lymph node metastases alone were detected in 8 patients by PET/CT imaging. Metastases in 4 patients confirmed by pathology (Table 2 and Figure 1). All four patients had 2 synchronous cancers, 3 patients had invasive ductal carcinomas in the left breast, accompanying left axillary lymph node metastasis, while the other patient had right colon carcinoma and clear cell renal carcinoma complicated with right paracolic lymph node metastasis. In another four patients, lymph node metastases were identified by PET/CT imaging because they were not operated; they also had 2 synchronous cancers which were confirmed by gastrointestinal endoscopy or bronchoscopy. The lymph nodes carrying metastasis of these four patients were located in the mediastinum (n=3) and in the left supraclavicular fossa (n=1).

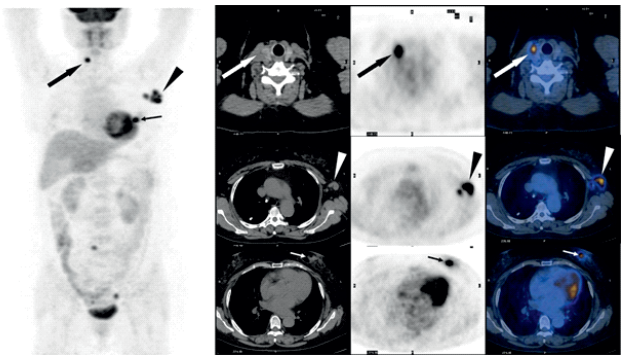

Figure 1. ^{18}F-FDG PET/CT images of a 57 years old woman with papillary carcinoma in the right lobe of the thyroid gland, invasive ductal carcinoma in the left breast lymph node metastasis in the left axilla, all of which were diagnosed by pathology. In order, from left to right are: PET-MIP, CT, PET and PET/CT fused images. The CT image shows a low-density nodule in the upper pole of the right lobe of the thyroid (upper row) and a soft-tissue-density nodule in the medial quadrant of the left breast (middle row) with multiple lymphadenectasis in the left axillary fossa (lower row). The PET and PET/CT fusing images show intensively increased metabolic activities in both nodules of the thyroid (wide arrows) and of the left breast (arrowheads), with SUVmax being 17.5 and 9.9 respectively. The ΔSUVmax between the two lesions is 43.4%. The multiple lymphadenectasis in the left axillary fossa (thin arrows) also exhibits increased metabolic activity with a SUVmax of 15.7.

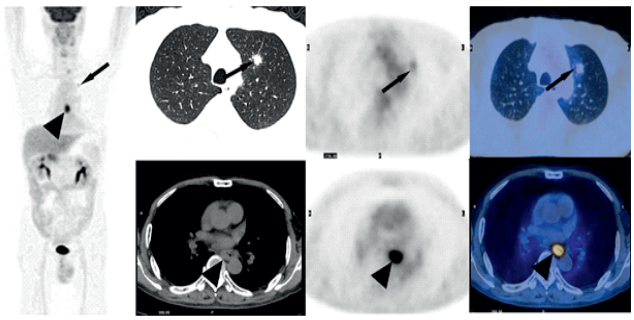

Figure 2. ^{18}F-FDG PET/CT images of a 69 years old man with a diagnosed by pathology, poorly differentiated adenocarcinoma in the anterior segment of upper lobe of the left lung and squamous-cell carcinoma in the mid-thoracic esophagus without metastasis. From left to right are: PET-MIP, CT, PET and PET/CT fused images. The nodule in the lung has irregular margin, lobulated shape and surrounding speculations (arrows) on the high resolution CT (up row). Wall thickening of the mid-thoracic esophagus (arrowheads) can also be seen on the CT image (down row). The PET and PET/CT fused images show that the nodule in left lung and the mass in the esophagus are ^{18}F-FDG hypermetabolic with SUVmax 2.8 and 11.7, respectively. The ΔSUVmax between the two lesions is 76.1%.

Discussion

In 1889, Billroth [13] published for the first time the clinical case of a patient with two primary malignant tumors, comprising a spinocellular carcinoma in the right ear and a gastric carcinoma. Not until 1932 was MPC first defined by Warren and Gates [14].

In different countries or districts, synchronous cancers may involve different organs or systems and thus present with different characteristics [15]. Therefore, our study helps in comprehensively understanding the variegated phenotypes of SMPC. We found that the SMPC were predominantly located in the digestive and less in the respiratory system. These findings are consistent with two other studies conducted in Japan and China [4, 16]. To explain this phenomenon, the well-known concept of "field cancerization" could be cited [17, 18], namely, the mucous epithelium in areas of the head, neck, lung, and esophagus is relatively more frequently exposed to common carcinogenic agents and thus results in a high prevalence of multiple carcinomas in these regions. In addition, cigarette smoking and alcohol consumption induced malignancies may also partially contribute to the high prevalence of MPC in these areas [19-20].

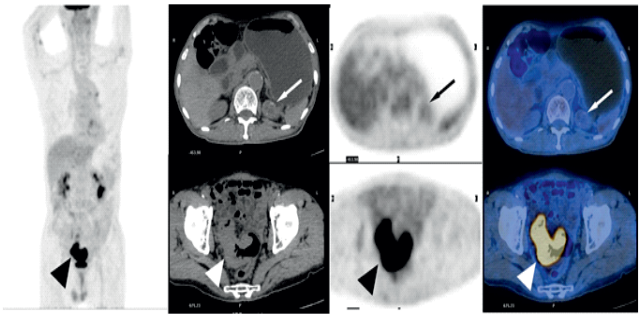

Figure 3. ^{18}F-FDG PET/CT images of an 80 years old man with a diagnosed by pathology adenocarcinoma in the junction of rectum and sigmoid colon and clear cell carcinoma in the left kidney. From left to right are: PET-MIP, CT, PET and PET/CT fused images. On CT image, calcification in the left kidney (up row) and wall thickening of colon in the junction of the rectum and sigmoid colon (down row) can be seen. The PET and PET/CT fused imaging shows that the mass in left kidney is ^{18}F-FDG hypometabolic (arrows) with SUVmax 1.6, whereas the mass in the junction of the rectum and sigmoid colon is ^{18}F-FDG hypermetabolic (arrowheads) with SUVmax 21.5. The ΔSUVmax between the two lesions is 92.6%.

Timely identification of SMPC has great clinical significance, as it may alter treatment plan [11]. There have been several investigations on the utility of ^{18}F-FDG PET/CT in the detection of MPC, advocating that ^{18}F-FDG PET/CT is indispensable in detecting synchronous primary cancers [10, 11]. Sun et al (2010) [4] reported that the sensitivity, specificity, accuracy, negative predictive value and positive predictive value of ^{18}F-FDG PET/CT in detecting MPC in the upper gastrointestinal tract were 90.9%, 85.7%, 89.4%, 80% and 93.7%, respectively. Chen et al (2013) [21] reported that the sensitivity of ^{18}F-FDG PET/CT in detection of SMPC was 88.2%, which was significantly higher than that of conventional imaging modality (sensitivity, 52.9%). Hiraoka et al (2013) [10] found that ^{18}F-FDG PET/CT could improve the detection rate of synchronous neoplasms in hepatocellular carcinoma. However, these studies were limited in discussing multiple primary malignant tumors in the upper gastrointestinal tract [4, 11, 21]. In the present study, we also found SMPC involving the lung (10/38), the breast (4/38) and other organs, beside those in the upper gastrointestinal tract. This may supplement recognition of the diversity of SMPC.

Compared to conventional imaging modalities like US, CT and MRI, the main advantage of ^{18}F-FDG PET/CT relies on the fact that it is commonly whole-body imaging, which allows

all tissues and organs to be evaluated in a single-step examination. Thus, ^{18}F-FDG PET/CT could be used as a screening tool for detecting asymptomatic malignancies at an early stage [9, 21], which may bring to the patients the potential of a survival benefit [21]. Meanwhile, ^{18}F-FDG PET/CT played an important role in preoperative staging, in treatment selection of SMPC. In our study, most of the SMPC were of an early stage without lymph nodes metastases or distant metastases. Sun et al (2010) [4] reported that clinical treatment plans had changed in 11 (11/15) patients of SMPC because of ^{18}F-FDG PET/CT examination. In this study, the management of all patients had been changed because of the PET/CT examination.

Maximum standardized uptake value is commonly used as semi-quantitative index in differentiating malignancies from benign lesions in ^{18}F-FDG PET/CT imaging, with ≥2.5 being most commonly used as the cutoff value [22]. However, some authors advocated that SUVmax did not reliably differentiate benign lesions from pre-malignant ones [23-24]. In this study, 8 malignant lesions were hypometabolic in ^{18}F-FDG PET imaging with SUVmax<2.5. For these lesions, CT greatly contributed to the final diagnosis. The CT signs in the lung that always indicate malignancy are the irregular margin, a circumstance full of spicules, a lobulated shape, irregular cavity, signs of bronchiole inflation and/or of pleural indentation [25].

Of note is ΔSUVmax, which is helpful in distinguishing SMPC from metastases. Dijkman BG et al (2010) [12] revealed that the ΔSUVmax was significantly higher in patients with SMPC than in those with metastatic diseases, and proposed an optimal cut-off for ΔSUVmax of more than 41% in distinguishing SMPC patients from those with metastases. In our study, ΔSUVmax of 14 (73.7%) patients was higher than 41%, which was partially supported by a previous study [12]. This phenomenon might be explained by the fact that tumors of different pathology tend to have different patterns of ^{18}F-FDG metabolism.

In conclusion, we found SMPC were most commonly in the gastrointestinal tract and adenocarcinomas were the most common type of cancer. Fluorine-18-FDG PET/CT played a useful role in diagnosing SMPC and the ΔSUVmax showed that synchronous cancers were of different type.

Acknowledgment

This work is supported by: 1) the Scientific Research Foundation for Young Doctors of Zhongshan Hospital, Fudan University (Grant No.: 2015ZSQN05); 2) the foundation from Shanghai Municipal Commission of Health and Family Planning (Grant No.: 2013SY008); and 3) the National Natural Scientific Foundation of China (Grant No.: 81271608).

The authors declare that they have no conflicts of interest

Bibliography

1. Luciani A, Balducci L. Multiple primary malignancies. *Sem Oncol* 2004; 31: 264-73.
2. Stalker LK, Philips RB, Pemberton J. Multiple primary malignant lesions. *Surg Gynec Obstet* 1939; 68: 595-602.
3. Moertel CG, Dockerty MB, Baggenstoss AH. Multiple primary malignant neoplasms: introduction and presentation of data. *Cancer* 1961; 14: 221-30.
4. Sun L, Wan Y, Lin Q et al. Multiple primary malignant tumors of upper gastrointestinal tract: A novel role of ^{18}F-FDG PET/CT. *World J Gastroenterol* 2010; 16: 3964-9.
5. Cunliffe WJ, Hasieton PS, Tweedie DE et al. Incidence of synchronous and metachronous colorectal carcinoma. *Br J Surg* 1984; 71: 941-3.
6. Beyer T, Townsend DW, Brun T et al. A combined PET/CT scanner for clinical oncology. *J Nucl Med* 2000; 41: 1369-79.
7. Barber TW, Duong CP, Leong T et al. ^{18}F-FDG PET/CT has a high impact on patient management and provides powerful prognostic stratification in the primary staging of esophageal cancer: a prospective study with mature survival data. *J Nucl Med* 2012; 53: 864-71.
8. Ishimori T, Patel P, Wahl R. Detection of unexpected additional primary malignancies with PET/CT. *J Nucl Med* 2005; 46: 752-7.
9. Agress HJr, Cooper BZ. Detection of clinically unexpected malignant and premalignant tumors with whole-body FDG PET: histopathologic comparison. *Radiology* 2004; 230: 417-22.
10. Hiraoka A, Hirooka M, Ochi H et al. Importance of screening for synchronous malignant neoplasms in patients with hepatocellular carcinoma: impact of FDG PET/CT. *Liver Int* 2013; 33: 1085-91.
11. Malik V, Johnston C, Donohoe C et al. ^{18}F-FDG PET-Detected Synchronous Primary Neoplasms in the Staging of Esophageal Cancer Incidence, Cost, and Impact on Management. *Clin Nucl Med* 2012; 37: 1152-8.
12. Dijkman BG1, Schuurbiers OC, Vriens D et al. The role of 1^{8}F-FDG PET in the differentiation between lung metastases and synchronous second primary lung tumors. *Eur J Nucl Med Mol Imaging* 2010; 37: 2037-47.
13. Billroth T. Allgemeine chirurgie pathologie UHD therapie. *Reimer* 18-89: 908.
14. Warren S, Gates O. Multiple primary malignant tumors. *Am J Cancer* 1932; 10: 1358-414.
15. Chirila DN, Turdeanu NA, Constantea NA et al. Multiple malignant tumors. *Chirurgia* 2013; 108: 498-502.
16. Kumagai Y, Kawano T, Nakajima Y et al. Multiple primary cancers associated with esophageal carcinoma. *Surg Today* 2001; 31: 872-6.
17. Poon RT, Law SY, Chu KM et al. Multiple primary cancers in esophageal squamous cell carcinoma: incidence and implications. *Ann Thorac Surg* 1998; 65: 1529-34.
18. Van Westreenen HL, Westerterp M, Jager PL et al. Synchronous Primary Neoplasms Detected on ^{18}F-FDG PET in Staging of Patients with Esophageal Cancer. *J Nucl Med* 2005; 46: 1321-5.
19. Day GL, Blot WJ. Second primary tumors in patients with oral cancer. *Cancer* 1992; 70: 14-9.
20. Lin Y, Totsuka Y, He Y et al. Epidemiology of esophageal cancer in Japan and China. *J Epidemiol* 2013; 23: 233-42.
21. Chen S.H, Chan S., Chao Y.K et al. Detection of synchronous cancers by fluorodeoxyglucose positron emission tomography/computed tomography during primary staging workup for esophageal squamous cell carcinoma in Taiwan. *PLoS One* 2013; 8: e82812.
22. Wainer Z, Daniels M.G, Callahan J et al. Sex and SUVmax: sex-dependent prognostication in early non–small cell lung cancer. *J Nucl Med* 2012; 53: 1676-85.
23. Gutman F, Alberini JL, Wartski M et al. Incidental colonic focal lesions detected by FDG PET/CT. *Am J Roentgenol* 2005; 185: 495-500.
24. Yasuda S, Fujii H, Nakahara T et al. ^{18}F-FDG-PET detection of colonic adenomas. *J Nucl Med* 2001; 42: 989-92.
25. Xue XY, Xue QL, Wang N et al. Early clinical diagnosis of synchronous multiple primary lung cancer. *Oncol Lett* 2012; 3: 234-7.