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Cancer Imaging

^{18}F-FDG PET/CT as a Diagnostic Tool in Patients with Extracervical Carcinoma of Unknown Primary Site: A Literature Review

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ABSTRACT

Background. **Carcinoma of unknown primary (CUP) represents a heterogeneous group of metastatic malignancies for which no primary tumor site can be identified after extensive diagnostic workup. Failure to identify the primary site may negatively influence patient management. The aim of this review was to evaluate ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) as a diagnostic tool in patients with extracervical CUP.**

Materials and Methods. **A comprehensive literature search was performed and four publications were identified (involving 152 patients) evaluating ^{18}F-FDG PET/CT in CUP patients with extracervical metastases. All studies were retrospective and heterogeneous in in-** clusion criteria, study design, and diagnostic workup prior to ^{18}F-FDG PET/CT.

Results. ^{18}F-FDG PET/CT detected the primary tumor in 39.5% of patients with extracervical CUP. The lung was the most commonly detected primary tumor site ($\sim$50%). The pooled estimates of sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT in the detection of the primary tumor site were 87%, 88%, and 87.5%, respectively.

Conclusions. **The present review of currently available data indicates that ^{18}F-FDG PET/CT might contribute to the identification of the primary tumor site in extracervical CUP. However, prospective studies with more uniform inclusion criteria are required to evaluate the exact value of this diagnostic tool.** *The Oncologist* 2011;16:445–451

INTRODUCTION

Carcinoma of unknown primary (CUP) represents a heterogeneous group of metastatic malignancies for which no primary site of the tumor can be identified following a thorough medical history, careful clinical examination, and extensive diagnostic workup. CUP accounts for approxi-

mately 5% of all cancer diagnoses and is characterized by early dissemination, uncommon metastatic sites, and usually a poor prognosis [1, 2].

Although the conventional diagnostic workup has improved over the years, it remains a significant diagnostic challenge to identify the primary tumor site in CUP patients. In <30% of CUP patients, a primary site is identified ante mortem. Postmortem examinations reveal a putative primary site in 60%–80% of CUP patients, most often in the lung (27%), pancreas (24%), and hepatobiliary tree (8%) [3]. Failure to identify the primary tumor site may negatively influence patient management, because tailored chemotherapeutic regimens and targeted agents have been increasingly developed over the last decade for a number of solid tumors.

Although positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG PET) and ^{18}F-FDG PET/computed tomography (CT) are now recommended as additional diagnostic tools to conventional workup in CUP patients with cervical lymph node metastases [4–7], the value of ^{18}F-FDG PET/CT in CUP patients with extracervical metastases remains to be established. Sève et al. [8] recently provided a thorough review of ^{18}F-FDG PET studies in CUP patients with extracervical metastases. ^{18}F-FDG PET revealed a primary tumor site in 41% of patients (range, 24%–63%).

^{18}F-FDG PET/CT studies in CUP patients with extracervical metastases are mainly retrospective and small. Further, inclusion criteria vary among these studies. Thus, both cervical and extracervical CUP patients are included. In addition, some studies have included patients not fulfilling the generally accepted criteria for a CUP diagnosis (e.g., germ cell tumor, malignant melanoma, sarcoma), or the conventional diagnostic workup before the ^{18}F-FDG PET/CT has been insufficient (e.g., no CT or biopsy performed). Most previous reviews on ^{18}F-FDG PET/CT have included studies using the above rather broad definition of CUP, thus potentially leading to biased conclusions regarding the value of ^{18}F-FDG PET/CT, in particular in CUP patients with extracervical metastases [9–11].

In the present review, we used a more stringent definition of CUP and identified four ^{18}F-FDG PET/CT studies that fulfilled the definition and included CUP patients with extracervical metastases.

MATERIALS AND METHODS

Search Criteria and Study Selection
A comprehensive literature search of English-language publications in the PubMed online database was performed using the search string (cancer OR carcinoma OR neoplasm OR malignant OR tumour) AND (unknown primary OR unknown origin OR occult primary OR unidentified origin) AND (FDG-PET/CT OR fluorodeoxyglucose-PET/computed tomography OR ^{18}F-FDG PET/CT). The above search string was also used in combination with the thorough search strategy for ^{18}F-FDG PET literature published by Mijnhout et al. [12]. This did not result in additional publications. No date limit was used and the search was updated until May 2010. For completeness, the reference lists of the retrieved articles were reviewed for additional publications.

The following criteria were used to select articles for this review: (a) ^{18}F-FDG PET/CT studies in CUP patients with extracervical metastases, (b) conventional workup that included a thorough history and physical examination and adequate imaging procedures prior to ^{18}F-FDG PET/CT (chest x-ray or CT of the chest and CT of the abdomen and pelvis) but failed to detect the primary site, and (c) data were sufficient to allow calculation of sensitivity and specificity for detection of the primary site. Abstracts presented at congresses, reviews, meta-analyses, editorials, letters, and comments were excluded as well as duplicated studies with overlapping patient populations. In addition, we excluded studies in which (a) results for the subset of CUP patients with extracervical metastases were not extractable, (b) CUP patients had isolated cervical lymph node metastases, (c) results using ^{18}F-FDG PET/CT were not extractable from those using ^{18}F-FDG PET alone, and (d) the diagnosis of malignancy was not histologically confirmed.

Study Quality Assessment
Two authors (K.P. and A.K.H.M.) independently assessed the quality of the included studies using the quality assessment of diagnostic accuracy studies criteria modified by Kwee and Kwee [10]. Twelve methodological quality items were assessed for each study using the scores "yes," "no," or "unclear" for each item. No and unclear responses were interpreted as the quality item was not met. Disagreements between the two authors were discussed and resolved by consensus. A quality score for each study is expressed as a percentage of the maximum score of 12. The 12 methodological quality criteria items are specified in Table 1.

Data Analysis
To calculate the sensitivity, specificity, and detection rate of the primary site, a true positive (TP) result was considered when ^{18}F-FDG PET/CT suggested the location of the primary site and the location could be confirmed subsequently, whereas a result was considered false positive (FP)

Table 1. Quality assessment

Study	Quality items												Quality score
	1	2	3	4	5	6	7	8	9	10	11	12	
Gutzeit et al. (2005) [18]	+	−	+	−	+	+	−	−	+	+	+	+	66% (8/12)
Ambrosini et al. (2006) [17]	−	−	+	−	−	−	−	−	+	+	+	−	33% (4/12)
Pelosi et al. (2006) [19]	+	−	+	+	−	−	−	−	−	+	+	−	42% (5/12)
Yapar et al. (2010) [20]	−	−	+	−	−	+	−	−	−	+	−	−	25% (3/12)

Methodological quality was assessed using quality assessment of diagnostic accuracy studies criteria modified by Kwee and Kwee [10].
Quality item 1: Was the spectrum of patients representative of the patients who will receive the test in practice?
Quality item 2: Were selection criteria clearly described?
Quality item 3: Is the reference standard likely to correctly classify the target condition?
Quality item 4: Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?
Quality item 5: Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?
Quality item 6: Was the execution of the index test described in sufficient detail to permit replication of the test?
Quality item 7: Was the execution of the reference standard described in sufficient detail to permit replication?
Quality item 8: Were the index test results interpreted without knowledge of the results of the reference standard?
Quality item 9: Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
Quality item 10: Were uninterpretable/intermediate test results reported?
Quality item 11: Were withdrawals from the study explained?
Quality item 12: Was comparator review bias avoided?

when the location of the primary site could not be confirmed. The sites suggested by ^{18}F-FDG PET/CT were confirmed by biopsy and histopathological analysis; however, imaging procedures or clinical follow-up were accepted if no tissue could be obtained. A true negative (TN) result was considered when neither ^{18}F-FDG PET/CT nor other diagnostic procedures (including other imaging tests) detected the primary tumor site in the clinical follow-up period. The finding was classified as false negative (FN) if the primary tumor site was detected by other diagnostic procedures after a negative ^{18}F-FDG PET/CT. Sensitivity, specificity, and accuracy were calculated using the following formulas: sensitivity = TP/(TP + FN), specificity = TN/(TN + FP), and accuracy = TP + TN/(TP + TN + FP + FN).

RESULTS

Literature Search and Study Description
The PubMed search identified eight articles potentially eligible for inclusion. Four articles/studies were excluded for the following reasons: (a) duplicate study [13], (b) data on CUP patients with extracervical metastases were not extractable [14, 15], and (c) part of the study population underwent ^{18}F-FDG PET alone and was not analyzed separately from patients undergoing ^{18}F-FDG PET/CT [16].

Based on the above, four studies [17–20] were identified and included in this systematic review. These studies comprise a total of 225 patients. However, to include only patients who stringently fulfilled the extracervical CUP definition, patients with the following malignancies were excluded: germ cell tumors, malignant melanoma, neuroendocrine tumors, and lymphoma. Likewise, we excluded patients with only cervical lymph node metastases of any histology and patients with only a clinical suspicion of malignancy. In total, 152 of the 225 patients (67.6%) were included in the data analysis.

Study Characteristics
The four studies included in this review are summarized in Table 2. None of the studies were prospective, comprising only retrospective case series of patients referred for ^{18}F-FDG PET/CT scan. In three of the studies, CUP was diagnosed only after a conventional workup failed to identify the primary site. However, the definition of conventional workup varied among the studies (Table 2). In the study by Yapar et al. [20], the ^{18}F-FDG PET/CT scan was performed either before or after the conventional workup.

In all studies, the pathological evaluation included light microscopic evaluation with morphologic descriptions of the tumors; no immunohistochemistry (IHC) or histopathological suggestions of the primary site were reported.

PET/CT Imaging
Only in the study by Gutzeit et al. [18] could the CT in the combined ^{18}F-FDG PET/CT be classified as a diagnostic

Table 2. Study characteristics

Study	*n* of patients fulfilling extracervical CUP definition/total *n* of patients in study	Study design	Age mean (range)	Diagnostic workup before FDG PET/CT	Oral contrast/i.v. contrast	CT image quality (mAs, Kv, slice width)
Gutzeit et al. (2005) [18]	27/45	Retrospective	57 (29–95)	Conventional diagnostic strategies including comprehensive lab analysis, projectional and cross-sectional imaging, and endoscopic procedures when indicated	Yes/yes	130, 130, 5 mm
Ambrosini et al. (2006) [17]	30/38	NR	59 (41–77)	Physical examination, lab analysis, and imaging tests (CT and MRI)	NR/NR	NR[a] (80 mA, 140, NR)[a]
Pelosi et al. (2006) [19]	46/68	Retrospective	63 (42–79)	Lab analysis, chest x-ray, CT of abdomen; all other workup not performed systematically in all patients	NR/NR	60 mA, 140, NR (discovery)/80 mA, 120, NR (gemini)
Yapar et al. (2010) [20]	49/74	Retrospective	56 (22–84)	PET/CT either before or after conventional imaging methods	Yes/no	54, 130, 4 mm (biograph)/ 80, 140, 3.75 (discovery)
Total	152/225					

[a]In the study by Ambrosini et al. [17], the CT image quality was not reported, whereas this information was reported by Nanni et al. [13], which is a duplication of the study.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; NR, not reported.

CT scan, with a radiation dose of 130 mAs and i.v. and oral contrast. In all other studies, CT scans were performed with low radiation doses (54–80 mAs or 60–80 mA), with either no reported use or no use of i.v. contrast (low-dose CT). Therefore, the CT scans in these latter studies were used as a fast transmission source for attenuation correction and approximate anatomical mapping but not for diagnostic purposes.

Nuclear medicine physicians evaluated the combined ^{18}F-FDG PET/CT scans in three of the studies, whereas in the study by Gutzeit et al. [18], nuclear medicine physicians and radiologists evaluated the PET data and the CT data separately. In addition, the PET and CT data were evaluated side by side and the fused PET/CT data were evaluated by both a radiologist and a nuclear medicine physician.

Quality Assessment

The quality scores of the included studies were generally low to moderate, in the range of 25%–67% (Table 1). The study by Gutzeit et al. [18] obtained the highest quality score. All studies were retrospective case series, and the selection criteria (item 2) for the included patients were not well described and may vary in each study as well as between studies. Additionally, in the majority of the studies, the ^{18}F-FDG PET/CT might have been a part of the reference standard (item 5), which was inadequately described in all studies (item 7). It is unclear whether the ^{18}F-FDG PET/CT results were interpreted without knowledge of the results of the reference standard (item 8).

Diagnostic Performance

^{18}F-FDG PET/CT detected the primary tumor site in 60 patients with extracervical CUP (39.5%), with a range of 33.3%–44.9% (Table 3). The pooled estimates of sensitivity, specificity, and accuracy of ^{18}F-FDG PET/CT in the detection of the primary tumor site were 87%, 88%, and 87.5%, respectively.

The lung was the most commonly detected primary tumor site, accounting for ~50% of all cases ($n = 31$), followed by pancreas ($n = 5$), colon ($n = 5$), and breast ($n = 4$) (Table 4). In total, 10 FP (6.6%) and nine FN (5.9%) ^{18}F-FDG PET/CT cases were reported (Table 4). The lung and ovary were the most commonly reported locations of FP results, whereas the breast and ovary were the most common locations of FN results. Only in the study by Gutzeit et al. [18] were the causes of the two FP results described in detail. The pathological evaluation revealed one case of colitis and one case of pulmonary infarction. In the study by Ambrosini et al. [17], one patient with a negative ^{18}F-FDG PET/CT had a positive urine cytology with transitional cell carcinoma. The primary tumor site could be in the bladder or the urinary tract and was therefore interpreted as FN.

Gutzeit et al. [18] evaluated and compared the diagnostic performance of PET alone, CT alone, PET and CT side by side, and fused PET/CT [18]. Although more primary tumors were detected on fused PET/CT images (33.3%, nine of 27) than with other modalities (PET: 25.9%, seven of 27; CT: 14.8%, four of 27; PET and CT side by side: 29.6%, eight of 27), the differences were not statistically signifi-

Table 3. Sensitivity, specificity, and accuracy of PET/CT in tumor detection

Study	n of patients	Detection rate of primary tumor site	TP	FP	TN	FN	Sensitivity (%)	Specificity (%)	Accuracy (%)
Gutzeit et al. (2005) [18]	27	33.3% (9/27)	9	2	15	1	90.0	88.2	88.9
Ambrosini et al. (2006) [17]	30	43.3% (13/30)	13	1	15	1[a]	92.9	93.8	93.3
Pelosi et al. (2006) [19]	46	34.8% (16/46)	16	3	23	4	80.0	88.5	84.8
Yapar et al. (2010) [20]	49	44.9% (22/49)	22	4	20	3	88.0	83.3	85.7
Total	152	39.5% (60/152)	60	10	73	9			
Pooled PET/CT results (%)							87.0	88.0	87.5

[a]In one patient, the PET/CT was negative, but the patient had a positive urine cytology with transitional cell carcinoma. The primary tumor site could be located in the bladder or the urinary tract and was therefore interpreted as FN.
Abbreviations: FN, false negative; FP, false positive; PET/CT, positron emission tomography/computed tomography; TN, true negative; TP, true positive.

Table 4. PET/CT scans, true positive, false positive, true negative, and false negative results by location

Result	n of patients	Head and neck	Lung	Esophagus	Stomach	Pancreas	Bile ducts	Colon	Breast	Ovary	Uterus	Kidney	Bladder	Other
TP	60	3 (5%)	31 (52%)	1 (2%)	2 (3%)	5 (8%)	1 (2%)	5 (8%)	4 (7%)	1 (2%)	2 (3%)	3 (5%)		2 (3%)[a]
FP	10		3 (30%)		1 (10%)			1 (10%)	1 (10%)	2 (20%)	1 (10%)			1 (10%)[b]
FP rate			(9%)		(33%)			(17%)	(20%)	(67%)	(33%)			
FN	9				1 (11%)				3 (33%)	2 (22%)			1 (11%)	2 (22%)[c]
TN	73													

[a]One thymus and one thyroid.
[b]One peritoneal.
[c]One cutaneous epidermoid cancer and one germ-cell testicular cancer.
Abbreviations: FN, false negative; FP, false positive; PET/CT, positron emission tomography/computed tomography; TN, true negative; TP, true positive.

cant. The authors of that study attributed the rather favorable results when CT scan was used either alone or in combination to their high diagnostic standard achieved with the whole-body CT protocol.

DISCUSSION

For the majority of CUP patients, identification of the primary tumor site remains a significant challenge. The use of ^{18}F-FDG PET/CT scans combines functional and anatomical information, and its use in cancer patient diagnostics and staging has increased very rapidly since it was introduced in 2001. ^{18}F-FDG PET/CT is particularly useful when the CT scan of a combined ^{18}F-FDG PET/CT examination is performed as a high-quality CT scan with i.v. and oral contrast agents. As an example, ^{18}F-FDG PET/CT produced a significantly higher accuracy in staging of nonsmall cell lung cancer than with PET or CT alone, and positively affected therapeutic management [21]. When interpreting PET/CT, the nuclear physician/radiologist should be aware of misalignment phenomena and artefacts if the chest CT is performed during deep inspiration.

It seems likely that ^{18}F-FDG PET/CT could also be of significant value in detecting the primary tumor site in CUP patients. Indeed, ^{18}F-FDG PET and ^{18}F-FDG PET/CT are of great importance in the detection of the primary tumor site in CUP patients with cervical lymph node metastases, and thus the treatment planning [6, 7]. In contrast, the value of ^{18}F-FDG PET/CT is less well studied in CUP patients with extracervical metastases. We performed a rigorous literature search to identify publications that specifically address this important diagnostic issue. By using a set of defined search and selection criteria we identified eight studies in the PubMed database evaluating ^{18}F-FDG PET/CT in this patient population. Furthermore, analysis of these studies revealed that relevant data could be extracted from only four of these publications [13–16]. Of these four studies, only the study by Gutzeit et al. [18] used a diagnostic CT scan with a standard radiation dose (130 mAs) and i.v. and oral contrast.

The four studies discussed in the present review are all retrospective, representing a total of 225 patients. Patients not fulfilling the definition of extracervical CUP were ex-

cluded, leaving a total of 152 patients for our analysis (Table 2). In summary, ^{18}F-FDG PET/CT detected the primary tumor site in 60 patients with extracervical CUP (39.5%) (Table 1).

This is in agreement with the data presented in the study by Sève et al. [8] wherein ^{18}F-FDG PET revealed a primary tumor site in 41% of patients (range, 24%–63%).

The lung was the most commonly detected primary tumor site, accounting for ~50% of all cases. The pooled estimates of sensitivity, specificity, and accuracy for ^{18}F-FDG PET/CT in the detection of the primary tumor site were 87%, 88%, and 87.5%, respectively. The causes of FP and FN results were described only in the study by Gutzeit et al. [18]. Furthermore, a TN result was considered if the primary tumor site remained unknown using other diagnostic procedures in the clinical follow-up period, but only in the study by Pelosi et al. [19] was the clinical follow-up period defined and described (the minimum follow-up period was 3 months).

Similar to the review by Sève et al. [8] on ^{18}F-FDG PET [8], lung cancer seems to be overrepresented in our review. CT scanning of the chest was not performed in most of these patients before ^{18}F-FDG PET/CT. Thus, it is possible that not all patients fulfilled the stringent CUP definition because of a possible incomplete diagnostic workup prior to ^{18}F-FDG PET/CT. Because minor pulmonary tumors may remain undetected by conventional x-ray, the lack of chest CT in the conventional workup may partly explain the overrepresentation of lung cancer. In accordance with this notion, in the study by Gutzeit et al. [18], CT alone revealed a primary tumor site in four cases (three lung cancers), whereas PET alone and fused PET/CT were used to detect a primary tumor site in seven (three lung cancers) and nine (five lung cancers) cases, respectively.

Selection bias may have been introduced because of the retrospective nature of the studies. As an example, only a few of the CUP patients were reported to have liver metastases, and in general only a few patients had multiple metastases. This is in contrast to findings in recent prospective therapeutic studies in which >50% of patients were diagnosed with multiple metastatic sites, including liver metastases [22, 23].

Current recommendations for CUP diagnostics by the European Society of Medical Oncology emphasize the need for inclusion of IHC in the diagnostic workup [24]. None of the four studies included in this review reported the use of IHC. Furthermore, the performed quality assessment of the included studies resulted in rather low quality scores (Table 1). Three of the studies [17–19] also were quality assessed by Kwee and Kwee [10]. Although there were some specific differences, their overall scores and conclusions were similar. Conclusively, the diagnostic performance of ^{18}F-FDG PET/CT in CUP patients with extracervical metastases might be overestimated in the studies discussed here.

Nonetheless, a multidisciplinary expert panel of oncologists, radiologists, and nuclear physicians with expertise in ^{18}F-PET/CT concluded that ^{18}F-PET/CT would be beneficial in the diagnostic workup of CUP patients [5]. The four studies discussed in this review support the notion that ^{18}F-FDG PET/CT might contribute to the identification of the primary tumor site in extracervical CUP. However, prospective studies with a sufficient number of patients and with more uniform inclusion criteria are required to evaluate the diagnostic value of ^{18}F-FDG PET/CT (high-quality contrast-enhanced CT) in CUP patients with extracervical metastases.

AUTHOR CONTRIBUTIONS

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