Screening May Not Be Accurate Word to Represent the Cases Submitted to PET/CT Evaluation for Primary Tumor in a Patient Who Has Abnormal Serum Tumor Marker

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Objective: *Determine the value of PET/CT in unknown primary cancer patient with high tumor marker and negative study for clinical and conventional imaging.*
Material and Method: *A retrospective database review of 417 patients who received PET/CT between July 2006 and August 2007 in National cyclotron and PET center at Chulabhorn cancer center was done. Patients were included in this study if the diagnosis were unknown primary cancer and rising tumor marker. Twelve patients were included in this study. Data included age, gender, tumor marker rising, anatomical imaging finding (CT and MRI), PET finding and clinical follow-up.*
Results: *Nine cases had normal PET/CT. This showed that PET/CT does not get more information than conventional imaging. The PET scan showed positive in three cases, #5, #6 and #10. Two cases were false positive, #5 and #6. Case #5 had clinical follow-up for one year and revealed to be normal. Case #6 PET showed markedly glucose avid lesion at tumor thrombus but contrast CT confirm blood clot and the patient was treat with wafarin and claxane. The follow-up clinical showed improvement. The high serum CA 125 explained by lung infarction caused the false positive. In case#10, the PET/CT suggested lung cancer at basal segment of LLL.*
Conclusion: *Screening ^{18}F FDG PET/CT is not appropriate in unknown primary with rising tumor marker and normal conventional imaging is required.*

Keywods: *Screening ^{18}F FDG PET/CT, Rising tumor marker*

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Present-day medical practice generally assumes that early detection of cancer offers the best chance of a good outcome. Finding a cancer in an asymptomatic person provides more treatment options, offers a better prognosis, curative treatment, increased life quality, and cuts down on expenses compared with the cost incurred when cancers are detected at later stages. To detect cancers at an early stage, self-referral for mammography, routine or virtual colonoscopy, sigmoidoscopy, Pap smear screening, prostate-specific antigen testing, and measurements of other tumor-specific markers have been actively recommended by consensual medical opinion. There has also been some continuing debate as to the value of these measures. Serum tumor markers represent a class of tests that can serve as adjuncts in defining the source of metastasis

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tumor. Serum tumor markers are tumor derived and are shed into the bloodstream. These markers can be detected in peripheral blood specimens by commercially available assays. Although most markers lack adequate specificity for determining the site of the primary, their use with the pathologic and clinical information may be helpful in diagnosing the cause of the primary. The most commonly used Serum tumor markers and their corresponding primaries are listed in Table 1.

It is worthwhile to note that an isolated elevation is not a diagnostic and does not predict response to therapy. Elevations in tumor markers must be interpreted with the complete clinical picture and should only be used in specific situations in which the clinicopathologic data support their use.

The primary goal of an efficient tumor screening is to reduce overall patient mortality by detecting early stages of malignant diseases that are accessible to curative therapy or potentially have a better outcome in the case of a palliative approach. The secondary goal is to increase the quality of life of the patient and decrease the costs for the health care system through shorter and more efficient patient management.

This is principle underlying cancer detection by glucose analogue ^{18}F-fluoro-2-deoxy-D-glucose (FDG). Increased FDG accumulation in neoplastic tissues is a function of increased expression and activity of glucose transporter proteins and the glucose phosphorylating enzyme hexokinase. This result from an increased anaerobic metabolism in cancer cells, as well as metabolic trapping of FDG within tumor cells due to the lack of further metabolic pathways for FDG[1]. The PET/CT combines the advantages of two modalities by giving anatometabolic information through a fusion of data provided by pathological tumor tracer uptake in the PET examination together with an accurate delineation of anatomical structures of spiral CT. The PET can also be used successfully in patients with unknown primary tumor[2].

Table 1.

Tumor marker	Differential diagnosis
Alpha-Fetoprotein	Hepatocellular, germ cell
β-HCG	trophoblastic, germ cell
CA15-3	breast, ovary, lung, gastrointestinal
CA19-9	pancreas, gastrointestinal
CA125	ovary, uterine, breast, lung
CEA	carcinoma versus mesothelioma

The available data suggest positive FDG-PET findings in about 1-2% of the screened population[3-5]. The characteristics of whole-body ^{18}F FDG-PET seem to satisfy the requirements for cancer screening. Whole-body ^{18}F FDG-PET comes close to being an ideal modality for cancer screening in that it achieves high sensitivity without any apparent hazard. It also provides information on the extension of the cancer, because the primary tumor and metastatic foci can be detected simultaneously. To our knowledge, a few studies have reported the PET scan screening unknown primary cancer patient with high tumor marker level. The objective of our study was to determine the value of PET/CT in unknown primary cancer patient with high tumor marker and negative study for clinical and conventional imaging.

Material and Method

Patients

We retrospective reviewed the data of 417 patients that had PET/CT between July 2006 and August 2007 in National cyclotron and PET center at Chulabhorn cancer center. Patients are included in this study if the diagnosis were unknown primary cancer and rising tumor marker. Twelve inclusion patients were reviewed. Age, gender, tumor marker rising, anatomical imaging finding (CT and MRI), PET finding, and clinical follow-up were analyzed.

Imaging

All patients fasted for at least 6 hours before the PET/CT study. An average of 10 mCi of ^{18}F FDG was injected intravenously and scanning began 50 minutes later. None of the patient had blood glucose level exceeding 150 mg/ml before activity injection. No contrast agent was used for CT Image. A combined PET/CT (Biograph LSO, Siemen Medical Solution) was used to acquire all data. There were 6-8 bed positions and the acquisition time was 3 minutes per bed position.

Interpretation

All PET/CT images were reviewed at a work-station with fusion software that provided multiplannar reformatted images and displayed PET image before and after attenuation correction, CT images, and PET/CT fusion images.

Results

The result showed nine cases of normal PET/CT. This showed that PET/CT does not get more information than conventional imaging. Three cases

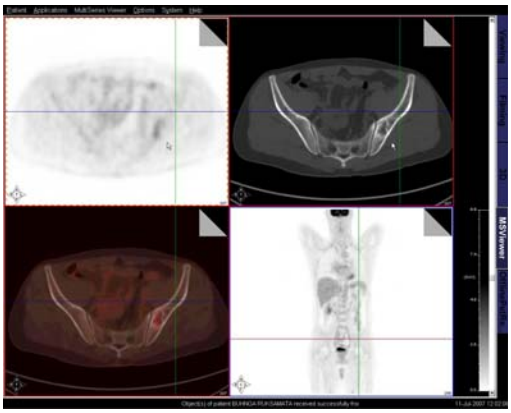
were PET positive, case #5, case #6, and case #10. There were two cases of false positive, case #5 and case #6. There was one case of true positive, case #10. PET/CT suggested lung cancer at basal segment of LLL. Unfortunately, we did not have the tissue confirmation. However, PET/CT information can be used to guide for tissue diagnosis. This case had very high tumor marker all the information shows in Table 2.

Discussion

Due to our small and limited clinical data, PET/CT scan did not give more information for unknown primary patient with rising tumor marker than normal conventional imaging in nine of 12 cases (75%). Two cases out of 12 patients were false positive (16.67%). In one patient (8.33%), the PET/CT provided guidance to find tissue confirmation of lung cancer. The results of this study indicate that it is inappropriate to use tumor marker testing and PET/CT as a tool for searching primary tumor except in case of very high tumor marker. PET/CT should be indicated for patient with primary tumor for initial staging, detection of distant metastasis, detection of recurrence tumor, or evaluation of treatment response. There are other indications to predict malignant pulmonary nodule or patient with lymphadenopathy besides the unknown primary. Despite the excellent sensitivity of PET/CT in tumor detection, interpretative pitfalls must be taken into account. The PET-negative cases can be attributed to the following four reasons:

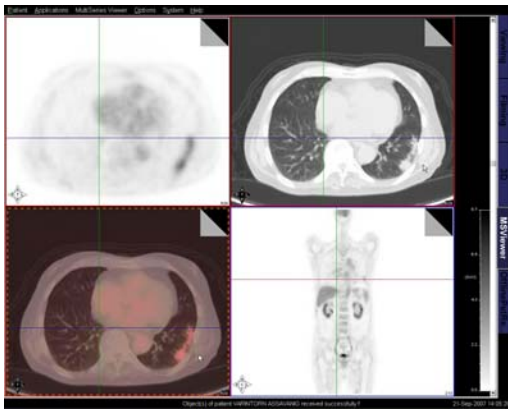
Table 2. Demonstrate the result of our study point of view age, sex, tumor marker rising, conventional imaging finding and PET/CT finding. Nine cases of negative PET/CT result and 3 cases of positive PET/CT results and the positive PET/CT images were shown in the image finding after this

Patient, age (yr)	Clinical	Tumor marker	Anatomical imaging	PET finding
1. Male, 70	FUO 2 months	CEA 12.1 CA 19.9 215.7	CT whole body: normal	PET/CT normal
2. Female, 56	Healthy	CEA 12.8 CA 125 42.6	CT chest and whole abdomen: normal	PET/CT normal
3. Male, 82	Healthy	CEA 25	CT chest and whole abdomen: normal	PET/CT normal
4. Female, 45	Healthy	AFP 10 CA 19.9 80	MRI upper abdomen: normal	PET/CT normal
5. Male, 45	Healthy	AFP 8.6	MRI abdomen: normal	Mildly increased uptake at left iliac bone (CT lytic and sclerotic) (Fig. 1)
6. Female, 52	Pulmonary embolism	CA 125 56.73	CXR, U/S abdomen: normal	Increased activity at right pulmonary thrombus Mild rt. lung increased uptake at right upper lung with thick wall cavity Normal and mildly increased activity at right lower lung mass (Fig. 2)
7. Male, 79	Healthy	CA 19-9 70.02	Barium enema: normal	PET/CT normal
8. Female 56	Gastritis	CA 19-9 85.93		PET/CT normal
9. Male 73	Healthy	CEA 10.1ng/ml, PSA 37 mg/ml		Increased uptake right parotid
10. Male 68	Healthy	AFP 388.59 IU/ml, CA19.9 102.60	CT whole abdomen: normal	Moderate glucose avid lesion in speculated nodule in periphery of lateral basal segment of LLL
11. Male 63	Healthy	CEA 8	CXR, CT abdomen, Gastroscope, Bronchoscope, Colonoscope: normal	PET/CT normal
12. Female 60	Healthy	CEA 8	Colonoscope, Mammogram: normal	PET/CT normal



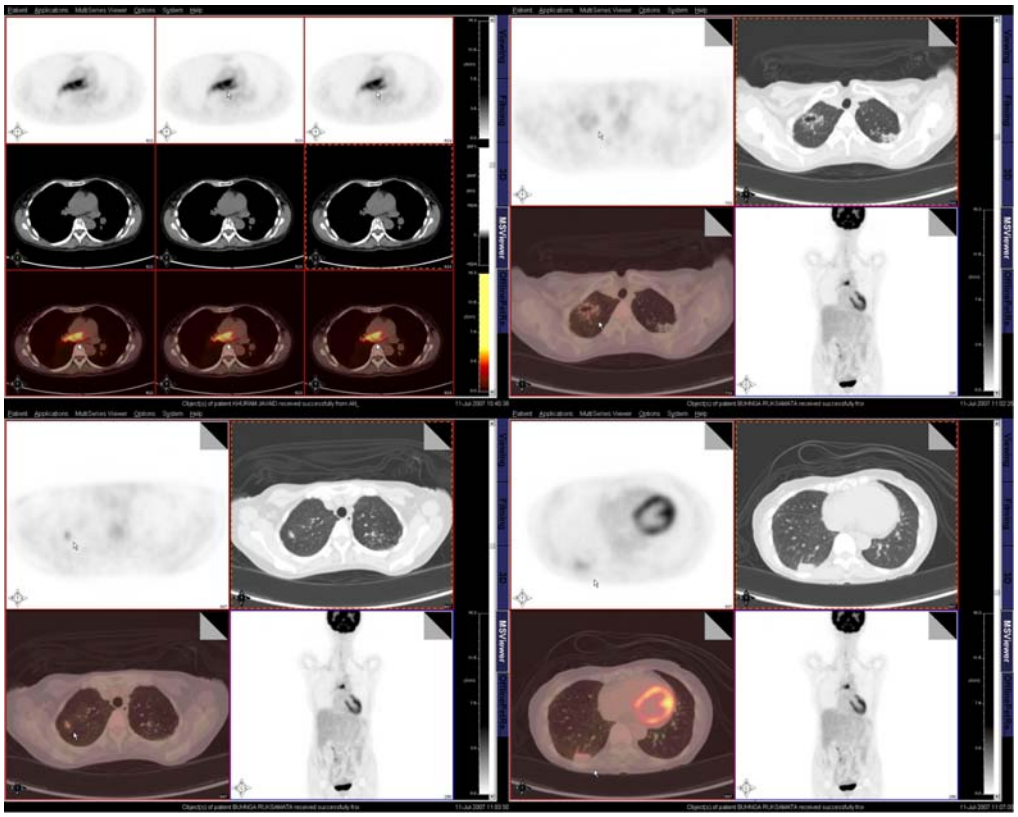
The PET/CT image of 45 years old male reveals mild increased glucose activity correspond osteolytic and sclerotic left iliac bone (arrow sign) and clinical follow-up 1 year reveals no detectable abnormality

Fig. 1 Case #5



The PET/CT reveals increased glucose avid lesion in spiculate nodule (arrow sign) at periphery lateral segment of left lower lung suggestive of lung cancer

Fig. 3 Case #10



The PET/CT show markedly glucose avid lesion at pulmonary thrombus and contrast CT confirm blood clot with mild increased glucose activity in pulmonary infiltration right upper lung and pulmonary nodules at right upper and right lower lung. The patient was treated with wafarin. Follow up clinical is improvement. The high serum CA 125 explained by lung infarction cause of false positive

Fig. 2 Case #6

(1) High urinary tract activity: Renal excretion of FDG may hamper the detection of urological cancers and lesions in the pelvic cavity

(2) Cancers of low cell density: signet ring cell cancer of the stomach and the scirrhous type of breast cancer

(3) Hypometabolic or FDG-negative cancers: lung cancer such as bronchoalveolar and well-differentiated lung adenocarcinomas and malignant hepatoma[6]

(4) Small cancers: The spatial resolution of the PET camera is around 6 mm[7] and in tumor smaller than twice the resolution, the sensitivity is decreased due to partial volume effects. Tumors smaller than 10 mm in diameter are difficult to detect.

The PET/CT can give false positive in metabolically active but benign conditions involving inflammation or infection (*e.g.*, tuberculosis granulomas, coccidioidomycosis, or aspergillosis). In addition, physiologically increased FDG uptake is observed in brown fat or muscle tissue due to patient motion or speech activity (typically in the tongue base) during patient preparation. Furthermore, tracer accumulations in the urinary tract or due to bowel muscle activity may impair diagnostic performance. The PET/CT specific pitfalls may occur when different breathing patterns are used for PET and CT image acquisition. This can lead to a misregistration of structures located near the diaphragm, such as pulmonary nodules in the lower lung fields or lesions in upper liver segments. It has been reported that high-density contrast agents or metallic objects can lead to "hot spot" artifacts by overestimating PET activity when the CT data are used for attenuation correction. However, these artifacts could be recognition by analyzing the uncorrected images. False-positive lung FDG uptake has also been attributed to pulmonary infarction secondary to pulmonary embolus[8].

With specific reference to the thorax and supraclavicular areas, low-level activity may be seen in the thyroid gland, breast, and mediastinal blood pool. Talking commonly gives rise to laryngeal uptake, while physical activity (or simply anxiety) can cause uptake within muscle groups such as the sternocleidomastoids. Tumor marker higher than normal value in your blood or urine may suggest cancer. However, tumor marker test results need to be interpreted carefully, as non-cancerous conditions also can cause abnormal results. For example, CEA can be elevated with other non-cancerous diseases such as cirrhosis, inflammatory bowel disease, chronic lung disease, and pancreatitis. CA125 can be elevated during menstruation, pregnancy endometriosis or in individuals with ovarian cysts, pericarditis, hepatitis, cirrhosis of the liver or peritonitis, an infection of the lining of the abdomen, and even in 1-2% of healthy individuals. CA 15.3 values are often elevated in patients with breast cancers. Besides breast cancer, other non-malignant conditions (*e.g.*, cirrhosis, benign diseases of ovaries & breast) have also been known to cause elevated CA 15.3 levels. Alpha fetoprotein (AFP) levels are often elevated in liver cancers (hepatocellular) and testicular cancers (non-seminomatous). Raised levels are also present during pregnancy or some gastrointestinal cancers.

Review article for PET/CT scan for screening cancer

Michiru Ide et al presented that malignant tumors were discovered in 526 participants (1.35%) when 39,785 (23,431 male and 16,354 female, average age 53.6 years) patients received a cancer screening PET scan[9]. There were 358 PET-positive cases and 168 PET-negative cases. Most of the thyroid, lung, colon and breast cancers were PET positive, but the prostate, liver, renal, and bladder cancers were generally PET negative. PET-negative cancers were detected by conventional methods such as computed tomography, ultrasound, magnetic resonance imaging, and tumor-specific markers.

Among the 3631 FDG-PET (including 1687 PET/CT) ultrasound and tumor markers examinations, malignant tumors were discovered in 47 examinees (1.29%)[10].

PET findings were true-positive in 38 of the 47 cancers (80.9%). Thirty-two of the 47 cancers were screened with the PET/CT scan. PET detected cancer lesions in 28 of the 32 examinees. However, the CT detected cancer lesions in only 15 out of 32 examinees. Most cancer can be detected with FDG-PET at a resectable stage.

Yasuda S et al[11] study of 1,105 healthy subjects that undergone 1,138 PET scan in fifteen months shows that malignant tumors were detected with PET in nine patients (0.81%) (2 lung cancers, 2 colonic cancers, 1 breast cancer, 1 thyroid cancer, 1 gastric cancer, 1 renal cancer and 1 lymphoma). Eight of these patients underwent surgery (excepting the lymphoma patient). Lymph node metastasis was not observed in any of the eight cases and surgery was curative. PET scan results were negative in the cases of three prostatic cancers, one bladder cancer, and two colonic mucosal cancers. High FDG accumulations were noticed in benign lesions such as sarcoidosis,

chronic thyroiditis, pulmonary tuberculoma, Warthin's tumor of the parotid gland, and chronic sinusitis.

The incidences of malignant tumor detection on screening with PET/CT from the review articles vary between 0.81% and 1.35%. In our study, malignant lesion in patients with rising tumor marker and normal anatomical imaging were detected at 8.33%.

Radiation protection

The effective dose of FDG-PET can be estimated at about 10 mSv, when 370 MBq is injected[12]. According to the International Commission on Radiation Protection (ICRP), the risk of radiation-induced cancer is as high as 5/10,000 for an effective dose of 10 mSv[13]. Although these figures are estimates only, they are widely used in radiation protection. Applying these data to FDG-PET screening, one radiation-induced cancer is to be expected with 2,000 FDG-PET studies. If only 1-2% of these studies are positive, this means one additional cancer for every 20 to 40 cancer detected. This risk can only be accepted if a benefit for the majority of patients has clearly been demonstrated. Performing FDG-PET as a screening test in healthy persons is not legally possible in many countries.

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การตรวจ ^{18}F FDG PET/CT ในผู้ป่วยที่มีระดับ tumor marker สูง โดยการตรวจโดยทั่วไปยังไม่ทราบตำแหน่งของมะเร็งมีความเหมาะสมหรือไม่

สุนันทา เชี่ยววิทย์, สายเพชร ผาสุข, สาวิตรี สุราทะโก, วรรณธนะ จุ้ยกล่อม, พิพัฒน์ เชี่ยววิทย์

วัตถุประสงค์: *เพื่อประเมินความเหมาะสมของการตรวจ ^{18}F FDG PET/CT ในผู้ป่วยที่มีระดับ tumor marker สูง โดยการตรวจโดยทั่วไปยังไม่ทราบตำแหน่งของมะเร็ง*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลังในผู้ป่วยจำนวน 417 รายที่มารับการตรวจ ^{18}F FDG PET/CT ที่ศูนย์ไซโคลตรอนและเพทสแกนแห่งชาติ สถาบันวิจัยจุฬาภรณ์ ตั้งแต่ มิถุนายน พ.ศ. 2549 ถึง สิงหาคม พ.ศ. 2550 ทีสถานวิจัยบำบัดมะเร็ง มีผู้ป่วยจำนวน 12 ราย ที่มีระดับ tumor marker สูง และการตรวจ โดยทั่วไปไม่พบว่าเป็นมะเร็ง ทำการพิจารณาเกี่ยวกับ อายุ เพศ ระดับ และชนิดของ tumor marker ผลการตรวจ CT, MRI, ^{18}F FDG PET/CT และการติดตามผู้ป่วย*

ผลการศึกษา: *ผู้ป่วย 9 ราย พบว่าการตรวจ ^{18}F FDG PET/CT ให้ผลปกติดังนั้นการตรวจ ^{18}F FDG PET/CT ให้ข้อมูลเท่ากับการตรวจโดยทั่วไปผู้ป่วย 3 ราย ให้ผลบวกจากการตรวจ ^{18}F FDG PET/CT คือผู้ป่วยรายที่ 5, 6 และ 10 มีผลบวกลวง 2 ราย คือ ผู้ป่วยรายที่ 5 ติดตามเป็นระยะเวลาหนึ่งปีผู้ป่วยปกติ ผู้ป่วยรายที่ 6 ที่พบสารเภสัชรังสีในก้อนเลือดในปอดทำการรักษาด้วยยาละลายลิ่มเลือดแล้วผู้ป่วยอาการดีขึ้น การที่มีระดับ CA 125 สูงน่าจะเป็นผลบวกลวงจากภาวะการตายของปอด ผู้ป่วยรายที่ 10 เข้าได้กับมะเร็งที่ปอดล่างซ้าย*

สรุป: *การตรวจ ^{18}F FDG PET/CT ไม่เหมาะสมกับการตรวจผู้ป่วยที่มีระดับ tumor marker สูงและการตรวจโดยทั่วไปไม่พบว่าเป็นมะเร็ง*