Role of whole body positron emission tomography/computed tomography scan with $^{18}$F-fluorodeoxyglucose in patients with biopsy proven tumor metastases from unknown primary site

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Aim. The aim of this study was to evaluate the role of whole body PET/CT scan with $^{18}$F-fluorodeoxyglucose (FDG) in the detection of the primary tumor in patients with metastatic cancer from unknown primary origin (CUP syndrome).

Methods. Sixty-eight consecutive patients, with CUP syndrome (39 lymph nodes, 29 visceral biopsy proven tumor metastases), underwent a whole-body FDG-PET/CT study. All enrolled patients were unsuccessfully studied, within the previous month, with physical examination, laboratory tests and conventional diagnostic procedures. All the pathological findings identified at PET/CT scan and suspected for primaries, were further investigated. After PET study, the minimum follow-up period for the inclusion in the studied population was 3 months.

Results. The primary tumor site was correctly identified by FDG-PET/CT in 24 patients (24/68, 35.3%): lung (n=9), rino/oro-pharynx (n=6), pancreas (n=5), colon (n=2), uterus (n=2). In 5 cases, FDG-PET scan did not identify a primary pathological focus, which was subsequently detected by other diagnostic methods within 3 months. In 39 patients (39/68, 57.4%), the primary tumor site was not localized. However, in 9 of them, FDG-PET/CT scan identified further unexpected metastases, modifying the stage of disease. Overall, the following oncological treatment was influenced by the PET scan, in a total of 33 patients (33/68, 48.5%).

Conclusion. Our data strongly support the diagnostic contribution of whole body FDG-PET/CT scan in the evaluation of patients with CUP syndrome and suggest its use in an early phase of the diagnostic iter to optimize patient management.

KEY WORDS: Fluorodeoxyglucose - Tomography, emission computed - Computed tomography - Neoplasms, etiology - Tumor staging - Metastases.

The site of origin of a histologically documented carcinoma is not identified clinically in approximately 3% to 5% of the patients; this situation is often referred to as carcinoma of unknown primary origin or occult primary malignancy (CUP syndrome).1, 2 CUP syndrome is the fourth cause of cancer death in both men and women, with a median age of 60 years at presentation.3 It includes an extremely heterogeneous group of tumors with various clinical sets and with a common feature, i.e. the presence of at least one biopsy proven tumor metastases.4 In this patient population, the research of the primary tumor site is often costly, time consuming, and multifaceted. However, even if the median survival time is short (nearly 8 months)1 a complete disease staging and the detection of the primary tumor could significantly change the prognosis by allowing a more rational and efficient treatment.

Previous reports describe that in CUP syndrome only 10-35% of the primary sites are detected by conventional imaging modalities;1, 4, 5 on the other hand, several studies have indicated positron emission...
tomography (PET) with $^{18}$F-fluorodeoxyglucose (FDG) as a useful tool to locate primary disease, both in patients presenting tumor metastases within the head and neck region $^{6-8}$ and in patients presenting extracervical metastases,$^{9-12}$ with a detection rate ranging between 24% and 53%.$^{13,14}$

Today, the extensive availability of combined PET/computed tomography (CT) tomographs equipped with both a multi-slice CT and a current generation PET tomograph, has provided new insights in the diagnosis, staging and follow-up of oncological patients.$^{15-17}$ The main advantage of combined PET/CT imaging is its ability to accurately correlate the abnormal metabolic changes, detected on the PET study, to the anatomic structures defined at the CT imaging. The accuracy of PET/CT versus that of PET alone has been evaluated by several authors and a gain in definitive diagnosis ranging between 20% and 40% by using integrated PET/CT is commonly reported.$^{18-21}$

In patients with tumor metastases from unknown primary site, similar benefits could be expected by using the PET/CT instead of the PET tomograph alone. Recently two studies have been published on this topic and this hypothesis seems to be confirmed.$^{22,23}$

The aim of our study was to evaluate the role of whole body FDG-PET/CT scan in the detection of the primary site in patients presenting with histologically proven metastases from unknown primary tumor.

### Materials and methods

**Patients population**

This retrospective study included 68 consecutive patients (enrolled from June 2004 to June 2005, 36 males and 32 females, age range 42-79 years and mean age 65 years), presenting with histologically proven metastases from unknown primary site. We had: 39 lymph node metastases (18 of which cervical, 3 supraclavlear, 11 axillary, 1 mediastinic, 2 retroperitoneal, 4 inguinal), 7 skeletal metastases, 6 liver metastases, 2 brain metastases, 1 cutaneous localization and 10 pleural and/or peritoneum malignant effusions. The remaining 3 patients presented with multiple metastases involving both bone and lymph nodes. A total of 46 metastases (46/68, 67.6%) were from carcinoma (5 poorly differentiated carcinoma, 8 squamous cell carcinoma, 1 urothelial cell carcinoma, and 32 undefined carcinoma), 18 (18/68, 26.5%) from adenocarcinoma, and 4 (4/68, 5.9%) from melanoma (Table I).

All enrolled patients were unsuccessfully studied, within the previous month, with physical examination,
laboratory tests and conventional diagnostic procedures, i.e. chest X-ray, abdominal contrast enhancement CT, and, on the basis of suspected primary disease, chest contrast enhancement CT, magnetic resonance imaging (MRI), ultrasonography (US), mammography and endoscopic procedures. All patients were referred to the University Nuclear Medicine Service (ASO San Giovanni Battista, Turin, Italy) or to a private PET/CT Center (IRMET SpA, Turin, Italy) for a whole body FDG PET/CT scan. The patients were informed on the procedure and written informed consent was obtained.

Whole body FDG PET/CT scan

PET/CT studies were acquired using two different combined tomographs. In 47 patients, PET scan was performed by using a Discovery ST tomograph (General Electric Medical Systems, Waukesha, WI, USA), and in 21 patients by using a Gemini tomograph (Philips Medical Systems, Cleveland, OH, USA). The patients were requested to fast for at least 6 h before scanning; at the time of the tracer injection, all patients presented glycemia blood levels under 200 mg/dL (mean 105 mg/dL; range 75-146 mg/dL). No signiﬁcant differences were found in body mass index and glycemic blood level between the two groups of patients, studied with each tomograph.

Whole body emission scans (8-9 bed position for 3 min per each bed position) were acquired beginning 60 min after the intravenous injection of FDG (dose range: 222-370 MBq). No adverse events were observed in any of the patients after the administration of FDG. The acquisition protocol started with a scout view (a CT bidimensional projection of the patient) which was used to deﬁne the body axial extension (start and end position) over which to acquire the CT and PET data. Once deﬁned the scan range, the CT scan was performed from neck to pelvis or from skull to feet (in patients with metastases from melanoma), with a voltage of 140 kV and tube current of 60 mA for Discovery ST, and 120 kV, 80 mA for Gemini. This scan lasted approximately 1 min and it was used for both anatomical localization and attenuation correction of PET emission data. At the end of the CT scan the bed position was translated into the PET field of view (FOV) for the PET study. The PET emission data of the whole body distribution of the tracer were acquired (3 min per FOV) in 3D mode with both of the scanner (from pelvis to neck or from feet to skull).

Images reconstruction was performed as: 3D reconstruction algorithm FORE-Iterative, FOV 50 cm, image matrix size 128×128 (Discovery ST); RAMLA 3D-Iterative, FOV 50 cm, image matrix size 128×128 (Gemini).

Image analysis

Whole body PET/CT images were evaluated by two nuclear medicine physicians generating a clinical report in conference after reviewing previous imaging results and clinical information. All viewing of co-registered images were performed with a dedicated software: eNTEGRA for images obtained with the Discovery ST, and Syntegra for images obtained with Gemini.

FDG-PET/CT findings confirmation

The FDG pathological findings, suspected for primaries, were further investigated with other imaging examination, biopsy and/or surgery and clinical follow-up. After PET/CT study, the minimum follow-up period for the inclusion in our patients population was 3 months.

Statistical analysis

To correlate the accuracy of PET scan with the tumor histotype, differences between identification rate in patients with metastases from adenocarcinoma and patients with metastases from carcinoma were evaluated with the χ² test. The same test was used to evaluate differences in the identification rate between the group of patients with cervical lymph node metastases and extra-cervical metastases.

Results

Whole body FDG-PET/CT scan findings in the 68 CUP syndrome cases enrolled are reported in Table I. The primary tumor site was identiﬁed and conﬁrmed in 29 cases out of the 68 (29/68, 42.6%). In 24 of these patients the primitive neoplasm location was correctly identiﬁed by whole body PET/CT scan (24/68, 35.3%). In the 5 remaining cases (5/68, 7.35%), FDG-PET/CT scan did not identify a primary pathologic focus, which was subsequently detected by other diagnostic methods, performed within 3 months.
after the PET scan (breast: n=2; larynx: n=1; stomach: n=1; ovary: n=1). Whole body PET/CT scan allowed an easier identification and a better anatomical definition of primary tumor site in at least 13 cases: the 6 rino/oro-pharynx tumors, the 5 pancreas tumors and 2 cases of uterus cancer.

Of the 24 primary tumors detected by PET/CT, 12 were adenocarcinoma and 12 carcinoma (6 squamous...

Figure 1.—Patient presenting with latero-cervical lymph nodes metastases from unknown primary tumor. FDG-PET/CT showed a pathological uptake of the tracer in the right rino-pharynx (confirmed primary site) and in several bilateral latero-cervical lymph nodes.
cell carcinoma, 2 poorly differentiated carcinomas, 1 clear cell carcinoma and 3 undefined carcinomas). Therefore, we obtained an identification rate of the primary site significantly different in presence of adenocarcinoma and carcinoma metastases: 12/18 (66.6%) versus 12/46 (26.1%), respectively; \( P=0.006 \) (\( \chi^2 \) test).

Whole body FDG-PET/CT allowed the detection of the primary tumors in 8 patients out of the 18 (44.4%) presenting with cervical lymph nodes metastases (Figure 1), and in 16/50 cases (32%) presenting with other metastases (Figures 2 and 3; Table I). No significant differences in the detection rate of primary tumor were found between patients with cervical and extra-cervical metastases (\( P=\text{NS} \); \( \chi^2 \) test).

At PET study 12 out of the 68 biopsy proven metastases, were not visualized: 8 lymph node metastases (in all cases, the suspected lymph node was excised for the histo-pathological examination), 2 cerebral metastases (due to the limitation in the extent of PET scan), and 2 pleural malignant effusions.

In 39 patients (39/68, 57.4%), the primary tumor site was not localized at the end of the diagnostic iter. In 34 of these patients, PET/CT scan was negative for primary focus, while in 5 cases PET/CT scan identified a suspect pathological up-takes (Table I), which were not confirmed by clinical follow-up and/or biopsy (false positive rate: 5/68; 7.35%). The positive predictive value of PET/CT study resulted to be 24/29, 82.8%.

FDG-PET/CT identified further unexpected metastases in 9 out of these 39 patients (23.1%), modifying the stage of disease. In fact, these 9 patients were referred to the PET study with proven lymph node metastases confined to a singular lymphatic station and the PET/CT scan identified further parenchymal and/or bone metastases. Finally, in our patient population the following oncological treatment was influenced by the whole body FGD-PET/CT scan, in a total of 33 patients (33/68, 48.5%): the 24 cases in which the primary site was identified (that started a specific oncological treatment), and the 9 cases in which disease stage was modified (in these latter, only symptomatic pharmacological supports were used).

**Discussion**

Although the patient population with CUP syndrome includes a heterogeneous group of pathologies,
the prognosis of these patients still remains poor, with a median survival time ranging between 4 to 11 months.

The identification of the primary tumor may offer the possibility of a more specific and effective treatment with an improvement of survival time. The key role of whole body FDG-PET scan in this field has been showed by previous studies, and these data led the German Consensus Conference to recognize in 2001 the whole body FDG-PET study as diagnostic technique (i.e. scientifically proved benefit and established clinical use) in patient with CUP syndrome. The recent clinical introduction of combined PET/CT tomographs, allowing the simultaneous acquisition of accurately aligned whole body anatomical and functional images, seems to be more accurate than PET alone in assessing presence and location of tumor foci, and therefore in tumor staging. At this moment, at the best of our knowledge, there are only two published papers on CUP syndrome and whole body FDG-PET/CT scan. In 2005, Gutzeit et al. studied 45 patients with tumor metastases from unknown primary site by PET/CT, obtaining an identification rate of the primary cancer in 33% of cases, while in the same period, in a group of 21 patients, Nanni et al. reached a detection rate of the unknown primary focus of 57%. Our study supports these results with an identification rate of 35.3% in a group of 68 cases with CUP syndrome.

Our paper and those of Gutzeit et al. agree on the concept that dual-modality PET/CT is “a promising alternative to separate acquisition of morphologic and functional data when assessing patients with cancer of an unknown primary tumor”. This finding, although not statistically confirmed, is mainly achieved in anatomical complicated districts such as head and neck, and/or in the abdomino-pelvic region, where physiological tracer up-takes may mimic pathological lesions.

However, although the literature data and our findings agree on the concept that whole body FDG-PET/CT scan is an useful diagnostic tool in CUP syndrome, the use of this imaging modality in the early phase of the diagnostic iter is still object of controversies. It is our opinion that several reasons interact among them leading this result. First of all, the...
limitations in the available scientific studies, and in particular, the limited number of the included cases in each single study, compared to the extremely heterogeneous cohort of patients presenting with CUP syndrome. The difficulties in enrolling enough patients to obtain statistically significant results is also due to the definition of CUP syndrome itself, which includes only those patients presenting with “a biopsy-proven malignancy from unidentified anatomical origin following conventional diagnostic evaluation”. The inclusion in our study of only those patients with biopsy proven metastases, and the exclusion of those cases with highly suspected clinical findings at the diagnostic imaging procedures (such as multiple parenchymal lesions at CT or MRI, scintigraphic bone scans with multiple pathological up-takes, etc.) led to a selection of a limited cohort of patients. Furthermore, our group resulted to be different from those included in other studies on the same topic, which, despite the CUP syndrome definition, enrolled their patients with other selection criteria (i.e. exclusion of patients with metastases from melanoma, inclusion of patients with highly suspected but not biopsy proven metastases), not allowing a comparison among the study results.20

Furthermore, in FDG-PET studies of CUP syndrome, a great heterogeneity still remains also between groups of cases selected with same criteria, due to the primary tumor histology, grading, biological behavior and site. As far as tumor histology and grading are concerned, cancers of unknown primary origin may be divided in 4 histological subsets, including: well- and moderately- differentiated adenocarcinoma (60%), poorly differentiated carcinoma (30%), squamous cell carcinoma (5%), and poorly differentiated neoplasms (5%).1 Nevertheless, in our paper, the metastatic lesions were predominantly from primitive carcinomas (67.6%), while the identification of the primary site resulted to be significantly different among the histological subsets: 66.6% in adenocarcinoma, 26.1% in carcinoma, and none in melanoma. This finding could be referred to a different biological and metabolic behavior of these histotypes or to casualty. The limited number of our patients population and the few data available in literature do not permit further evaluation. Moreover, FDG uptake can be influenced by tumor grading. High grade epithelial tumors show an elevated glucose consumption with a high FDG uptake, while in low grade epithelial tumors, as in tumors with neuroendocrine differentiation, uptake can be lower or absent.

Regarding the biological behavior, it is reported that there is almost 70% of CUP syndromes, in which the primary tumor still remains unknown after an autopic investigation.3 In fact, there are slow growing tumors with a genotype favoring metastatic capability over local tumor growth or tumors that may involute during the course of the disease.27 Furthermore some invasive cancers, not switching to the angiogenic phenotype, are unable to grow beyond the size of 1-2 mm, thus remaining subclinical.28

Last but not the least, a crucial element influencing tumor identification with FDG-PET/CT technique, is its primary site. The 18F-fluorodeoxyglucose is not an optimal tracer for some anatomical districts. The physiological tracer uptake in gastrointestinal tract, in urinary tract for the renal excretion of the radiotracer, in the head and neck region, in the brain, and the eventually concomitant inflammatory processes, may hide neoplastic lesions or “simulate cancer”, creating false negative or false positive results.1 Although, some of these tracer limitations could be overcome by the introduction of the combined PET/CT tomographs,22 difficulties still remain in the study of these anatomical districts. In our study whole body FDG-PET/CT scan not allowed the identification of 5 primary tumor sites, further confirmed by other imaging techniques, located in breast, larynx, stomach and ovary. This can be explained by the presence of physiological FDG uptakes in these sites (especially in larynx and stomach) which hid the primary lesion or by the presence of a small tumor foci which had a low FDG uptake.

Nevertheless, even if there is a high heterogeneity in CUP syndrome and in the available scientific literature on this topic, our study results are in good agreement with the previous ones, showing that whole body FDG-PET/CT technique has an interesting sensitivity associated with a high positive predictive value (respectively 35.3% and 82.8% in the present study). Furthermore, because FDG-PET scan today is strongly indicated in the disease staging of most oncological patients, this indication should be considered in patients with CUP syndrome to plan an adequate oncological treatment (in our study, in 48.5% of patients, the disease management was influenced by PET scan findings). These results support the idea that, in CUP syndrome, whole body PET/CT scan with FDG has a high clinical impact and should be performed early in the workup of the patients.
Conclusions

Considering recent studies and our results, whole body FDG-PET/CT has to be considered an useful tool in CUP syndrome allowing an identification of primary tumors in 1 out of 3 cases, and modifying the stage of the disease and oncological treatment in about 50% of cases. These results suggest the use of PET/CT with FDG in an early phase of the diagnostic iter to optimize the management of these patients.

Acknowledgments. We thank Fabrizio Bottari, MD, and Vincenzo Arena, MD, for their help in the follow-up of selected patients.

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