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The value of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography in carcinoma of an unknown primary: diagnosis and follow-up

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Background **The management of the patients with carcinoma of an unknown primary represents a difficult challenge in oncology. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has provided new insights in the diagnosis, staging, and follow-up of oncological patients.**

Aim **This study aimed to investigate the value of FDG PET/CT in clarifying the primary site in our patients with histologically proven tumor metastasis (HPM) or with a high clinical suspicion of malignancy, and the clinical impact of this technique on the management of these patients.**

Methods **In total 94 patients from two centers underwent FDG PET/CT imaging; 78 patients with HPM and 16 patients with a clinical suspicion of malignancy. The histology and/or follow-up data were used as the gold standard. Hypermetabolic findings at the site of the pathological CT changes or at physiological FDG uptake sites were the criteria for malignancy. PET/CT findings were analyzed for the identification of the primary tumor site, for the relationship with survival, and also for the effect in chemotherapy monitoring.**

Results **Primary malignancy was discovered in 53 of 90 patients (59%) histologically and 37 (41%) patients' primary tumor sites were not found during the study period. Amongst 90 patients, five (6%) were normal on FDG PET/CT. Of 85 patients (94%) with pathological findings on FDG PET/CT, 27 patients (32%) had solitary and 58 (68%) patients had multiple organs affected. Regarding the whole study population, a sensitivity of 74% and a specificity of 78% were calculated for FDG PET/CT imaging. Regarding the patients with HPM, the sensitivity and specificity values were 84 and 81%, respectively. The mean survival time of the patients with disseminated disease was significantly shorter than those of the patients with single or no lesion (13.44 ± 1.61, 20.98 ± 2.0 and 26.67 ± 2.73 months, respectively, $P = 0.014$). In seven of eight patients, follow-up FDG PET/CT scans effectively monitored the patients' therapies.**

Conclusion **Whole-body FDG PET/CT has to be considered a useful method, especially in an early phase of the diagnostic workup of patients with carcinoma of an unknown primary syndrome, to optimize the management.** *Nucl Med Commun* **31:59–66 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: carcinoma of an unknown primary, diagnosis, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, prognosis, therapy response

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Introduction

Carcinoma of an unknown primary (CUP) is a proven tumor metastasis without evidence of a primary site. The management of patients with CUP represents a difficult challenge in oncology, as histopathological analysis frequently does not provide sufficient information to locate the primary site, and not all primary tumors are identified despite a comprehensive diagnostic workup.

About 2–5% of all newly diagnosed cancers are said to be CUP [1,2]. The site of the primary tumor is often detected in only 10–35% of all cases after conventional imaging modalities [3,4]. Even after autopsy, the primary site can remain unidentified [5]. The low rate of detection has been attributed to both a lesion size that is smaller than the spatial and contrast resolution of the technique used, and the involution of the primary mass as a result of limited angiogenic competence [6]. Identification of the primary tumor has been shown to impact patient management and thereby life expectancy in patients with CUP [7–9].

Positron emission tomography/computed tomography (PET/CT) has provided new insights in the diagnosis,

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staging, and follow-up of oncological patients [10–12]. The contribution of ^{18}F-fluorodeoxyglucose (FDG) PET/CT to the diagnosis of CUP has been investigated by various authors [13–17]. In this era, the technique has been shown to be more helpful in searching for the presence of malignancy than in identifying exactly the site of the primary by Fencl *et al.* [18]. The same group also showed that FDG PET/CT imaging offers accurate prognostification as additional information.

This study aimed to investigate the value of FDG PET/CT in clarifying the primary site in our patient population with proven tumor metastasis or with a high clinical suspicion of malignancy, and the clinical impact of this technique on the management of the patients of whom the primaries could not be found using all available tests.

Materials and methods

Patients

A total of 94 patients (66 male, 34 female; age range: 22–84 years; mean ages: 52.74 ± 13.34, 57.06 ± 13.56 years, respectively) from two nuclear medicine centers (Medical Faculties from Cukurova University and Baskent University Adana Hospital) were included in the study. The CUP attribute was assigned to patients in two categories as 78 patients with histologically proven metastatic disease (group I), 16 patients with clinical suspicion of malignancy (group II). In the second group, medical history and laboratory examinations had suggested a high suspicion for malignancy, which was later proved histologically. The histological types of primaries found in these patients are summarized in Table 1. The patients were referred for FDG PET/CT imaging either before or after conventional imaging methods with no suspected primary site.

Table 1 Patient demographics and clinical characteristics ($n = 90$)

Characteristics	No. of patients
Age (mean ± SD, years)	
55.86 ± 14.11	90
Men/women	60/30
I. Patients with histologically proven metastatic lesions (Pretest histologic types of metastases are presented in Table 2)	74
II. Patients with clinical suspicion of malignancy	16
Posttest histologic diagnosis	
Lung cancer (2 non-small-cell, 1 small-cell cancer)	3
Lymphoma (3 non-Hodgkin lymphoma, 1 anaplastic)	4
Invasive ductal breast cancer	1
Prostatic cancer	1
Neurofibroma	1
Multiple myeloma	2
Gastric adenocancer	1
Chronic lymphocytic leukemia	2
Histologically proven primary could not be found[a]	1

[a]In this case, after ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography imaging, multiple generalized bone/bone marrow hypermetabolic lesions were detected and metastatic malignancy was diagnosed histologically, which could not be characterized for the primary.

The histology and/or follow-up data were used as gold standards. This study was reviewed and approved by the ethics review committee of our institute.

Fluorodeoxyglucose positron emission tomography/computed tomography imaging

Data acquisition was performed using two different PET/CT scanners (Biograph 6 LSO PET/CT scanner by Siemens, Knoxville, Tennessee, USA, and Discovery STE 8 PET/CT scanner by General Electric, Milwaukee, Wisconsin, USA). Patients fasted for at least 6 h before scanning to minimize blood insulin levels and glucose utilization of normal tissue. Blood glucose level was checked in each patient before the FDG injection and all patients presented glycemia blood levels below 200 mg/dl. Water-soluble iodinated contrast material diluted in 1500 ml water was given to each patient orally before scanning. Patients were positioned on the table in a supine head-first position and whole-body scanning from the top, including the skull, to the upper thighs was carried out 60–90 min after intravenous injection of FDG (dose range: 222–370 MBq). The parameters used for CT investigation were as follows: effective current, 54 mAs; 130 kV; slice width, 4.0 mm; collimation, 10 mm; caudocranial table feed, 14 mm/rotation for Biograph 6 LSO PET/CT scanner, and effective current, 80 mAs; 140 kV; slice width, 3.75 mm; collimation, 10 mm; caudocranial table feed, 16.75 mm/rotation for the Discovery STE 8 PET/CT scanner. Immediately after the CT examination, the process continued with a three-dimensional PET acquisition in seven bed positions (3 min/bed position). If necessary, two-dimensional PET acquisition was also applied with the Discovery STE. PET images were reconstructed using CT data for attenuation correction with an iterative approach.

Image analysis

Whole-body PET/CT images were evaluated by two nuclear medicine physicians by consensus. Foci showing increased FDG uptake were evaluated by comparison of the background and blood pool activity and the presence of morphological alterations in CT images. Fused FDG PET/CT images were analyzed in at least three planes (coronary, sagittal, and axial) in the hot body color table for PET, and with appropriate settings of center/width for CT.

The analysis of malignant involvement was based on qualitative visual interpretation of the images. The criterion for malignancy was FDG hypermetabolism at the site of pathological changes on CT or marked focal hypermetabolism at physiological uptake sites such as the liver and the bone marrow despite absence of signs of pathology on CT. To obtain the pretherapeutic baseline metabolic status of the lesions, the maximal standardized uptake value (SUV_{max}) was calculated for all lesions, and these data were used only for the evaluation of

chemotherapy response in seven patients as follows: progressive metabolic disease: greater than 25% increase in SUV or new lesions; stable metabolic disease: between less than 25% SUV increase and less than 15% SUV decrease; complete metabolic response: complete resolution of FDG uptake. To identify the primary site, the distribution of pathological lesions, a prior knowledge of the pattern of spread of different tumors, and the patient's history were taken into consideration. When any lesion as the site of the primary in cases with many foci in different organs was not identified, we interpreted the changes as a sign that the CUP syndrome was generalized, with no known site of primary.

Data analysis

The diagnosis of the primary site of malignancy was classified as true positive (TP) only when it was confirmed histologically. If the finding was not confirmed histologically, the diagnosis was classified as false positive (FP). Evaluation was classified as true negative (TN), despite the fact that FDG PET/CT imaging revealed multiple hypermetabolic lesions for which no primary site could have been differentiated if neither FDG PET/CT nor histological findings or clinical follow-up (including subsequent imaging tests) determined the primary site [18]. The finding was classified as false negative (FN), when the site of the primary was not identified, but was proven histologically. In three patients, the primary malignancies were missed and another falsely diagnosed; for statistical reasons, these lesions were regarded as being both FP and FN findings, and the group was regarded as having 93 patients in total.

During overall survival analysis, one patient with a primary site was excluded because of insufficient follow-up. Furthermore, during survival analysis based on disease extension on PET/CT, patients with normal findings were excluded because no death was observed in this group.

The cases that remained primary unknown and were monitored with FDG PET/CT during follow-up were evaluated one by one, because a sufficient number of patients could not be reached for statistical analysis.

Statistical analysis

TP/FPs and TN/FNs were defined based on the results of the above-mentioned confirmation methods and the sensitivity and specificity values of FDG PET/CT were calculated. The Kaplan–Meier test was used for survival analysis. The log-rank test was applied for comparison of the survivors.

Results

Among the total study population, 74 (82%) patients had histologically proven metastasis (HPM), 16 (18%) had a high clinical suspicion of malignancy (CSM) (Table 1). In the second group, the primaries were proven histologically in all patients except one. Although the primary could not be located in one patient, FDG PET/CT revealed generalized multiple skeletal lesions, which were later proven to be metastatic lesions histologically.

The histopathological and localization profiles of the metastases in the patients with HPM are shown in Table 2. Of these, 30 of 74 (41%) metastases were localized in lymph nodes, of which most were in the cervical region (21 of 30, 70%). Most of the metastases were of epithelial origin (55 of 74, 74%). The histological subgroup of the malignancy in metastatic lesions could not be differentiated in 22% of the patients (16 of 74).

Among 90 patients, five (6%) were normal on FDG PET/CT. In 85 patients (94%) with pathological findings on FDG PET/CT, 27 patients (32%) had solitary and 58 (68%) patients had multiple organs that were affected. Primary malignancy was discovered in 53 of 90 patients (59%) histologically. FDG PET/CT was able to reach primaries in 12 of 27 (44%) patients with single site and in 39 of 58 (67%) patients with multiple site involvement. In one patient, a second primary tumor was also identified. During the follow-up period, 37 patients (41%) remained primary unknown (RPU).

Accuracy of FDG PET/CT in discovering the primary site regarding the whole patient population ($n=90$)

In the identification of a primary site, the findings of FDG PET/CT were concordant with those of the gold standard in 70 of 90 patients (78%) with regard to all the study population. Of these, 31 were TN and 39 were TP. In 20 of 90 patients (22%), the findings of FDG PET/CT were discordant with those of the gold standard (Tables 3 and 4). In three patients, the localization of the

Table 2 Histological types of metastases found in the 74 patients with histologically proven metastasis

	Histology			
Localization of metastases	Epithelial	Mesenchymal	Cancer metastasis[a]	Total
Cervical LNs	14		7	21 (28%)
Axillary LNs	2		2	4
Inguinal LNs	2			2
Mediastinal LNs	1		1	2
Retroperitoneal LNs	1			1
Lungs	1			1
Bones	11		2	13 (18%)
Brain	5			5
Liver	9	2	1	12 (16%)
Pleura	1			1
Omentum	3			3
Muscle		1	1	2
Adrenal glands	1			1
Peritoneal fluid	2		1	3
Pleural fluid	1			1
Bone marrow			1	1
Thymus	1			1
Total	55 (74%)	3 (4%)	16 (22%)	74

LN, lymph node.
[a]Metastases could not be categorized for epithelial or mesenchymal origin.

primaries, which FDG PET/CT suggested, was discordant with the correct sites found by the gold standard. These results were regarded as both FP and FN, and the number of patients was accepted as 93 during the calculation of sensitivity and specificity because of statistical considerations. Thus, FN and FP cases were 14 and 9, respectively. Finally, a sensitivity of 74% and a specificity of 78% were calculated. Positive predictive value (PPV) and negative predictive value (NPV) were 81 and 69%, respectively.

Accuracy of FDG PET/CT in discovering the primary site of the patients with histologically proven tumor metastasis ($n = 74$)

When the results of the other group (the patients with CSM) were excluded, the final values that were found were as follows: TP = 32, TN = 30, FP = 7, FN = 6. Accordingly, the calculated sensitivity, specificity, PPV, and NPV values were 84, 81, 82 and 83%, respectively.

FDG PET/CT performance in patients with clinical suspicion of malignancy ($n = 16$)

Among 16 patients with CSM, FDG PET/CT revealed a solitary organ involvement in seven patients and multiple organ involvement in eight patients. Of these, eight of 14 primaries were correctly identified (TP and TN), whereas six were missing (FN). Primary malignancies were missing in two patients and were falsely diagnosed in another, and these lesions were regarded as being both FP and FN findings. In one patient, there were multiple generalized skeletal system lesions, which were diagnosed as metastatic lesions histologically. The result of FDG PET/CT was regarded as TN for this patient,

Table 3 Totally 48 FDG PET/CT-positive results with clinical and gold standard findings

Sex	Age (years)	Metastatic localization	Metastatic histology	FDG PET/CT	Gold standard	Accuracy
M	51	Cervical LN	Malign epithelial tumor	Nasopharynx cancer	Nasopharynx cancer	TP
M	43	Bone	Adenocarcinoma metastasis	Lung cancer	NSCLC	TP
M	46	Bone	Adenocarcinoma metastasis	Lung cancer	NSCLC	TP
M	63	Brain	Malign epithelial tumor	Lung cancer	NSCLC	TP
F	53	Inguinal LN	Malign tumor	Lymphoma	DLBCL	TP
F	67	Pleura	Adenocarcinoma metastasis	Lung cancer	NSCLC	TP
M	55	Brain	Malign epithelial tumor	Lung cancer	NSCLC	TP
F	44	Bone	Adenocarcinoma metastasis	Lung cancer	NSCLC	TP
M	41	Mediastinal LN	Metastatic cancer	Lung cancer	Bronchoalveolar cancer	TP
M	48	Muscle	Malign tumor	Renal cancer	Renal cell cancer	TP
M	48	Adrenal gland	Adenocarcinoma metastasis	Lung + colon cancer	Lung + colon cancer	TP
M	33	Clinical suspicion	–	Lung cancer	Lung small cell cancer	TP
M	52	Cervical LN	Malign tumor	Lymphoma	DLBCL	TP
M	49	Clinical suspicion	–	Multiple myeloma	Multiple myeloma	TP
M	36	Liver	Adenocarcinoma metastasis	Renal cancer	Renal cell cancer	TP
F	54	Clinical suspicion	–	Gastric cancer	Gastric adenocarcinoma	TP
M	62	Bone	Metastatic cancer	Renal cancer	Renal cell cancer	TP
M	82	Pleural liquid	Adenocarcinoma metastasis	Lung cancer	Lung adenocarcinoma	TP
F	46	Cervical LN	Metastatic cancer	Thyroid cancer	Thyroid papillary cancer	TP
M	67	Liver	Adenocarcinoma metastasis	Colonic cancer	Colon cancer	TP
M	45	Lung	Adenocarcinoma metastasis	Lung cancer	NSCLC	TP
M	53	Cervical LN	Metastatic cancer	Nasopharynx cancer	Nasopharynx cancer	TP
M	33	Cervical LN	Metastatic cancer	Lung cancer	NSCLC	TP
F	59	Clinical suspicion	–	Breast cancer	Invasive ductal breast cancer	TP
F	30	Bone	Malign epithelial tumor	Breast cancer	Epidermoid breast cancer	TP
F	47	Thymus	Metastatic cancer	Thymic cancer	Thymic cancer	TP
M	51	Clinical suspicion	–	Lymphoma	Anaplastic lymphoma	TP
F	49	Clinical suspicion	–	Lymphoma	DLBCL	TP
M	47	Cervical LN	Malign epithelial tumor	Lung cancer	NSCLC	TP
M	73	Brain	Malign epithelial tumor	Lung cancer	NSCLC	TP
M	74	Cervical LN	Malign epithelial tumor	Lung cancer	NSCLC	TP
F	62	Liver	Malign epithelial tumor	Breast cancer	Invasive ductal breast cancer	TP
M	66	Bone	Malign epithelial tumor	Lung cancer	NSCLC	TP
M	63	Bone	Malign epithelial tumor	Lung cancer	NSCLC	TP
M	61	Cervical LN	Malign epithelial tumor	Lung cancer	NSCLC	TP
M	66	Clinical suspicion	–	Lung cancer	NSCLC	TP
M	74	Cervical LN	Malign epithelial tumor	Oropharynx cancer	Oropharynx cancer	TP
M	70	Liver	Adenocarcinoma metastasis	Colon cancer	Colon cancer	TP
M	77	Brain	Malign epithelial tumor	Esophagus cancer	Esophagus cancer	TP
M	27	Cervical LN	Adenocarcinoma metastasis	Thyroid cancer	–	FP
M	66	Liver	Adenocarcinoma metastasis	Ovarian cancer	–	FP
M	58	Bone	Adenocarcinoma metastasis	Lung cancer	–	FP
F	46	Cervical LN	Adenocarcinoma metastasis	Colon cancer	–	FP
F	38	Bone	Adenocarcinoma metastasis	Ovarian cancer	–	FP
M	54	Peritoneal liquid	Metastatic cancer	Peritoneal cancer	–	FP
F	72	Peritoneal liquid	Malign epithelial tumor	Colon cancer	Ovarian cancer	FP + FN
M	47	Clinical suspicion	–	Hepatic cancer	Lung adenocarcinoma	FP + FN
M	81	Clinical suspicion	–	Lung cancer	CLL	FP + FN

CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; F, female; FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; FN, false negative; FP, false positive; FN, false negative; LN, lymph node; M, male; NSCLC, non-small cell lung cancer; TP, true positive.

Table 4 Totally 42 FDG PET/CT-negative results with clinical and gold standard findings

Sex	Age (years)	Metastatic localization	Metastatichistology	FDG PET/CT	Gold standard	Accuracy
M	60	Bone	Adenocarcinoma metastasis	Generalized disease	–	TN
M	60	Cervical LN	Metastatic cancer	Lymphatic metastasis	–	TN
F	67	Omentum	Adenocarcinoma metastasis	Normal	–	TN
F	38	Liver	Epithelial cancer metastasis	Generalized disease	–	TN
M	62	Liver	Adenocarcinoma metastasis	Generalized disease	–	TN
M	56	Clinical suspicion	–	Generalized disease	–	TN
F	56	Axillary LN	Metastatic cancer	Lymphatic metastasis	–	TN
F	34	Cervical LN	Metastatic cancer	Lymphatic metastasis	–	TN
F	47	Axillary LN	Adenocarcinoma metastasis	Normal	–	TN
M	61	Bone	Epithelial cancer metastasis	Generalized disease	–	TN
M	26	Cervical LN	Epithelial cancer metastasis	Lymphatic metastasis	–	TN
M	59	Axillary LN	Metastatic cancer	Lymphatic metastasis	–	TN
F	49	Bone	Epithelial cancer metastasis	Bone metastasis	–	TN
M	43	Cervical LN	Metastatic cancer	Generalized disease	–	TN
M	64	Retroperitoneal LN	Neuroendocrine tumor metastasis	Generalized disease	–	TN
M	76	Cervical LN	Undifferentiated cancer metastasis	Generalized disease	–	TN
F	65	Cervical LN	Epithelial cancer metastasis	Generalized disease	–	TN
F	26	Liver	Epithelial cancer metastasis	Generalized disease	–	TN
M	62	Cervical LN	Epidermoid cancer metastasis	Generalized disease	–	TN
F	54	Bone	Metastatic cancer	Generalized disease	–	TN
M	65	Omentum	Epithelial cancer metastasis	Generalized disease	–	TN
F	52	Liver	Epithelial cancer metastasis	Hepatic metastasis	–	TN
M	82	Omentum	Adenocarcinoma metastasis	Generalized disease	–	TN
M	52	Mediastinal LN	Epithelial cancer metastasis	Lymphatic metastasis	–	TN
M	52	Liver	Malign tumor	Generalized disease	–	TN
M	76	Muscle	Metastatic cancer	Metastatic lesion	–	TN
F	73	Cervical LN	Metastatic cancer	Lymphatic metastasis	–	TN
M	77	Liver	Epithelial cancer metastasis	Hepatic metastasis	–	TN
M	64	Liver	Epithelial cancer metastasis	Hepatic metastasis	–	TN
M	75	Brain	Epithelial cancer metastasis	Generalized disease	–	TN
M	54	Cervical LN	Malign epithelial tumor	Lymphatic metastasis	–	TN
M	54	Clinical suspicion	–	Bone metastasis	Neurofibroma	FN
M	46	Clinical suspicion	–	Generalized disease	Prostatic cancer	FN
M	53	Axillary LN	Malign epithelial tumor	Generalized disease	Germ-cell testicular cancer	FN
M	68	Cervical LN	Adenocarcinoma metastasis	Lymphatic metastasis	Prostatic cancer	FN
M	46	Inguinal LN	Epidermoid cancer metastasis	Lymphatic metastasis	Cutaneous epidermoid cancer	FN
M	84	Clinical suspicion	–	Lymphatic metastasis	Multiple myeloma	FN
F	77	Bone marrow	Metastatic cancer	Normal	Myeloproliferative disease	FN
F	56	Clinical suspicion	–	Bone metastasis	Low-grade B-cell NHL	FN
F	22	Clinical suspicion	–	Generalized disease	DLBCL	FN
F	62	Clinical suspicion	–	Normal	Chronic lymphocytic leukemia	FN
M	43	Cervical LN	Epithelial cancer metastasis	Lymphatic metastasis	Papillary thyroid cancer	FN

DLBCL, diffuse large B cell lymphoma; F, female; FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; FN, false negative; LN, lymph node; M, male; NHL, non-Hodgkin lymphoma; TN, true negative.

because the primary could not be found by the gold standard either. There was one normal FDG PET/CT study considered as FN, because this patient was later diagnosed as having chronic lymphocytic leukemia (CLL). Although the number of these patients was not sufficient for individual statistics, calculated sensitivity, specificity, PPV, and NPV values were 47, 33, 78 and 11%, respectively (TP = 7, TN = 1, FP = 2, FN = 8).

Survival analysis ($n = 90$)

According to our findings, the identification of the primary site did not change life expectancy in this clinical setting (log rank, Mantel–Cox), because there was no statistical difference between the mean survival times of the patients for whom primaries were reached (PR) and the RPU patients ($P = 0.232$). In our patient population, the ratios of PR and RUP patients were 59% (53 of 90) and 41% (37 of 90), respectively. The death rate was 32% (17 of 53) for the group of PR and 43% (16 of 37) for the group of RPU. The mean survival times were 17.75 ± 2.21 months for the patients of PR and 16.31 ± 1.95 months for RPU patients When the patients were evaluated on the basis of the extension of disease on FDG PET/CT, their mean survival time with disseminated disease was significantly shorter than that of patients with single or no lesion (13.44 ± 1.61, 20.98 ± 2.0 and 26.67 ± 2.73 months, respectively, $P = 0.014$).

Considering the group including RPU patients, the mean survival time of the patients with multiple system involvement on PET/CT was significantly shorter than that of the patients with single or no lesion (13.95 ± 1.69 and 20.69 ± 2.33, 26.67 ± 2.73, respectively; $P = 0.041$) (Fig. 1). According to the PET/CT findings, 51% (19 of 37) of these patients revealed generalized disease with multiple organ involvement, 40.5% (15 of 37) had single organ involvement, and 8% (three of 37) were normal. Among RPU patients, 43% (16 of 37) of the patients (12 of 19 generalized disease, three of 15 single organ

involvement, one of three normal) died with a mean survival time of 17.75 ± 2.21 months (mean ± SE). In the surviving group, 33% (7 of 21) of the patients revealed generalized disease with multiple organ involvement, 57% (12 of 21) had single organ involvement, and 10% (2 of 21) were normal. The mean survival time of these patients was 16.31 ± 1.95 months.

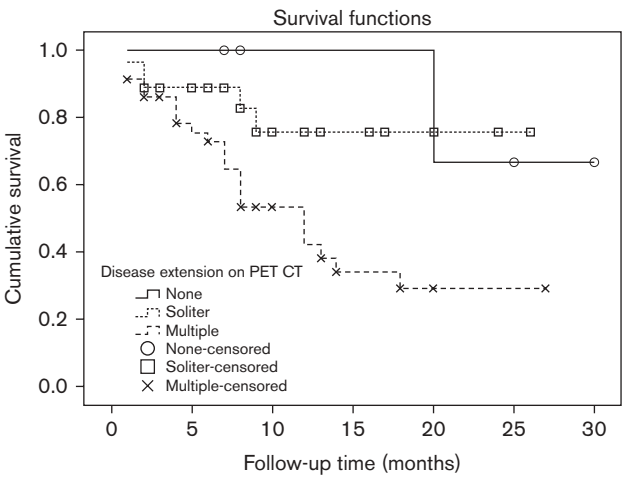
Follow-up data of patients with remained primary unknown

Among 21 surviving patients during follow-up, two patients had normal findings on FDG PET/CT, whereas 19 patients showed pathological findings. Two of the normal patients were female and metastatic lesions were detected from the axillary lymph node in one and T_{12} vertebra in the other (histopathological diagnoses were metastatic adenocarcinoma and malign epithelial tumor, respectively). These two patients have been alive without any symptom for 26 and 19 months, respectively.

Among 19 patients with pathological findings, 12 had single and seven had multiple organ involvement. Four solitary lesions were evaluated as suspicious for malignancy (SUV_{max} = 3–3.5). Of these, one patient has been alive for 26 months without any symptoms and there were no findings from various diagnostic tests. One patient has been alive for 25 months with bone metastasis detected in the last year with magnetic resonance imaging (MRI) from the thoracic vertebra. The other two patients have been relatively newly diagnosed and have been followed for 8 and 3 months.

In eight patients, including two with single and six with multiple organ involvement, FDG PET/CT examination was again performed to monitor the disease (Table 5). One patient underwent FDG PET/CT to clear some symptoms and a bone metastasis was missed, which was reached by MRI later. All the others were studied to search for the response to therapy. A complete response was achieved in three patients, of whom one relapsed 6 months later from the last normal FDG PET/CT examination. In the other four patients, of whom two had progressive disease and two had stable disease, chemotherapy regimes were modified.

Fig. 1



With regard to the patients with remained primary unknown, the survival of the patients having single positron emission tomography/computed tomography (PET/CT) finding was compared with the patients having multiple organ involvement.

Discussion

In this study, including 90 patients suffering from the CUP syndrome, ^{18}F-FDG PET/CT was able to identify 39 sites among 53 primaries confirmed by the gold standard. Our primary detection rate of 43% seems

Table 5 Data of RPU patients and repeated FDG PET/CT scans during follow-up (*n*=8)

Sex	Age (years)	Metastasis localization	Metastasis histology	FDG PET/CT			Follow-up period (months)	Clinical status
				First	Second	Third		
M	27	Cervical LN	Metastatic adenocarcinoma	1 (cervical)	0	0	25	Metastatic disease Symptomatic living
M	52	Hilar LN	Malign epithelial tumor	2 (cervical, mediastinal)	0	–	6	Complete response Asymptomatic living
M	62	Cervical LN	Metastatic cancer	2 (cervical, bone)	0	–	21	Complete response Asymptomatic living
M	76	Nasopharynx	Malign epithelial tumor	2 (cervical axillary, lung, bone)	2 (cervical, abd, bone, lung)	–	21	Progressive disease Symptomatic living
M	64	Para-aortic LN	Malign epithelial tumor	2 (intra/retro-peritoneal)	2 (intra/retro-peritoneal, liver)	–	8	Progressive disease Symptomatic living
M	60	Bone	Metastatic adenocarcinoma	2 (bone, soft tissue)	0	2 (bone, soft tissue)	20	Relapse Symptomatic living
F	38	Liver	Malign epithelial tumor	2 (generalized)	2 (generalized)	–	14	Stable disease Symptomatic living
M	60	Cervical LN	Malign epithelial tumor	1 (cervical)	2 (bone/soft tissue)	1 (bone)	26	Stable disease Symptomatic living

abd, abdominal; F, female; FDG PET/CT, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; LN, lymph node; M, male; RPU, remained primary unknown.

comparable with the report by Seve *et al.* [19], in which the 10 previous reports were reviewed showing detection rates ranging from 24 to 63%. As found in this review, the most common localization site of the primary tumor was the lung, with a ratio of 43%, with disseminated findings on FDG PET/CT in our study.

All but one lung primary were correctly identified with their metastases by FDG PET/CT. There were three patients in whom the FDG PET/CT directed the diagnosis of the primaries to the incorrect organs. All of them had disseminated disease on PET/CT and the incorrect organs that were suggested as the primaries were liver, lung, and colon. The correct localization sites were discovered to be lung, bone marrow (CLL), and ovarium, respectively.

Among the other 11 patients with FN results, the FDG distribution in the whole body was exclusively within normal limits in two patients, one with CLL and the other with myeloproliferative disease. The other types of malignancy missed on FDG PET/CT images were prostatic cancer, neurofibroma, testicular cancer, cutaneous epidermoid cancer, multiple myeloma, low-grade NHL, and papillary thyroid cancer. There were two patients in this group for whom the primaries were diagnosed by the gold standard as prostatic cancer in one and testicular cancer in the other. They had multiple hypermetabolic lymphoid masses in all the lymphoid compartments over the whole body from inguinal to the cervical region without any sign with regard to the other organs. When we retrospectively re-analyzed these organs of the primary sites, we could not find any pathological uptake except physiological FDG distribution.

In a fairly large series by Fencl *et al.* [18], overall sensitivity and specificity values in detecting the primary site were reported as 62 and 82%, respectively. When they divided the whole population into two groups as patients with HPM and CSM, the sensitivity and specificity were calculated as 54.5 and 75% for the first group and 76 and 86%, respectively, for the second group. In our study, although most of the patients had been studied by previous conventional imaging methods, some patients were initially studied with FDG PET/CT. For this reason, the overall sensitivity calculated in our study (74%) was rather higher than that found by Fencl *et al.* The overall specificity (78%) was found to be comparable. In contrast with their results, when the same calculations were carried out with regard to patients with HPM only, the sensitivity and specificity were relatively increased to 84 and 81%, respectively. As the ratio of the tumor types that could be easily missed by FDG PET/CT was rather higher in the group of patients with CSM in our study (Table 1) the value of a negative finding in this group was significantly lower (10%).

In the meta-analysis by Seve *et al.* [19] from 10 earlier reports, the sensitivity and specificity were calculated as 92 and 82%, respectively. Although the specificity values are comparable, the sensitivity is higher than that in our study. The reviewers of the meta-analysis commented that patients that were included in the PET studies were selected and did not reflect the overall population of patients with CUP, because 91% of the meta-analysis patients had only a single metastatic site, whereas the rate in the literature ranged from 29 to 43%. In accordance with this observation, the ratio of patients with single-site metastasis among all the groups (35%) was found to be within these limits in our study.

FDG PET/CT has also been shown to be useful for detecting second primary cancers [20]. In our series, a second primary cancer was confirmed in one patient when we were searching for the primary tumor with HPM in the adrenal gland. In this patient, not only did we locate the primary tumor in the lung, but, after FDG PET/CT imaging, we identified a second primary tumor in the colon. The second primary could be proved in only one patient, because an invasive application, such as biopsy, was not accepted by most of the patients in whom a primary site had already been reached and who had generalized disease.

Owing to the differences in patient selection criteria and natural heterogeneity between the groups, it was not possible to make direct comparisons with previous studies. Our experience supports the finding that FDG PET/CT is a useful tool for identifying the primary tumor site in addition to the metastatic sites involved. However, the literature reveals some doubts regarding whether the diagnostic tests, including FDG PET with or without CT, make any sense in the diagnosis of CUP, which looked like a sleuth in the investigation of a sinister crime [21]. From this perspective, we focused on the prognostic value of the test in addition to the value in identifying the primary site in our patient population. The identification of the primary site did not change life expectancy in survival analysis when the mean survival of the patients with PR and RPU was compared. However, the mean survival time of the patients with multiple lesions was found to be significantly shorter than that of patients with single/no lesion on FDG PET/CT with regard to all the study population. When the same analysis was carried out for only RPU patients, the finding did not change and suggested that sensitive staging plays an important role in determining life expectancy even in the patients with RPU. This finding was supported by the previous report by Fencl *et al.* [18], who showed a shorter life expectancy in patients with a positive FDG PET finding in comparison with patients with a negative FDG PET finding. The investigators concluded that the presence of a hypermetabolic lesion and the increase in the number of involved organs are sensitive prognostic indicators of a shorter life expectancy in patients with CUP.

In this study, FDG PET/CT was also used to monitor the chemotherapy response in some patients with RPU.

Although the number of these patients was not large enough to draw a conclusion in statistical means, the test effectively showed complete remission in three patients. Among them, relapse was diagnosed in one patient during follow-up. In four patients, FDG PET/CT revealed unchanged or increased findings after chemotherapy and their therapies were modified. These findings showed that the test has a potential in therapy monitoring in patients with RPU and effectively identifies the primary sites and gives the opportunity to optimize prognosis.

Conclusion

According to our findings, whole-body FDG PET/CT has to be considered as a useful method in CUP syndrome. In the management of these patients, the method offers several advantages such as (i) identification of the primary tumor in nearly half of the patients, (ii) optimal staging and thereby an opportunity to give a prognosis even when the primary could not be found, and (iii) identification of chemotherapy response. The role of the test seems important, especially in monitoring the chemotherapy response considering the metastatic state in most of these patients. Our preliminary results showed that FDG PET/CT could potentially detect therapeutic efficacy. Pretherapeutic scanning could also be useful in evaluating the response after therapy, in addition to helping in the decision of the therapeutic approach according to the findings with regard to the primary site and metastatic state.

These results suggest that FDG PET/CT can be used reliably in an early phase of the diagnostic workup of the patients with CUP syndrome to optimize their management.

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