
FDG PET Detection of Unknown Primary Tumors

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The management of patients presenting with metastases of unknown primary origin remains a clinical challenge despite a large variety of imaging modalities. The aim of this study was to evaluate FDG PET in detecting the sites of primary cancer in these patients. **Methods:** Fifty-three patients with metastatic cervical adenopathy ($n = 44$) or extracervical metastases ($n = 9$) of unknown primary origin were included after extensive but inconclusive conventional diagnostic work-up. Patients received 370 MBq FDG (10 mCi) intravenously, and whole-body images were acquired at 60 min after injection. Clinical, surgical, and histopathologic findings and complete correlative imaging were used to assess the results. **Results:** In 27 of 53 patients FDG PET showed focal tracer accumulations corresponding to potential primary tumor sites located in the lungs ($n = 12$), the palatine tonsil ($n = 5$), the salivary glands ($n = 2$), the nasopharynx ($n = 1$), the oropharynx ($n = 3$), the maxillary sinus ($n = 1$), and the larynx ($n = 1$). Moreover, in 2 patients FDG PET revealed lesions suspected to be tumors in the breast and the ileocolonic area. In 20 (37.8%) of these 53 patients FDG PET was true-positive, identifying the primary tumor in the lungs ($n = 10$), the head and neck region ($n = 8$), the breast ($n = 1$), and the ileocolonic area ($n = 1$). In 6 of 27 patients FDG PET was false-positive, predominantly identifying suspicious areas in the palatine tonsil ($n = 3$). One patient denied further diagnostic work-up after PET; thus, positive PET could not be evaluated. In 26 of 53 patients PET did not reveal lesions suspected to be the primary. However, primary tumors were not found in these patients at clinical follow-up. **Conclusion:** FDG PET is a valuable diagnostic tool in patients with cancer of unknown primary because it imaged unknown primary tumors in about one third of all patients investigated. In addition, FDG PET assists in both guiding biopsies for histologic evaluation and selecting the appropriate treatment protocols for these patients.

Key Words: FDG PET; cancer of unknown primary; metastases; oncology

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Cancer of unknown primary (CUP) encompasses a heterogeneous group of tumors with varying clinical fea-

tures. The enlargement of cervical lymph nodes is often one of the first clinical manifestations of a tumor disease (1,2). Palpation and localization of these enlarged lymph nodes may be helpful in determining their malignancy and the origin of the primary tumor site (3). Additional sonographically guided fine-needle aspiration cytology may provide evidence of tumor cells in cervical masses (1,4). However, despite an accurate diagnostic work-up, the primary tumor site cannot be identified in 12% of all patients with cervical lymph node metastases (5–8). Cytologic examination of patients with cancer of unknown origin, so-called CUP syndrome, often reveals squamous cell carcinoma or undifferentiated carcinoma cells (5). This is especially true for metastatic lymph nodes of the upper and middle cervical compartments. In contrast, lymph nodes of the inferior portion of the neck often contain adenocarcinoma cells.

Careful staging of CUP syndrome is of utmost importance because the therapeutic approach depends mainly on the extent of the tumor. The 5-y survival rate of patients with an occult primary is 29%–50% (9–13). However, in patients with bilateral cervical lymph node metastases (TX/N2C/M0), the 5-y survival rate decreases to 17%–28% (14–17). In contrast, in localized squamous cell carcinoma of the head and neck associated with bilateral lymph node metastases, 5-y survival rates of 55% are reported (18). This emphasizes the necessity for an accurate diagnostic work-up in these patients.

Moreover, patients with CUP syndrome include a subgroup of patients presenting with metastases located extracranially—e.g., in the skeleton, the liver, the brain, or the axillary region. Because of the heterogeneous nature of CUP syndrome, whole-body imaging with a single modality would be desirable in these patients.

PET using the glucose analog FDG offers an imaging approach to the entire body (19). Moreover, FDG PET is known to be useful in the detection of various tumor types—e.g., head and neck cancer (20–23), lung cancer (24–26), malignant melanoma (27), and primary breast cancer (28). Therefore, the aim of this study was to evaluate the impact of FDG PET in the detection of the primary tumor site in patients with metastases of unknown origin.

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MATERIALS AND METHODS

Patients

Between January 1997 and January 1999 53 patients (20 women, 33 men; age range, 38–82 y) presented with metastases from unknown primary sites. These patients were retrospectively investigated. Forty-four patients had cervical metastatic adenopathy, accounting for the largest subgroup of patients with CUP syndrome. Four patients had skeletal metastases, and 2 patients showed axillary lymph node metastases but had normal physical examination of the breast and normal mammograms. One patient had liver metastases, and 1 had cerebral metastases. The remaining patient had malignant pleural effusions, but a radiograph of the chest showed no primary lung cancer. Thus, the diagnosis of CUP syndrome made by the clinician was the only inclusion criterion for this study.

Histology or fine-needle biopsy revealed squamous cell carcinoma in 30 patients, undifferentiated carcinoma in 8 patients, and adenocarcinoma in 3 patients. One patient had lymphoepitheliomatous carcinoma. In the remaining 11 patients, histopathology was indecisive for the primary tumor.

Before PET a complete history and an accurate physical examination were performed in all patients. Additionally, all patients underwent diagnostic work-up—i.e., routine chest radiography. Patients with carcinoma confined to lymph nodes of the cervical region underwent sonography of the neck and panendoscopy with directed biopsies. Finally, patients were presumed to have CUP syndrome because all diagnostic studies did not detect the primary tumor.

PET Imaging

Patients fasted for at least 6 h before PET scanning to minimize blood insulin levels and glucose utilization of normal tissue. Whole-body images were acquired 60 min after intravenous injection of 370 MBq (10 mCi) FDG using an ECAT EXACT 47 scanner (model 921; CTI/Siemens, Inc., Knoxville, TN) with an axial field-of-view of 16.2 cm. No attenuation correction was performed. Emission data were reconstructed by filtered backprojection using a Hanning filter with a cutoff frequency of 0.4 of the Nyquist frequency. Thus, transaxial spatial resolution was approximately 12 mm. PET images were printed on transparency film (Helios 810; Sterling, Bad Homburg, Germany) using a linear gray scale with highest activity displayed in black. Images were displayed with an upper threshold of 5 times the mean activity in the lung. Standardized documentation included both 20 transversal and 20 coronal slices with a slice thickness of 13.5 mm each and maximum intensity projections (MIPs) in anterior, left lateral, right anterior oblique, and left anterior oblique views as published (29).

Evaluation

Whole-body images were interpreted by visual inspection. Clinical, surgical, and histopathologic findings and complete sets of correlative imaging modalities were used to assess the results of FDG PET. In patients with lesions suspected to be tumors of the lung, CT of the chest and subsequent biopsies were performed to evaluate PET findings.

RESULTS

Forty-four patients showed cervical metastatic adenopathy on conventional diagnostic work-up, accounting for the largest subgroup of patients presenting with CUP syndrome.

Nine patients had extracervically located metastases. Demographic data of all patients and findings of additional FDG PET are given in Table 1. A total of 27 of 53 patients showed pathologic FDG accumulations corresponding to potential primary tumor sites. This group included 22 patients with carcinoma confined to lymph nodes in the cervical region (subgroup 1) and 5 patients with metastases located outside the neck (subgroup 2). In contrast, FDG PET was unable to detect a potential primary tumor site in 26 patients.

In 13 patients from subgroup 1, an abnormal FDG uptake was localized in the head and neck area. An increased FDG uptake was seen in the palatine tonsils ($n = 5$), the oropharynx ($n = 3$), the submandibular ($n = 1$) and parotid gland ($n = 1$), the larynx ($n = 1$), the nasopharynx ($n = 1$), and the maxillary sinus ($n = 1$). The remaining 9 patients presented with pathologic tracer uptake outside the head and neck region—i.e., in the lungs. Additionally, 1 of these patients showed markedly decreased tracer accumulations in both occipital lobes.

In 15 patients from subgroup 1, PET led to the detection of the primary tumor. On the basis of biopsy findings, the primary tumor was confirmed in 8 patients in the head and neck area, specifically in the nasopharynx ($n = 1$), the larynx ($n = 1$), the palatine tonsil ($n = 1$, Fig. 1), the oropharynx ($n = 3$), the maxillary sinus ($n = 1$), and the parotid gland ($n = 1$). However, PET was false-positive in 3 patients with FDG accumulations suspected to be tumors in the palatine tonsil and in 1 patient suspected of having a primary tumor of the submandibular gland. One patient with increased uptake of FDG in the palatine tonsil refused biopsy. Thus, PET findings could not be evaluated in this patient. In addition, in 7 patients from subgroup 1, PET correctly identified the primary tumor site in the lungs. In 1 patient with an additional decreased tracer uptake in both occipital lobes, PET detected cerebral metastases, which were confirmed by subsequent MRI. In 2 patients PET imaging was false-positive, identifying the primary tumor site in the lungs.

In 5 patients from subgroup 2, FDG PET detected potential primary tumor sites located in the lungs ($n = 3$), the ileocolonic area ($n = 1$), and the breast ($n = 1$). This group included 2 patients with bone metastases and 1 patient each with liver metastases, axillary metastatic lymph nodes, and malignant pleural effusion. Moreover, in 1 patient with known cerebral metastases, FDG PET showed pathologic tracer accumulations located in the axillary and parailiac nodes and the mediastinum, corresponding to additional metastatic tumor spread. In all 5 patients FDG PET was true-positive. In 2 patients with bone metastases of the humerus and the ischiadic bone, PET imaging correctly identified the primary tumor site in the lungs (Fig. 2). Moreover, lung cancer was proven histologically to be the primary tumor site in a patient with malignant pleural effusions. In 1 woman with axillary lymph node metastases, FDG PET identified breast cancer as the primary tumor site. With the positive PET scan in mind, the mammogram was

TABLE 1
Data on 53 Patients with CUP Syndrome

Sex	Age (y)	Metastases	Cytology or histology	Suspicious lesion on FDG PET		PT evaluation
				PT	Additional lesions	
M	51	Cervical lymph node	Un-Ca	Negative	Cervical	NPTF
F	74	Cervical lymph node	Un-Ca	Negative	Cervical	NPTF
F	59	Cervical lymph node	Un-Ca	Negative	Cervical	NPTF
M	57	Cervical lymph node	Un-Ca	Negative	Cervical	NPTF
F	60	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	56	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	68	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	39	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	57	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	50	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	57	Cervical lymph node	SqC-Ca	Negative	Negative	NPTF
M	44	Cervical lymph node	SqC-Ca	Negative	Cervical	NPTF
M	58	Cervical lymph nodes	UCH	Negative	Cervical	NPTF
M	64	Cervical lymph nodes	SqC-Ca	Negative	Cervical	NPTF
M	64	Cervical lymph nodes	SqC-Ca	Negative	Cervical	NPTF
M	57	Cervical lymph nodes	SqC-Ca	Negative	Negative	NPTF
M	40	Cervical lymph nodes	UCH	Negative	Negative	NPTF
F	65	Cervical lymph nodes	SqC-Ca	Negative	Negative	NPTF
M	57	Cervical lymph nodes	UCH	Negative	Negative	NPTF
M	62	Cervical lymph nodes	UCH	Negative	Negative	NPTF
F	47	Cervical lymph nodes	UCH	Negative	Negative	NPTF
F	69	Cervical lymph nodes	Lymphoepitheliomatous	Negative	Negative	NPTF
M	58	Cervical lymph node	UCH	Palatine tonsil	Cervical	True-positive
F	57	Cervical lymph node	SqC-Ca	Oropharynx	Cervical	True-positive
F	55	Cervical lymph node	Un-Ca	Nasopharynx	Cervical	True-positive
F	57	Cervical lymph nodes	SqC-Ca	Parotid gland	Negative	True-positive
M	82	Cervical lymph nodes	SqC-Ca	Oropharynx	Cervical	True-positive
M	63	Cervical lymph nodes	SqC-Ca	Oropharynx	Negative	True-positive
M	38	Cervical lymph nodes	Un-Ca	Maxillary sinus	Cervical	True-positive
M	73	Cervical lymph node	Un-Ca	Larynx	Cervical	True-positive
M	63	Cervical lymph node	SqC-Ca	Submandibular gland	Cervical	False-positive
F	76	Cervical lymph node	SqC-Ca	Palatine tonsil	Cervical	False-positive
F	52	Cervical lymph node	UCH	Palatine tonsil	Cervical	False-positive
M	51	Cervical lymph node	SqC-Ca	Palatine tonsil	Cervical	False-positive
F	77	Cervical lymph node	SqC-Ca	Palatine tonsil	Cervical	Refused
F	59	Cervical lymph node	SqC-Ca	Lung	Cervical	True-positive
M	59	Cervical lymph node	SqC-Ca	Lung	Cervical	True-positive
F	61	Cervical lymph node	SqC-Ca	Lung	Cervical	True-positive
M	59	Cervical lymph node	SqC-Ca	Lung	Negative	True-positive
M	55	Cervical lymph node	SqC-Ca	Lung	Negative	True-positive
M	59	Cervical lymph nodes	UCH	Lung	Negative	True-positive
M	69	Cervical lymph nodes	SqC-Ca	Lung	Negative	True-positive
F	42	Cervical lymph node	SqC-Ca	Lung	Cervical, both occipital lobes	False-positive
F	61	Cervical lymph node	SqC-Ca	Lung	Cervical	False-positive
F	59	Axillary lymph node	UCH	Negative	Negative	False-negative
M	63	Cerebral metastases	Adeno-Ca	Negative	Brain, axilla, parailiac	False-negative
F	57	Tibia	UCH	Negative	Tibia	False-negative
M	38	Vertebra	UCH	Negative	Vertebra	False-negative
M	78	Humerus	SqC-Ca	Lung	Humerus	True-positive
F	46	Os ischiadicum	SqC-Ca	Lung	Os ischiadicum	True-positive
F	59	Malignant pleural effusions	Adeno-Ca	Lung	Negative	True-positive
M	69	Liver	Adeno-Ca	Ileocolonic region	Liver	True-positive
F	43	Axillary lymph nodes	Un-Ca	Breast	Axilla	True-positive

PT = primary tumor; Un-Ca = undifferentiated carcinoma; NPTF = no primary tumor found; SqC-Ca = squamous cell carcinoma; UCH = undecisive cytology or histology; Adeno-Ca = adenocarcinoma.

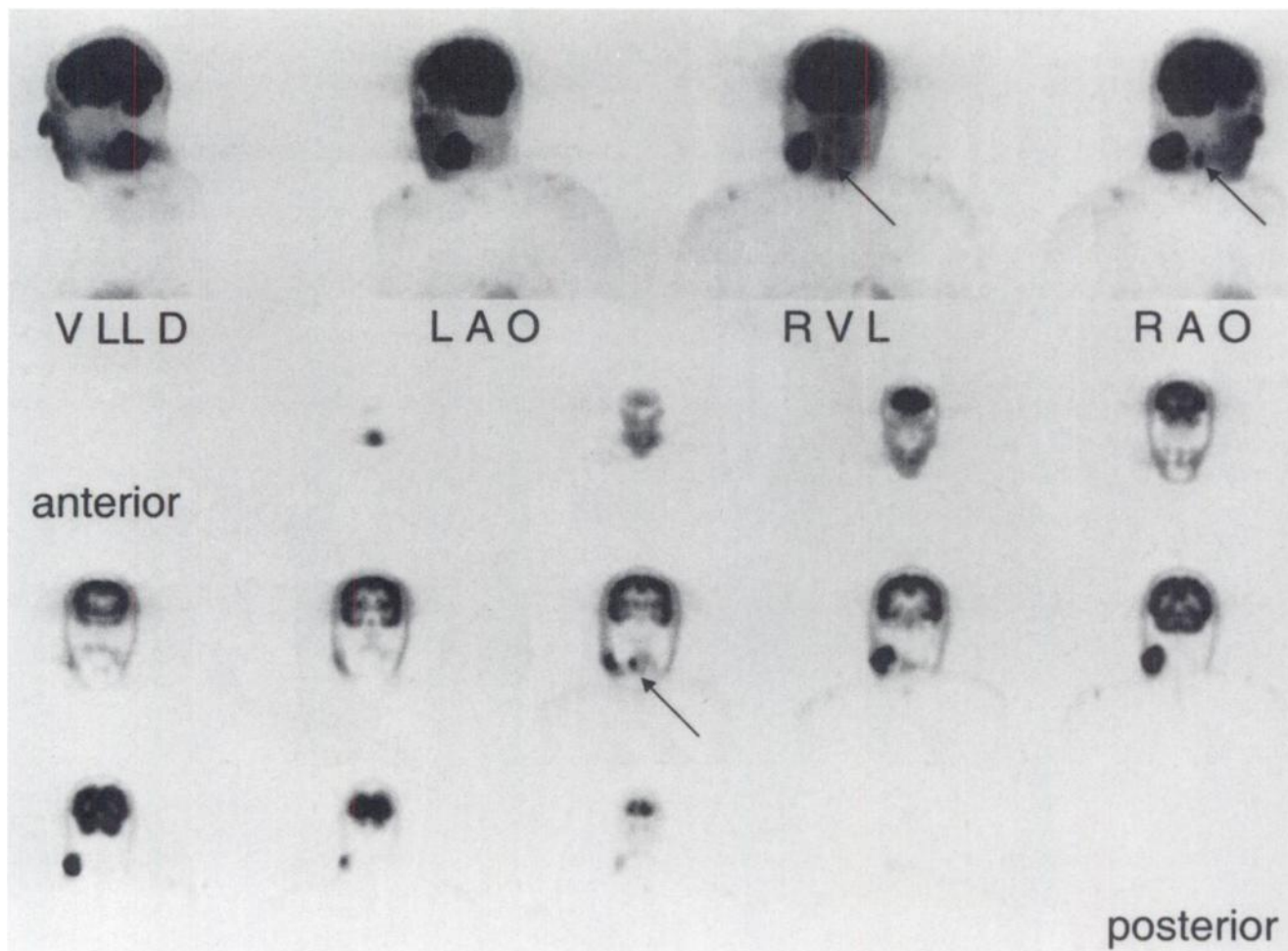


FIGURE 1. MIPs of bust from left lateral (VLLD), left anterior oblique (LAO), anterior (RVL), and right anterior oblique (RAO) views and coronal slices from anterior to posterior. Patient was 58-y-old man with cervical metastases of cytologically proven undifferentiated carcinoma of unknown primary. Note massive focal increased FDG uptake at site of known cervical metastases as well as additional single focus in right palatine tonsil (arrow). Histology confirmed undifferentiated carcinoma of palatine tonsil.

reevaluated, and a lesion considered benign before PET was biopsied. This lesion was proven to be primary breast cancer and the occult primary of the malignant adenopathy. In the remaining patient FDG PET detected a colonic adenocarcinoma as the primary tumor site of liver metastases (Fig. 3). In 1 patient with cerebral metastases PET correctly detected further metastatic spread located in the axillary area, the mediastinum, and the parailiac area but was unable to identify the primary tumor site.

Thus, PET correctly detected the primary tumor site in 20 (37.8%) of 53 patients. In contrast, in the remaining 33 patients FDG PET did not reveal lesions suspected to be primary tumors or was false-positive. However, the primary tumor site could not be found during a follow-up period of up to 24 mo in 33 patients with either false-negative or false-positive PET studies.

An increased focal uptake of FDG was observed in the head and neck region of 24 of 44 patients with cervical adenopathy. The other remaining 20 patients with cervical adenopathy and negative PET scans of the cervical region had undergone either complete neck dissection ($n = 8$) or

simple excision of the enlarged node before PET (12). These findings corresponded to known metastatic lymph nodes. Two of the latter 24 patients underwent neck dissection before PET. However, PET findings were consistent with physical examination findings of recurrent or remaining tumor tissue in the area pretreated surgically.

DISCUSSION

Management of patients with metastases of unknown origin remains a clinical challenge (30,31) because, despite extensive diagnostic work-up, the primary tumor site cannot be detected in a significant number of patients (32). Because the so-called CUP syndrome comprises a heterogeneous entity of patients (33–35), the clinical features of patients might vary widely, including, for example, hepatomegaly, bone pain, enlarged axillary lymph nodes, or cervical lymph nodes. Up to 12% of patients presenting with metastatic cervical adenopathy must be considered to have CUP syndrome (13,36).

The primary objective in patients with cervical lymph node metastases is the treatment of both cervical adenopathy

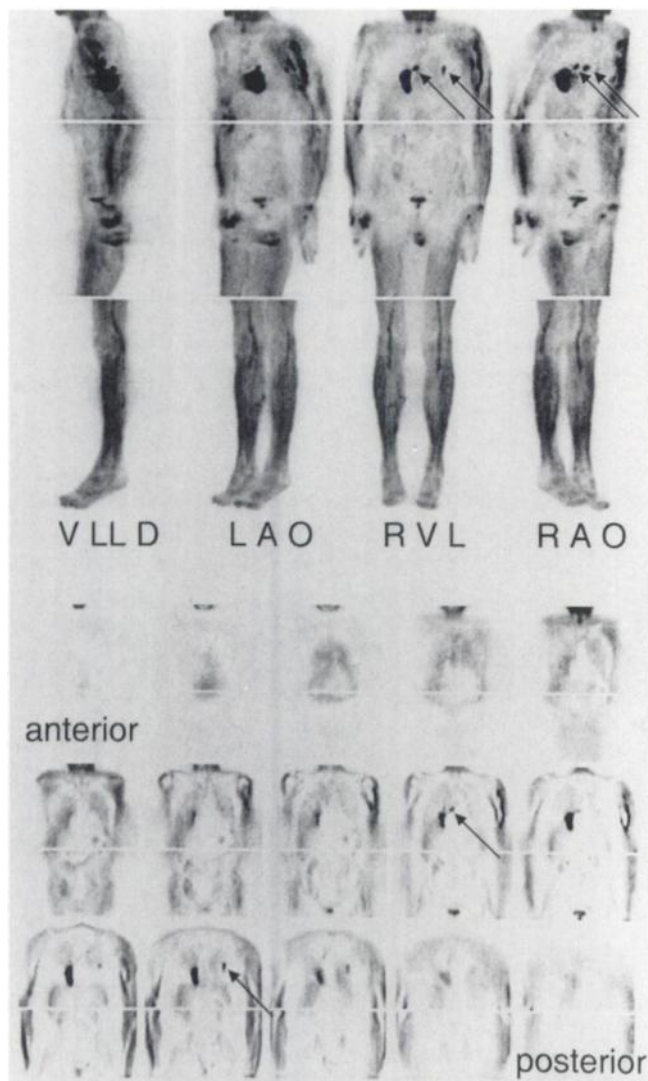


FIGURE 2. MIPs of truncus from left lateral (VLLD), left anterior oblique (LAO), anterior (RVL), and right anterior oblique (RAO) views and coronal slices from anterior to posterior. Patient was 78-y-old man with pathologic fracture of left humerus cytologically proven as bone metastases of squamous cell carcinoma of unknown primary. Note increased FDG uptake at site of known fracture as well as in both lobes of lung (arrows). Histology confirmed squamous cell carcinoma of lung.

and the primary tumor site. Therefore, treatment includes an irradiation of both sides of the neck as well as an irradiation of potential sites of the tumor-bearing mucosa. Other authors advocate an ipsilateral neck treatment alone, either by irradiation or by surgery (37). The current variety of therapeutic approaches emphasizes the diagnostic and therapeutic difficulties in patients with CUP syndrome confined to the neck. Nevertheless, an accurate diagnostic work-up is crucial (38) because both prognosis and survival rates depend mainly on detection of the primary tumor site. The 5-y survival rates of patients with localized squamous cell carcinoma and bilateral cervical metastases are significantly higher compared with those of patients with unknown primary tumor site and comparable lymph node status

(2,14–18). Consequently, the main goal of and justification for an extensive diagnostic work-up are to exclude a potentially curable malignancy (32,38), which would substantially increase survival time (31).

Because the glucose analog FDG is both accumulated and trapped within metabolically active cells, PET using FDG can be used to detect increased glycolytic rates of several malignancies—e.g., malignant melanoma (27), lung cancer (24–26), and primary breast cancer (28). Moreover, CUP syndrome is known to be a multisystem disease with potential metastatic spread to the entire body. Thus, whole-body imaging using FDG PET offers the advantage of locating both metastases and primary tumor sites. This is of

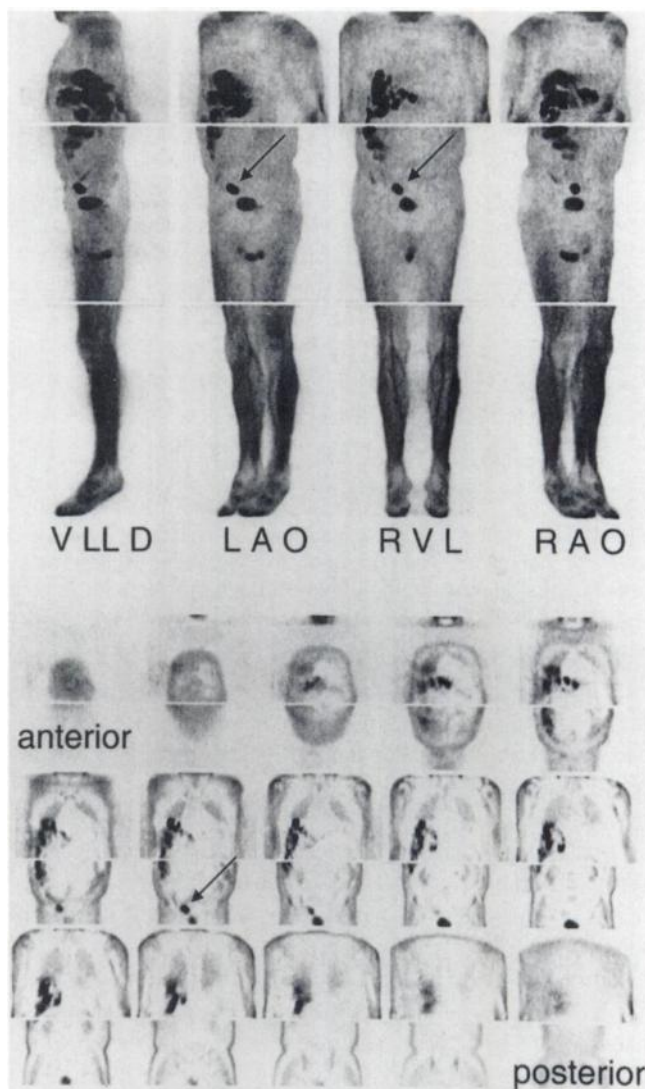


FIGURE 3. MIPs of truncus from left lateral (VLLD), left anterior oblique (LAO), anterior (RVL), and right anterior oblique (RAO) views and coronal slices from anterior to posterior. Patient was 69-y-old man with histologically proven liver metastases of adenocarcinoma of unknown primary. Note multiple sites of increased FDG uptake located in both lobes of liver, corresponding to known metastases. In addition, PET revealed single site of increased tracer uptake in projection of ileocolonic area (arrow). Histology confirmed colonic adenocarcinoma.

great importance because in up to 40% of patients with malignant cervical lymph nodes the primary is localized below the clavicles, with the most common site being in the lungs (2,14,38). On the basis of PET findings, clinical resources may be efficiently directed toward appropriate diagnostic and therapeutic procedures to substantially contribute to the patient's quality of life and survival.

Initial studies indicated the value of FDG PET for detection of unknown primary cancer located in the head and neck (15,39). Braams et al. (39) investigated 13 patients with cervical lymph node metastases of unknown origin. PET correctly identified the primary in 4 patients. In 1 patient a plasmocytoma was identified as the primary tumor. Schipper et al. (15) reported 25% true-positive PET findings in 16 patients with cervical metastases of unknown origin (15,40).

In 27 of 53 patients in this study, PET revealed pathologic accumulations of FDG corresponding to potential primary tumor sites. In 14 of these patients, sites accumulating FDG were localized outside the head and neck region, predominantly in the lungs (n = 12). In the remaining 13 patients, FDG PET revealed lesions suspected of being the primary tumor in the head and neck region. In 20 of 53 patients FDG PET correctly identified the primary tumor site. In 10 patients lung cancer was confirmed histologically as the primary tumor. Thus, on the basis of PET findings, the therapeutic approach was directly influenced in this patient subgroup. Of 9 patients with primary tumor lesions suspected in the head and neck, 5 were localized in the palatine tonsil. However, in 3 of these patients FDG PET was false-positive. Moreover, 1 patient refused additional evaluation of PET findings by biopsy. In total, focal accumulation of FDG in the palatine tonsil remained unclear in 4 patients, and primary cancer of the palatine tonsil was confirmed by histology in only 1 patient. In contrast, PET clearly identified a primary head and neck tumor in 8 of 53 patients, thereby guiding endoscopic biopsies for histologic diagnosis and further treatment.

Moreover, PET findings were correlated to clinical findings of known cervical metastatic adenopathy. In 24 of 44 patients PET confirmed known tumor tissue. In 20 patients negative PET findings correctly confirmed total surgical resection of metastatic lymph nodes. Thus, in the assessment of cervical metastases PET may assist the clinician in treating patients. Moreover, in this study PET imaging was helpful in approximately one third of all patients, resulting in a change of treatment strategies. The treatment protocol of cervical metastases from unknown primaries includes neck dissection as well as external irradiation of the potential tumor-bearing mucosa. Because PET detected the primary tumor outside the head and neck area in several patients, predominantly in the lungs, therapeutic procedure was adapted according to treatment protocols for primary lung cancer—i.e., surgery, chemotherapy, or external irradiation of the lungs.

CONCLUSION

FDG PET is a valuable diagnostic tool in patients with CUP syndrome because it detects the unknown primary tumor in about one third of all patients investigated. In addition, FDG PET assists in both guiding biopsies for histologic evaluation and selecting the appropriate treatment protocols in these patients.

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