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The role of 18F-FDG PET-CT in the detection of unknown primary malignancy: a retrospective study

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Background/aim: This study aimed to retrospectively evaluate the role of ^{18}F-FDG PET/CT imaging in the detection of unknown primary tumor sites in patients with a suspicious malignancy.

Materials and methods: We retrospectively examined the ^{18}F-FDG PET/CT images of 50 unknown primary malignancy patients. The malignancy of the lesions with increased ^{18}F-FDG uptake on PET images was defined by interpreting the nondiagnostic CT images that were obtained with the PET study. The primary tumor site was decided according to the combined PET/CT findings, and the results were subsequently confirmed with a histopathological examination.

Results: Fifty patients (29 M; 21 F) aged 18–85 years were included in the study. The sample included 32 malignant and 18 benign lesions according to the histopathological evaluation. ^{18}F-FDG PET/CT study accurately identified malignant lesions in 28 (average SUVmax ± SD: 8.27 ± 7.22) and benign lesions in 12 (average SUVmax ± SD: 3.63 ± 3.07) patients; these findings were histopathologically confirmed. PET/CT correctly detected the primary tumor site in 16 (50%) of 32 patients.

Conclusion: ^{18}F-FDG-PET/CT identified the primary tumor site well in 50% of our cases. We propose that ^{18}F-FDG PET/CT imaging may help to accurately detect malignant lesions in patients with unknown primary tumors.

Key words: Fluor-18 fluorodeoxyglucose, positron emission tomography/computerized tomography, unknown primary tumor, unknown malignancy, hypermetabolic lesions

1. Introduction

Unknown primary malignancies (UPMs) are histologically proven tumor metastases that lack evidence of a primary site. The early and rapid distribution of the disease, the clinical failure of the primary tumor diagnosis, and unexpected metastatic sites are the main features of UPM. Between 5% and 10% of all cancer patients are diagnosed with UPM; it is the tenth most frequent cancer and the fourth most common cause of cancer-related death (1,2). Despite the recent advances in diagnostic techniques, the diagnosis and treatment of patients with carcinoma of unknown primary origin remains a challenge in practice. Conventional imaging modalities may detect the site of the primary tumor in only 10%–35% of all cases. A histopathological analysis or even an autopsy examination may not identify a primary lesion (1–4). In this patient population, the diagnosis of the primary tumor site is often time consuming, costly, and complex. The low rate of detection of the primary cancer is attributed to the size of lesions, which are smaller than the spatial and contrast resolution of the techniques used for diagnosis, or to the involution of the primary mass due to limited angiogenic competence (5,6). Early and accurate diagnosis of the primary lesion dramatically changes survival of UPM patients. The median survival time for patients with UPM is short, almost 8 to 12 months; thus, the determination of the exact location of the tumor and prompt initiation of treatment can extend survival up to 23 months (3,7,8). Recently, whole body ^{18}F-FDG PET/ CT hybrid imaging has gained wide application in the diagnosis and follow-up of cancer patients. ^{18}F-FDG PET can accurately detect the primary lesion in 24%–53% of patients whose diagnoses were negative based on conventional diagnostic procedures (7,9–11). Initial studies of the diagnostic effect of ^{18}F-FDG PET/CT in UPM patients have revealed promising results. The aim of this study was to evaluate the role of ^{18}F-FDG PET/CT imaging in the detection of unknown primary tumor sites in patients with a suspicion of malignancy. We also intend to supplement the literature with the results of our experience.

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2. Materials and methods

We retrospectively examined ^{18}F-FDG PET/CT images of 82 consecutive patients with UPM whose test results were negative for conventional diagnostic procedures, including CT, MRI, mammography, and endoscopy. Despite the completion of comprehensive laboratory analyses for all patients, the primary site of malignancy could not be identified. A primary malignancy or at least one metastatic site or pathological lesion was histologically proven in only 50 patients. We analyzed only these 50 patients because the histopathological findings were used as the gold standard to evaluate the PET/CT results. The institution's Medical Ethics Review Committee approved the study protocol, and all patients provided written informed consent prior to the PET/CT imaging. A complete medical history and physical examination were performed for all patients. None of the patients had a history of cancer or received chemotherapy and/or radiation therapy prior to the ^{18}F-FDG PET/CT examination.

2.1. ^{18}F-flurodeoxyglucose PET/CT

Dual-modality PET/CT was performed using a Gemini TF TOF PET/CT scanner (Philips Medical Systems, USA). All of the subjects fasted for at least 6 h prior to imaging. The fasting blood glucose levels were measured prior to the F-18 FDG injection, and patients with glucose levels lower than 160 mg/dL received an intravenous injection of 3.7 MBq/kg ^{18}F-FDG. PET/CT scanning was performed 60 min after the injection of ^{18}F-FDG. Whole-body CT was performed using a 16-slice helical CT. The CT scan data were collected at 50–120 mAs and 90–140 kV and were adjusted to the patient's body weight. No intravenous or oral contrast material was used. After the CT scan, an emission scan was obtained from the head to the feet at a rate of 20–60 s per frame. The attenuation-corrected PET images with CT data were reconstructed using an ordered subset expected maximization (OSEM) algorithm (33 subsets, 3 iterations). Commercial software (Extended Brilliance Workspace, Philips Medical Systems) was used to accurately coregister the CT and PET scan data. The maximum standard uptake values (SUVmax) were calculated using the attenuation-corrected images, the amount of injected ^{18}F-FDG, the body weight of each patient, and the cross-calibration factors between the PET and the dose calibrator. Two experienced nuclear medicine physicians retrospectively visually and semiquantitatively reviewed the PET, noncontrast CT, and fused PET/CT images to locate the primary tumor. The nuclear medicine physicians were informed about the clinical background of patients, but were blinded to the results of the other conventional imaging procedures. The two physicians reached a consensus for all of the PET/CT results. On the PET images, the primary tumor assessment was based on the detection of focally increased glucose (^{18}F-FDG) metabolism with a SUVmax exceeding 2.5, whereas an enhanced mass or lymph node was the criterion for malignancy on nondiagnostic CT images. However, malignancy was not solely based on hypermetabolic ^{18}F-FDG findings; these lesions were also classified as malignant by evaluating the entire medical history, conducting a physical examination, conducting laboratory analysis of the patients, and correlating the nondiagnostic CT images that were simultaneously obtained with a PET study. The probable site of the primary tumor was identified based on the combined findings of PET and CT. All potential sites of the primary tumor described by PET/CT were subsequently confirmed by histopathological examinations. The rate of primary tumor detection was determined based on comparing the PET/CT and histopathological results. Ultimately, true and false positive as well as true and false negative findings were defined based on the histopathological results (Table 1). The diagnosis of malignancy by ^{18}F-FDG PET/CT, irrespective of known or unknown primary focus, was classified as true positive when it was proven to be a malignant lesion by histopathological evaluation.

3. Results

The 50 patients were aged 18–85 years (average ± SD: 61.64 ± 16.26 years); 29 were male and 21 were female. The clinical and histopathological data and the ^{18}F-FDG-PET/CT findings are reported in Table 1 according to the site of the primary tumor. The lesion localizations of 50 patients on ^{18}F-FDG PET/CT were evaluated (Table 2). The histopathological evaluation of all 50 patients identified 32 malignant and 18 benign lesions. The ^{18}F-FDG PET/CT accurately depicted the lesions as malignant or metastatic (Figure 1) in 28/32 (87%) patients (average SUVmax ± SD: 8.27 ± 7.22) compared with the histopathological findings. The PET/CT correctly detected the primary tumor site in 16 (50%) of 32 patients: in the lungs in three cases (# 6, 14, and 23); the lymph nodes (lymphoma) (#15 and 31), liver (# 12 and 22), stomach (# 5 and 20), and colon (# 4 and 21) in two cases; and the ovary (# 44), cerebrum (# 19), soft tissue (ganglioneuroma) (# 42), kidney (# 3), and endometrium (#30) in one case. However, PET/CT failed to identify the primary tumor site in 12 of the 32 patients (37.5%): the colon (Figure 2) in four cases (# 17, 18, 39, and 49); the stomach (# 10 and 50), skin malignancy (# 8 and 35), and malignant epithelial tumor of unknown origin in two cases (# 36 and 37); and the soft tissue malignancy (# 40) and a neuroendocrine tumor in one case (# 38). In the remaining 4 of the 32 patients who were histopathologically diagnosed as having a malignant lesion, PET/CT could not identify the malignant lesion or metastases (12.5%). Thus, our PET/CT results yielded a false negative in 4 patients (average SUVmax ± SD: 0.95 ± 1.10) (liver, lung, colon, and soft tissue in patient # 24, 28, 29, and 41, respectively).

Table 1. Details of the FDG PET/CT findings in the search for a primary (n = 50 patients).

No	Sex	Age	Histopathology	PET/CT	Results
1	M	46	Inflammation	Benign infectious nodule	TN
2	M	83	Infection	Infection and inflammation	TN
3	F	78	Renal cell cancer	Primary renal tumor	TP
4	M	73	Colon cancer (low differentiated)	Liver met lesions of colon cancer	TP
5	M	60	Gastric ca. (Sarcoma met.)	Gastric tumor	TP
6	M	67	Epithelial lung ca.	Malign lung tumor	TP
7	M	49	Benign lesion	Benign lesion	TN
8	F	60	Squamous cell ca. (skin)	Met. lesion of UPM	TP
9	M	40	Benign lesion	Benign	TN
10	F	73	met lesion of gastric ca.	Met.lesion of UPM	TP
11	F	45	Inflammation	Benign lesion	TN
12	F	38	Hepatocellular ca.	Primary liver tumor	TP
13	M	54	benign	Osteodegenerative findings	TN
14	M	66	Malign epithelial lung tumor	Primary lung tumor	TP
15	F	73	Lymphoma (NHL)	Lymphoma	TP
16	M	64	inflammation	Met. LNs of UPM	TN
17	M	53	Colon adeno ca. met.	Met. lesion of UPM	TP
18	F	66	Met. lesion (low differentiated colon tumor)	Met. lesion of UPM	TP
19	M	29	Glioblastoma	Primary brain tumor	TP
20	F	43	Gastric adeno ca.	Primary gastric tumor	TP
21	M	83	Met. of low differentiated colon tumor	Rectal tumor	TP
22	M	79	Hepatocellular ca.	Liver tumor and met LNs	TP
23	M	85	Lung adeno ca.	Primary lung tumor	TP
24	M	74	Met. of hepatocellular ca	Benign lesions	FN
25	F	18	Infection	infection	TN
26	F	77	Infection	Infection	TN
27	F	66	Benign lesions	Osteodegenerative findings	TN
28	F	47	Adeno ca. met (colon or lung)	Infection	FN
29	M	71	Colon adeno ca. met.	Infection	FN
30	F	74	Endometrium adeno ca.	Endometrium tumor	TP
31	M	69	Hodgkin disease	Lymphoma	TP
32	M	77	inflammation	Met. of UPM	FP
33	F	57	İnfectious disease	Malign disease	FP
34	M	51	İnfectious disease	Malign disease	FP
35	M	57	Met. lesion of squamous cell ca. (skin)	Met. lesion of UPM	TP
36	M	73	Malign epithelial tumor met.	Met. lesion of UPM	TP
37	F	79	Malign epithelial tumor met.	Met. lesion of UPM	TP
38	M	76	Neuroendocrine ca. met.	Met. lesion of UPM	TP
39	M	59	Colon adeno ca. met.	Met. lesion of UPM	TP
40	F	83	Soft tissue tumor met.	Met. lesion of UPM	TP
41	M	64	Liposarcoma	Benign infectious lesion	FN
42	M	18	Ganglioneuroma	Ganglioneuroma	TP
43	F	72	Benign lesion	Osteodegenerative	TN
44	F	56	Over ca.	Primary over ca. and met. lesions	TP
45	F	75	İnfectious disease	Lung malignancy	FP
46	M	42	Inflammation	Met. lesion	FP
47	F	53	Benign disease	Benign disease	TN
48	F	70	Inflammation	Malign disease	FP
49	M	51	met of colon adeno ca.	Met. lesion of UPM	TP
50	F	66	Gastric ca. met	Met. lesion of UPM	TP

F: female; M: male; TP: true positive; TN: true negative; FP: false positive; FN: false negative; met.: metastasis; LN: lymph node; UPM: unknown primary tumor; ca.: cancer.

Table 2. The patient numbers of malignant and benign results of the PET/CT and histopathological confirmation methods.

Histopathological evaluation		Malignant	Benign	Total
PET/CT evaluation	Malignant	28	12	40
	Benign	4	6	10
Total		32	18	50

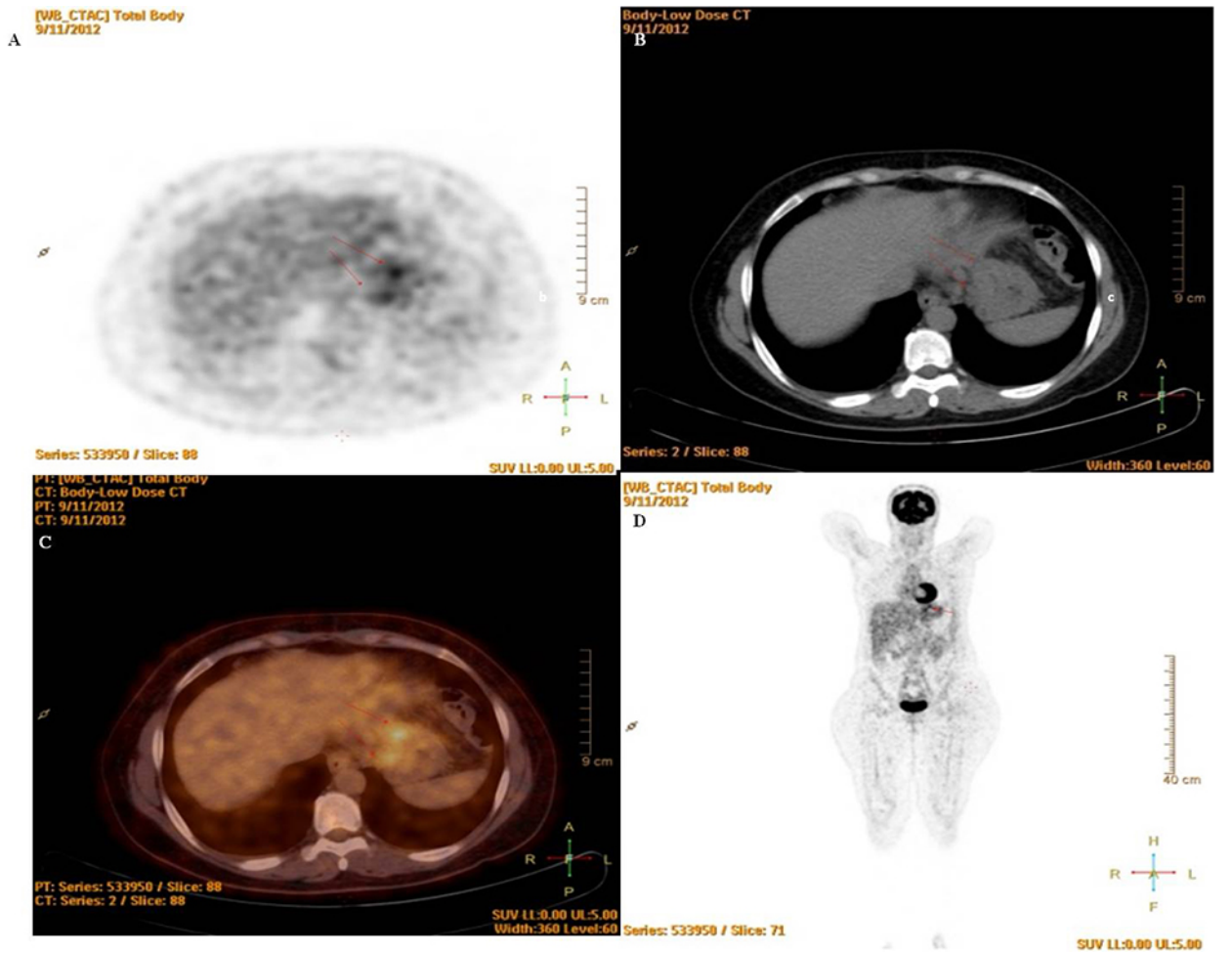

Figure 1. ^{18}F-FDG PET/CT transverse images of a 43-year-old woman (Patient number 20) with an unknown primary tumor. PET (A), CT (B), fusion (C), and MIP (D) images depict the primary tumor at the lesser curvature of the stomach with increased FDG uptake (SUVmax= 4.51), which was later confirmed at histopathologic examination as gastric adenocarcinoma.

The ^{18}F-FDG PET/CT accurately depicted lesions as benign (Figure 3) in 12 (67%) of 18 patients, with histopathological confirmation. In these 18 patients diagnosed with a benign lesion and the 12 true negative patients, the average SUVmax ± SD values were 3.95 ± 2.65 and 3.63 ± 3.07, respectively. In 6 of these 18 patients whose average SUVmax ± SD value was 4.52 ± 1.38, the PET/CT results yielded a false positive due to benign infectious and inflammatory cytomorphology (patient numbers are 32, 33, 34, 45, 46, and 48) based on histopathology (33%).

4. Discussion

Unknown primary malignancies include a heterogeneous group of malignant tumors that are generally accompanied by metastases. The clinical features of patients may widely vary and include enlarged lymph nodes anywhere in the body, hepatosplenomegaly, bone pain, or fever of unknown origin (1,2,12,13). Efforts to detect the primary tumor with conventional imaging methods in patients with UPM are often unsuccessful. This low success of detection prevents the initiation of effective

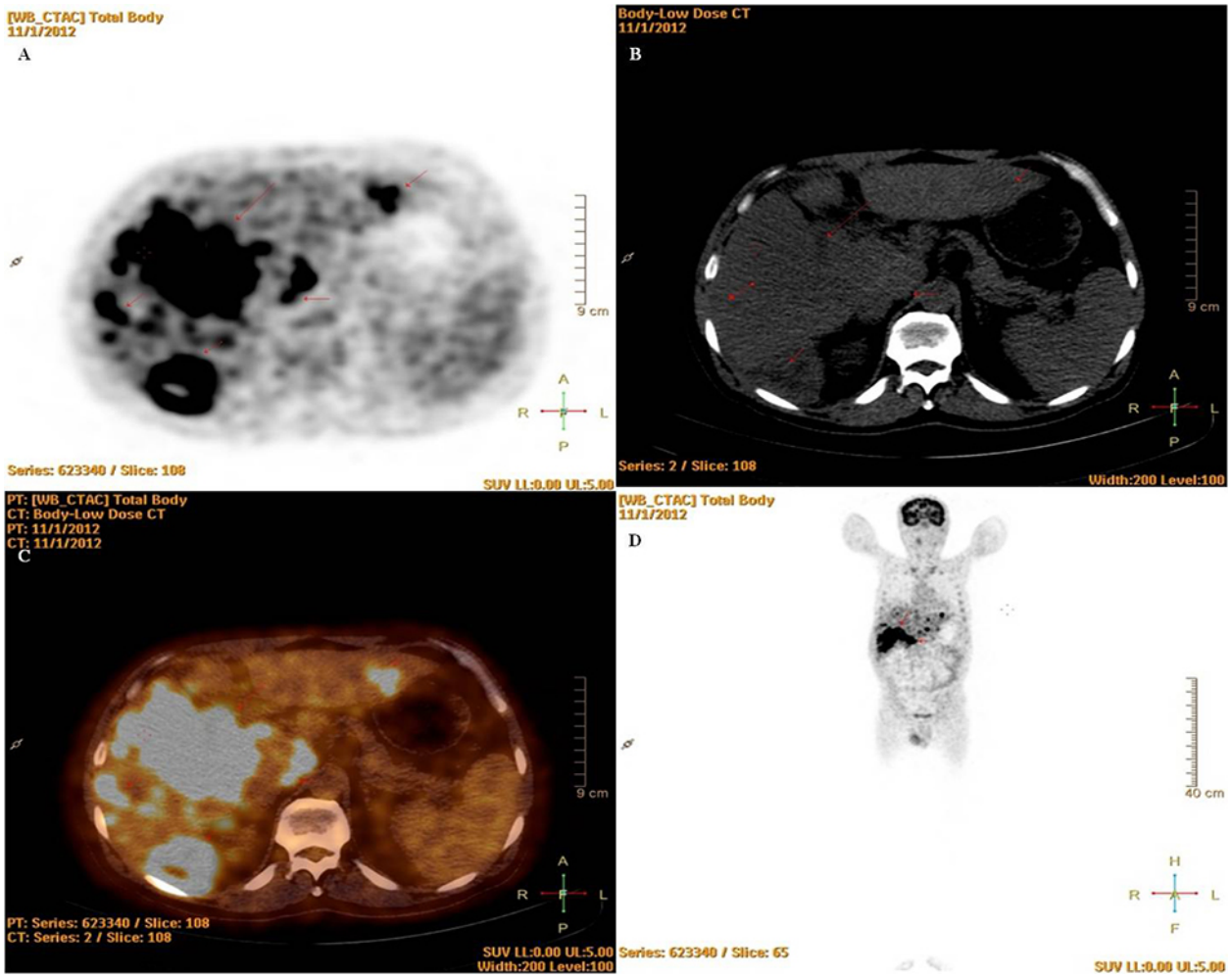

Figure 2. ^{18}F-FDG PET/CT images of a 53-year-old man (Patient number 17) who presented with multiple liver lesions. Transaxial PET (A), CT (B), fusion (C), and MIP (D) images demonstrate multiple hypodense lesions with pathologically increased FDG uptake (SUVmax = 17.84) in the liver and pathologically enlarged, hypermetabolic portal–precaval lymph nodes (SUVmax = 14.70). An excisional biopsy of the lesions and subsequent histopathological examination indicated metastatic colon adenocarcinoma.

treatment, which depends on tumor localization and differentiation. Although unknown primary malignancies are characterized by a poor prognosis, the identification of the primary tumor permits the initiation of more specific and effective treatments that improve survival. Therefore, the detection of the primary lesion significantly changes the prognosis and improves survival (10,14,15). In this study, ^{18}F-FDG PET/CT was able to conclusively identify 16 tumor sites among 32 primary malignant lesions, and these findings were confirmed by histopathological evaluation, which is accepted as the gold standard test. However, the detection rates reported in the literature significantly vary (24%–59%) (6–8,10,13,16–23). We herein report a relatively higher rate of detection (50%) of the primary tumor origin by ^{18}F-FDG PET/CT imaging as compared with many previous studies, which reported detection rates ranging from 24% to 45% (6,8,10,13,16,17,21–23). However, other previously published studies reported a similar rate of detection of the primary tumor origin (53%–59%) by ^{18}F-FDG PET/CT imaging (7,18–20). Another published article reported a significantly higher detection rate (73%) of the primary tumor origin by ^{18}F-FDG PET/CT as compared with our results and with those of other studies (24). This higher rate may be due to insufficient diagnostic work-up (such as medical history, physical examination, full blood count, blood biochemistry analysis, and conventional imaging methods). The results of another previously published systematic review and metaanalysis indicate that FDG-PET/CT study can detect 37% of primary tumors in patients with unknown primary tumors, which constitutes a rate lower than our detection rate (12). However, the results from the subgroup analysis may not be precise because of the small number of included studies.

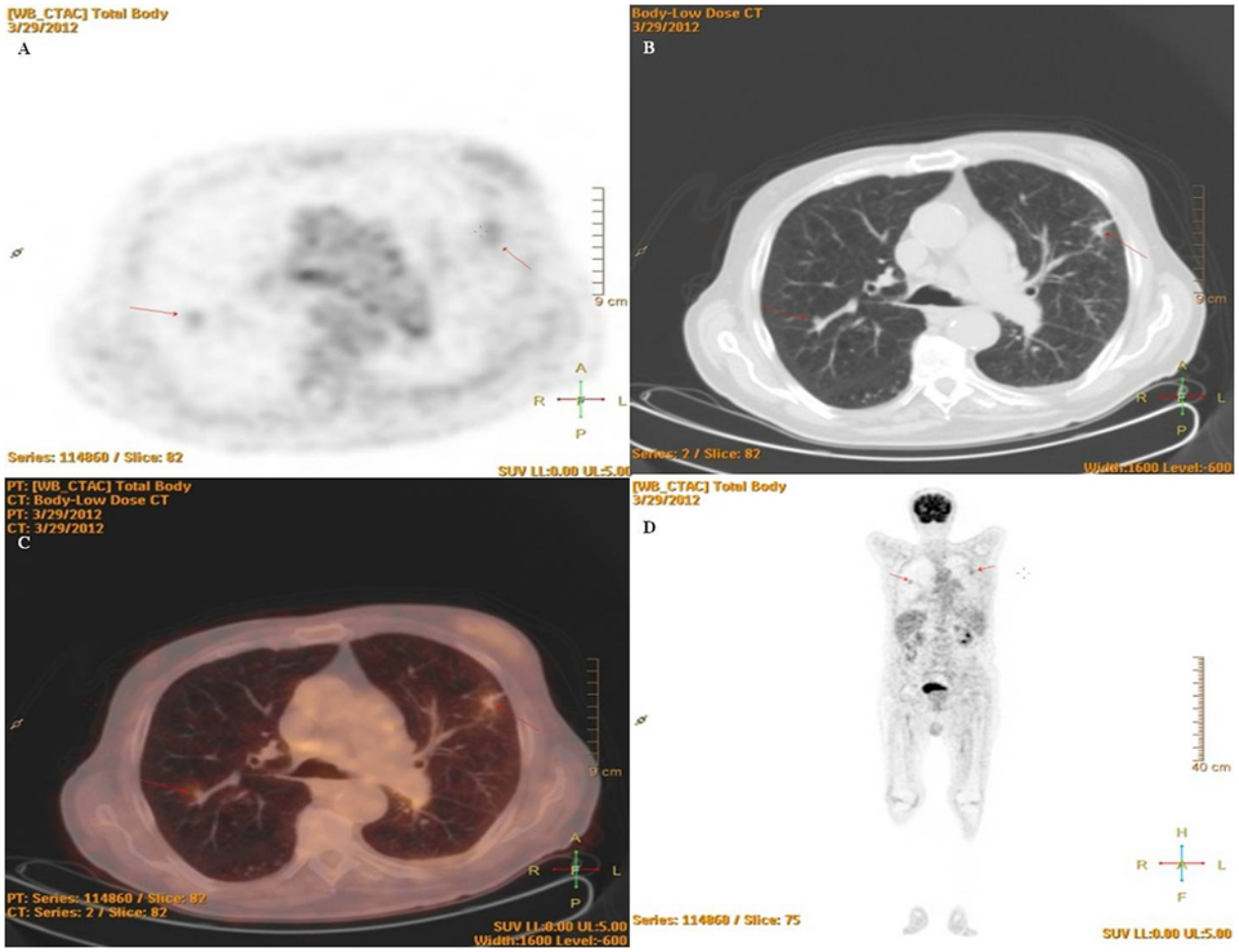

Figure 3. ^{18}F-FDG PET/CT transverse images of an 83-year-old man (Patient number 2) who presented with an unknown primary tumor. PET (A), CT (B), fusion (C), and MIP (D) images show pulmonary nodules in the upper lobes of both the right and left lungs with mild FDG uptake (SUVmax = 2.19), which was interpreted as a pulmonary infection. After PET/CT, a bronchoscopic biopsy was performed and a subsequent histopathological examination confirmed the F-18 FDG PET/CT diagnosis by showing only infectious findings in the specimens.

As a result of FDG being both captured and retained within metabolically active cells, ^{18}F-FDG can be used to determine the high glycolytic activity of various malignancies and imaging of these pathological lesions, such as malignant melanoma, lung cancer, breast cancer, gastrointestinal tract cancers, and genitourinary cancers, can be provided by PET/CT. In our study, ^{18}F-FDG PET/CT correctly identified the primary tumor site in several organs in 16 of 32 patients. In many other studies, the most common site of the primary tumor was the lung (4,8,12,18,21,22,25–27). However, we cannot directly identify the most common localization site for the primary tumor based on FDG PET/CT because the primary tumor regions were heterogeneous in this study. However, the most frequent primary tumor focus in our study was the lung (three patients), followed by the liver, colon, and lymph nodes (two patients each).

Despite the high detection rate of malignancies by ^{18}F-FDG PET/CT imaging, the ^{18}F-FDG PET/CT may not be able to detect final diagnosis of the primary site for various types of neoplasms (6,16). In our study, ^{18}F-FDG PET/CT failed to identify the primary tumor site in 12 of 32 patients with histopathological findings; patients had multiple organ metastases, and the malignancy could not be identified in 4 patients with a malignant histopathological diagnosis. The SUVmax values in the lesions were low (<2.10) in these 4 patients. As known, ^{18}F-FDG uptake can be influenced by tumor grading. High-grade tumors show elevated glucose consumption with high FDG uptake, while uptake can be lower or absent in low-grade tumors. In addition, some slow growing tumors can metastasize, while some invasive tumors cannot grow beyond 1–2 mm in size and thus remain subclinical (5,6). Therefore, it is reported that the primary tumor remains

unidentified after autopsy in almost 70% of UPM cases (1,2,4). Moreover, the primary lesion site is an important factor for tumor identification with PET/CT. ^{18}F-FDG is not an optimal radiopharmaceutical for certain anatomical locations that physiologically accumulate FDG. FDG is well known to be physiologically accumulated in the muscular, gastrointestinal, renal excretory systems, the brain, and especially in inflammatory lesions. These accumulation areas lead to uncertainty in the classification of lesions (1,3,28). Hany et al. showed that 21% of all lesions could not be specified with PET alone, and an additional 7% of all lesions could be specifically classified via the use of low-dose CT for image coregistration as a result of a change in localization (29). Our 4 patients with false negative results had a colon adenocarcinoma, intraabdominal liposarcoma, lung adenocarcinoma, and hepatocellular carcinoma, respectively. We think that our false negative findings may be attributed to decreased glucose consumption in the tumor tissues and/or their inappropriate anatomical locations.

Some studies have revealed that ^{18}F-FDG PET alone and PET/CT imaging yielded similar results in the detection of primary tumors of unknown origin (11,13). The efficiency of FDG-PET for the detection of an UPM has been assessed in a multicenter study of 208 patients, and ^{18}F-FDG PET detected a primary tumor in 24%–53% of the patients (11). However, recent clinical studies that also aimed to identify the primary lesion in UPM patients, similar to us, generally relied on the use of hybrid PET/CT equipment instead of PET alone. The hybrid system seems to be more accurate than PET alone in assessing the presence and location of tumoral lesions because it permits the simultaneous acquisition of accurately aligned whole body anatomical and functional images. Especially, PET/CT imaging is significantly superior to PET alone in tumor staging. PET/CT imaging can improve tumor staging by identifying more lesions than conventional imaging methods (6,29,30). Thus, FDG PET/CT is a very suitable technique to identify a prognosis because the prognosis depends on the accurate staging of the disease and the selection of the most appropriate treatment approaches (22). PET/CT can also direct a biopsy of the primary tumoral lesion and avoid other unnecessary invasive investigations. In our study, the detection of possible primary tumor locations guided the biopsy, and the treatment was modified and adapted to the location of the tumor in 16 patients based on ^{18}F-FDG PET/CT results alone.

Moreover, some situations may negatively affect the identification of the primary tumor site with the FDG PET/CT technique. ^{18}F-FDG is not an optimal tracer for inflammatory and infectious processes. False positive results may be due to FDG uptake in benign conditions that feature increased glycolysis (e.g., pulmonary infarction) or high physiological FDG uptake (e.g., muscle FDG uptake) (10,12). These conditions may simulate cancer and create false positive results. If the ^{18}F-FDG PET/CT findings indicate a malignancy, confirmatory invasive diagnostic investigations, such as a biopsy, are necessary because of the risk for false positivity (31). In our study, the PET/CT results were false positive in 6 of 18 (33%) cases with histopathologically proven benign disease (benign infectious and inflammatory cytomorphology). These infectious and inflammatory processes were mostly located in the lung (in 4 of 6). The false positive rates in other similar studies varied widely from 5.5% to 66.6% (8,10,13,16,22). Similar to our findings, the lung has been reported as one of two main locations in which false-positive FDG PET/CT results are highest in patients with UPM. The second main location is the oropharynx (12,25). The physiological FDG uptake in this location may be misinterpreted as a malignant lesion. False positive FDG-PET findings expose the patient to advanced invasive diagnostic evaluations (laryngoscopies and endoscopies), which incur associated costs and morbidities. Therefore, talking, swallowing, and chewing should be avoided in patients instantly before and after FDG injection to decrease FDG levels in the muscles of the larynx and pharynx (12,32). We strictly applied these rules, and did not record false positive lesions in the oropharyngeal or laryngeal region in any of the patients. Previous studies indicated that both attenuation-corrected and nonattenuation-corrected images need to be evaluated to minimize the chance of misinterpreting artifacts as malignant lesions (10,12,16,33).

Our study showed that ^{18}F-FDG PET/CT accurately depicted the malignant lesions in 28/32 patients whose lesions were not identified by conventional tests, but were histopathologically confirmed. Our results corroborate a retrospective study that reported 26 true positive results for 33 patients (20). Our high sensitivity of 87% indicates that ^{18}F-FDG PET/CT can effectively identify malignancies. ^{18}F-FDG PET/CT is superior to conventional diagnostic techniques, which could not identify the origin of the primary malignancy in our patient group. The superior performance of our PET/CT results as compared with conventional imaging methods is attributed to the whole-body PET/CT images that were analyzed by the same experienced nuclear medicine physicians, while conventional imaging methods were performed in different and specific locations and the images were not analyzed by the same radiologist. Our results support the advantage of metabolic information over conventional imaging methods in the search for a malignancy. We also found that PET/CT can change the staging of the disease by showing more lesions and more advanced disease than

conventional imaging methods. It can also direct a biopsy of the primary tumor (Figure 1) and avoid other invasive procedures. Irrespective of its capability to detect an unknown primary tumor, F-18 FDG PET/CT can detect or rule out other possible metastatic sites, which is important for patient therapeutic management and prognosis. We think that ^{18}F-FDG PET/CT is useful and highly sensitive for the diagnostic work-up of patients with metastases of unknown origin and can help explore the whole body in a single and noninvasive examination. Furthermore, our study is novel and more reliable and accurate than other studies on the same topic that enrolled UPM patients with different selection criteria, such as the exclusion of cases with highly suspected clinical findings based on the diagnostic work-up or the inclusion of cases with highly suspected, but not histopathologically proven, malignant or metastatic lesions.

^{18}F-FDG PET/CT identified the primary tumor site well in 50% of our cases. Although validation is required with a larger population, the present study indicates that ^{18}F-FDG PET/CT may help to accurately determine the lesion site in patients with unknown primary tumors. However, appropriate use and interpretation of ^{18}F-FDG PET/CT are necessary to maximize its diagnostic performance for unknown primary malignancies and optimize the management of these patients.

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