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ONCOLOGY

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Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis

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Abstract The aim of this study was to systematically review and meta-analyze published data on the diagnostic performance of combined 18F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) in the detection of primary tumors in patients with cancer of unknown primary (CUP). A systematic search for relevant studies was performed of the PubMed/MEDLINE and Embase databases. Methodological quality of the included studies was assessed. Reported detection rates, sensitivities and specificities were meta-analyzed. Subgroup analyses were performed if results of individual studies were heterogeneous. The 11 included studies, comprising a total sample size of 433 patients with CUP, had moderate methodological quality. Overall primary tumor detection rate, pooled sensitivity and specificity of FDG-PET/CT were 37%, 84% (95% CI 78–88%) and 84% (95% CI 78–89%), respectively. Sensitivity was heterogeneous across studies (P=0.0001), whereas specificity was homogeneous across studies (P = 0.2114). Completeness of diagnostic workup before FDG-PET/CT, location of metastases of unknown primary, administration of CT contrast agents, type of FDG-PET/CT images evaluated and way of FDG-PET/CT review did not significantly influence diagnostic performance. In conclusion, FDG-PET/CT can be a useful method for unknown primary tumor detection. Future studies are required to prove the assumed advantage of FDG-PET/CT over FDG-PET alone and to further explore causes of heterogeneity.

Keywords FDG-PET/CT · Cancer of unknown primary · Primary tumor detection · Systematic review · Meta-analysis

Introduction

Cancer of unknown primary (CUP), defined as the presence of histologically proven metastatic disease for which the site of origin cannot be identified at the time of diagnosis (despite comprehensive diagnostic workup), is one of the ten most frequent cancers (accounting for 3–5% of all malignancies) and is the fourth most common cause of cancer-related death [1, 2]. Failure to detect the primary tumor impedes optimization of treatment planning, which, in turn, may negatively influence patient prognosis. ^{18}F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) allows whole-body tumor detection [3] and has proven to be useful in patients with CUP for the detection of the primary tumor [4–6]. A disadvantage of FDG-PET, however, is its lack of anatomic information, which may impede precise localization of FDG accumulation. Furthermore, tumors with low or even no FDG uptake may be missed by FDG-PET. Complimentary anatomic information, provided by computed tomography (CT) or magnetic resonance (MR) imaging, may improve the diagnostic performance of FDG-PET alone. The relatively recently introduced combined FDG-PET/CT scanner allows obtaining both functional and anatomic images in

a single examination [7, 8] and may be of great value for the detection of primary tumors in patients with CUP. The purpose of this study was therefore to systematically review and meta-analyze published data on the diagnostic performance of FDG-PET/CT in unknown primary tumor detection.

Methods

Search strategy

A computer-aided search of the PubMed/MEDLINE and Embase databases was conducted to find relevant published articles on the diagnostic performance of combined FDG-PET/CT in primary tumor detection in patients with CUP. The search strategy is presented in Table 1. No beginning date limit was used. The search was updated until 13 March 2008. Only English-, German-, French-, Italian- or Spanish-language studies were considered because the investigators were familiar with these languages. To expand our search, bibliographies of articles that finally remained after the selection process were screened for potentially suitable references.

Study selection

Studies or subsets in studies investigating the diagnostic performance of FDG-PET/CT in primary tumor detection in patients with CUP were eligible for inclusion. Review articles, meta-analyses, abstracts, editorials or letters, case reports, guidelines for management and studies examining ten or fewer patients with CUP were excluded. Studies or subsets in studies were excluded if metastases were not histologically confirmed. Studies that provided insufficient data to construct a 2×2 contingency table to calculate sensitivity and specificity for primary tumor detection in patients with CUP were also excluded. When data were presented in more than one article, the article with the largest number of patients or the article with the most details was chosen.

Two researchers (T.C.K., R.M.K.) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. Articles were rejected if they were clearly ineligible. The same two researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

Data abstraction

For each included study, information was collected concerning basic study and patient characteristics (author names, year of publication, country of origin, study design, number, age and sex ratio of investigated patients, location of metastases of unknown primary, histology of metastases of unknown primary and diagnostic workup before FDG-PET/CT), FDG-PET/CT parameters (time of fasting before FDG administration, FDG dose, time interval between FDG administration and data acquisition, number of CT detector rows, reconstructed CT slice width, administration of intravenous and/or oral CT contrast agents and area of body examined) and FDG-PET/CT evaluation (evaluation of attenuation-corrected and/or non-attenuation corrected images, interpreters(s) of FDG-PET/CT, criteria for positivity and applied reference standard).

To calculate estimates of diagnostic performance (i.e., primary tumor detection rate, sensitivity and specificity), a true-positive result was considered when FDG-PET/CT suggested the location of the primary tumor and was subsequently confirmed. A false-positive result was considered when this location was not confirmed. The sites suggested by FDG-PET/CT were confirmed by histopathological analysis of tissue obtained by biopsy or surgery, considered as the reference standard. However, imaging procedures or clinical follow-up was accepted if no histopathological proof could be obtained. A true-negative result was considered when neither FDG-PET/CT nor the reference standard could detect the primary tumor. A false-negative result was considered if the primary tumor was detected in a particular location that was negative on FDG-PET/CT [4, 6].

Table 1 Search strategy and results as on 13 March 2008

#	Search string	PubMed/ MEDLINE	Embase
1	Fluorodeoxyglucose OR 2-fluoro-2-deoxy-D-glucose OR FDG OR positron emission tomography OR positron-emission tomography OR PET	39,616	46,549
2	Computed tomography OR computerized tomography OR computed tomographic OR CT OR CAT	430,940	317,859
3	Unknown primary OR unidentified primary OR occult primary OR unknown origin OR unidentified origin	32,203	25,105
4	#1 AND #2 AND #3	230	185

Study quality

For each included study, the methodological quality was assessed by using the Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews (QUADAS) criteria, which is a 14-item instrument [9, 10]. The item "Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?" was removed from the standard QUADAS list, since follow-up is required to verify negative FDG-PET/CT findings. The item "Did patients receive the same reference standard regardless of the index test result?" was removed from the standard QUADAS list, since positive FDG-PET/CT findings can be confirmed by means of histology, but negative FDG-PET/CT findings require follow-up. The item "Were the reference standard results interpreted without knowledge of the results of the index test?" was also removed from the standard QUADAS list, since

Table 2 Criteria list used to assess the methodological quality of the studies

Quality item	Positive score
Was the spectrum of patients representative of the patients who will receive the test in practice?	Patients with histologically confirmed metastatic cancer, in whom medical history, physical examination, full blood count, basic biochemistry battery, urinalysis, stool occult blood testing, immuno-histochemistry with specific markers as well as imaging technology with chest X-ray, computed tomography of the chest abdomen and pelvis or mammography and MR imaging in certain cases failed to detect the primary tumor, were included
Were selection criteria clearly described?	It was clear how patients were selected for inclusion
Is the reference standard likely to correctly classify the target condition?	Histopathological analysis of tissue obtained by biopsy or surgery, or imaging procedures or clinical follow-up if no histopathological proof could be obtained
Did the whole sample, or a random selection of the sample, receive verification using a reference standard of diagnosis?	All patients, or a random sample of patients who underwent FDG-PET/CT, also underwent the reference standard
Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?	FDG-PET/CT did not form part of the reference standard
Was the execution of the index test described in sufficient detail to permit replication of the test?	All of the following parameters were described: -Time of fasting before FDG administration, FDG dose, time interval between FDG administration and scanning -Application of intravenous and/or oral CT contrast -Scanned area -Evaluated images (AC and/or nAC) -Interpreter(s) of FDG-PET/CT mentioned
Was the execution of the reference standard described in sufficient detail to permit replication?	Besides histopathological analysis of FDG-PET/CT positive findings, additional diagnostic procedures (e.g., gastroscopy, CT, MR imaging) and duration of follow-up were described, if applicable
Were the index test results interpreted without knowledge of the results of the reference standard?	FDG-PET/CT was interpreted without knowledge of the findings of the reference standard
Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?	Interpreter(s) of FDG-PET/CT was/were aware of the histologic nature of the metastases of unknown primary
Were uninterpretable/intermediate test results reported?	All FDG-PET/CT results, including uninterpretable/ indeterminate/ intermediate were reported
Were withdrawals from the study explained?	It is clear what happened to all patients who entered the study
Was comparator review bias avoided?	Blinding FDG-PET/CT to the other imaging modality, if more than one imaging modality was applied

AC: attenuation-corrected images
nAC: non-attenuation-corrected images
CT: computed tomography
FDG-PET: ^{18}F-fluoro-2-deoxyglucose
FDG-PET/CT: ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography
MR: magnetic resonance

positive FDG-PET/CT findings can be verified by means of histopathological analysis of tissue obtained by biopsy or surgery. One item was added to the standard QUADAS list: "Was comparator review bias avoided?" The complete list of quality items is displayed in Table 2. For each item, the two researchers (TCK, RMK) independently assessed whether it was fulfilled (yes or no). If it was unclear from the information provided in an article as to whether an item was fulfilled, the item was rated as "unclear." Both "no" and "unclear" responses were interpreted as indicating that the quality criterion was not met. Disagreements were discussed and resolved by consensus. The total quality score was expressed as a percentage of the maximum score of 12.

Statistical analysis

Primary tumor detection rates of individual studies were calculated and totaled. Locations of primary tumors detected by FDG-PET/CT, locations of false-positives FDG-PET/CT findings and locations of false-negative FDG-PET/CT findings were recorded and summarized. Sensitivities and specificities of FDG-PET/CT in primary tumor detection (with corresponding 95% CIs) were calculated from the original numbers given in the included studies and meta-analyzed using a random effects model. Where sensitivity or specificity estimates for an individual study were zero, a continuity correction of 0.5 was added to every value for that study in order to make the calculation of sensitivity and specificity defined.

A chi-squared test was performed to test for heterogeneity between studies. Heterogeneity was defined as $P < 0.10$. Differences in sensitivities and specificities due to different cut-offs (thresholds) used in different studies to define a positive (or negative) FDG-PET/CT results were assessed by computing the Spearman correlation coefficient between the logit of sensitivity and logit of 1-specificity. A strong positive correlation would suggest the presence of a threshold effect. Other potential sources for heterogeneity were explored by assessing whether certain predefined covariates significantly influenced (i.e., $P<0.05$) the relative diagnostic odds ratio (RDOR) [11]. Although the findings of such analyses should be regarded mainly as hypothesis generating, statistical significance may suggest substantial changes in the diagnostic performance of the test under study as the covariate changes. Specifically, analyses were performed according to completeness of diagnostic workup before FDG-PET/CT (studies that fulfilled quality item 1 vs. studies that did not fulfill quality item 1 [Table 2]), location of metastases of unknown primary (cervical vs. extracervical), administration of CT contrast agents (both intravenous and oral contrast vs. no intravenous or oral contrast agent, or not reported), type of FDG-PET/CT images evaluated (both attenuation-corrected and non-attenuation-corrected images vs. attenuation-corrected images only, or not reported) and way of FDG-PET/CT review (reported blinding to reference test vs. no or unreported blinding to reference test.

Statistical analyses were executed using the Statistical Package for the Social Sciences version 14.0 software (SPSS Inc., Chicago, IL) and Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) [11].

Results

Literature search

The computer-aided search revealed 230 articles from PubMed/MEDLINE and 185 articles from Embase (Table 1). Reviewing titles and abstracts from PubMed/MEDLINE revealed 17 articles potentially eligible for inclusion. Reviewing titles and abstracts from Embase

Table 3 Basic study and patient characteristics (1)

Study and year	Country of origin	Study design	No. of patients	Age in years (mean, range)	Sex (M/F)
Fencl et al. [12], 2007	Czech Republic	Retrospective	82	NR	NR
Nassenstein et al. [13], 2007	Germany	NR	39	60, 39–89	31/8
Fleming et al. [14], 2007	USA	Retrospective	22	NR	NR
Bruna et al. [15], 2007	France	Retrospective	37	59, 31–85	14/23
Wartski et al. [16], 2007	France	Retrospective	38	57, 36–80	31/7
Ambrosini et al. [18], 2006	Italy	NR	38	59, 41–77	22/16
Fakhry et al. [20] 2006	France	Retrospective	22	48, 43–71	17/5
Pelosi et al. [22], 2006	Italy	Retrospective	68	63, 42–79	36/32
Nanni et al. [26], 2005	Italy	NR	21	60, 41–87	12/9
Freudenberg et al. [27], 2005	Germany	Retrospective	21	64, 46–94	16/5
Gutzeit et al. [29], 2005	Germany	Retrospective	45	57, 29–95	26/19

NR: not reported

Table 4 Basic study and patient characteristics (2)

Study and year	Location of metastases of unknown primary (N)	Histology of metastases of unknown primary (N)	Diagnostic workup before FDG-PET/CT
Fencl et al. [12], 2007	-Cervical (20) -Extracervical (61)	-Anaplastic carcinoma (35) -Adenocarcinoma (24) -Squamous-cell carcinoma (5) -Spinocellular carcinoma (7) -Mucinous carcinoma (10) -Small-cell carcinoma (1)	In all patients detailed medical history, full physical and laboratory examinations and diagnostic imaging methods
Nassenstein et al. [13], 2007	Cervical (39)	-Squamous-cell carcinoma (27) -Adenocarcinoma (5) -Undifferentiated carcinoma (2) -Lymphoepithelioid cancer (1) -Malignant melanoma (1) -Neuroendocrine cancer (1) -Papillary carcinoma (1) -Undifferentiated carcinoma (1)	In all patients tumor workup including physical examination, ultrasound, chest X-ray as well as complete endoscopic exploration with multiple blind biopsies of the nasopharynx, tonsils and tongue base
Fleming et al. [14], 2007	Cervical and extracervical (22)	NR	NR
Bruna et al. [15], 2007	Cervical and extracervical (37)	-Adenocarcinoma (17) -Squamous-cell carcinoma (14) - Undifferentiated carcinoma (6)	In all but three patients, CT of the neck and thorax; the three patients without a CT of the neck and thorax had at least a chest X-ray. In all patients CT and/or ultrasound of the abdomen and pelvis. In 13/23 females mammography and ultrasound of the breasts, in five females an additional MR of the breasts. In 25 patients, invasive diagnostic tests (endoscopic or surgical), of which 16 were bronchoscopies, 10 upper airway endoscopies, 9 colonoscopies and 8 gastroscopies
Wartski et al. [16], 2007	Cervical (38)	-Squamous-cell carcinoma (32) -Undifferentiated carcinoma (4) -Mucoepidermoid carcinoma (2)	In all patients systematic palpation, fiber-optic laryngoscopy and nasopharyngoscopy, CT and/or MR imaging with sections from the skull base to the mediastinum and rigid panendoscopy with randomized biopsies at the most frequent sites of primary tumor
Ambrosini et al. [18], 2006	NR	-Adenocarcinoma (13) -Epithelial carcinoma (8) -Squamous-cell carcinoma (5) -Mucoid adenocarcinoma (2) -Poorly differentiated carcinoma (2) -Undifferentiated adenocarcinoma (2) -Flat-cell tumor (1) -Germ-cell tumor (1) -Melanoma (1) -Spindle-cell tumor (1) -Spinous-cell carcinoma (1) -Transitional-cell carcinoma (1)	In all patients physical examination and negative laboratory and imaging tests; all patients underwent multislice CT and MR imaging

Table 4 (continued)

Study and year	Location of metastases of unknown primary (N)	Histology of metastases of unknown primary (N)	Diagnostic workup before FDG-PET/CT
Fakhry et al. [20] 2006	-Cervical (22)	-Squamous-cell carcinoma (22)	In all patients CT and nasofibroscopy
Pelosi et al. [22], 2006	-Cervical (18) -Extracervical (50)	-Undefined carcinoma (32) -Adenocarcinoma (18) -Squamous-cell carcinoma (8) -Poorly differentiated carcinoma (5) -Melanoma (4) -Urothelial-cell carcinoma (1)	In all patients 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, MR imaging, ultrasonography, mammography and endoscopic procedures
Nanni et al. [26], 2005	-Cervical (3) -Extracervical (17) -Cervical and extracervical (1)	-Adenocarcinoma (8) -Squamous-cell carcinoma (7) -Poorly differentiated carcinoma (1) -Melanoma (1) -Transitional-cell carcinoma (1) -Germ-cell tumor (1) -Spindle-cell carcinoma (1) -Flat-cell tumor (1)	In all patients physical examination (digital rectal examination with tests for occult blood in the stool, breast palpation and pelvic examination in women, prostate and testicular examination in men) and traditional diagnostic procedures according to international guidelines (complete blood counts, liver and renal function tests, urine analysis, chest radiography, CT and/or MRI of the abdomen and pelvis plus X-ray mammography in women and prostate-specific antigen test in men)
Freudenberg et al. [27], 2005	Cervical (21)	-Squamous-cell carcinoma (14) -Adenocarcinoma (4) -Undifferentiated malignancy (3)	In all patients clinical, endoscopic, sonographic and planar radiological staging (none of the patients had received a dedicated head and neck CT before)
Gutzeit et al. [29], 2005	-Cervical (18) -Extracervical (27)	-Adenocarcinoma (25) -Squamous-cell carcinoma (15) -Undifferentiated carcinoma (5)	In all patients a complete medical history, thorough physical examination and conventional diagnostic strategies (including comprehensive laboratory analysis, projectional and cross-sectional imaging and endoscopic procedures where indicated)

CT: computer tomography
FDG-PET/CT: ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography
MR: magnetic resonance
NR: not reported

revealed 17 articles potentially eligible for inclusion, of which 15 were all already identified by the PubMed/MEDLINE search. Thus, 19 studies [12–30] remained for possible inclusion and were retrieved in full text version. Screening of the references of these 19 articles did not bring up new articles. After reviewing the full article, two articles [17, 19] were excluded because a part of the study population underwent FDG-PET alone and was not separately analyzed from patients undergoing FDG-PET/CT, two articles [25, 30] were excluded because sensitivity and specificity for primary tumor detection could not be calculated, one article [28] was excluded because it did not separately analyze patients with CUP, one article [21] was excluded because fewer than ten patients with CUP were included, one article [23] was

Table 5 FDG-PET/CT parameters

Study and year	Time of fasting before FDG administration (h)	FDG dose (MBq)	Time interval between FDG administration and data acquisition (min)	No. of CT detector rows	Reconstructed slice width (mm)	Intravenous CT contrast	Oral CT contrast	Area of body scanned
Fencl et al. [12], 2007	≥6	350–450	60–90	2	4.0	Yes and no	Yes	From the skull base to below the groin
Nassenstein et al. [13], 2007	≥4	350	60	2	-3.0 (head and neck) -5.0 (chest and abdomen)	Yes	Yes	From the head to the upper thigh
Fleming et al. [14], 2007	NR	555	75	16	NR	NR	NR	From the top of the head to midthigh
Bruna et al. [15], 2007	≥6	5.5/kg (max. 550)	60	NR	NR	NR	NR	From the top of the head to midthigh
Wartski et al. [16], 2007	≥6	4–5/kg	60	NR	5.0	No	No	From the skull to the midthigh
Ambrosini et al. [18], 2006	6	370	60–90	NR	NR	NR	NR	"Whole-body"
Fakhry et al. [20] 2006	≥6	260–330	60	NR	NR	NR	NR	From the skull base to the thighs
Pelosi et al. [22], 2006	≥6	222–370	60	NR	NR	NR	NR	From neck to pelvis or from skull to feet
Nanni et al. [26], 2005	≥6	370	60–90	NR	NR	NR	NR	"Total body scan"
Freudenberg et al. [27], 2005	≥10	360	60	2	-3.0 (head and neck) -5.0 (from thorax to pelvis)	-No (head and neck -Yes (thorax to pelvis)	-No (head and neck) -Yes (thorax to pelvis)	Head, neck, thorax, abdomen and pelvis
Gutzeit et al. [29], 2005	≥4	350	60	2	5.0	Yes	Yes	Head, neck, thorax, abdomen and pelvis

CT: computed tomography
FDG: ^{18}F-fluoro-2-deoxyglucose
NR: not reported

excluded because it was an editorial, and one article [24] was excluded because the same data were used in a later study. Eventually, 11 studies [12–16, 18, 20, 22, 26, 27, 29], comprising a total sample size of 433 patients with CUP, met all inclusion and exclusion criteria, and they were included in this systematic review. The characteristics of the included studies are presented in Tables 3, 4, 5 and 6.

Methodological quality assessment

Twelve methodological quality items were assessed for each of the 11 included studies (Table 7). The total methodological quality score, expressed as a fraction of the maximum score, ranged from 42% to 75% (median, 50%).

Table 6 FDG-PET/CT evaluation

Study and year	Evaluated images	Interpreter(s) of FDG-PET/CT	Criteria for positivity	Reference standard
Fencl et al. [12], 2007	AC and nAC	Seven physicians experienced in both PET and CT reading were randomly involved in routine evaluation of findings; in the event of any uncertainty, a second or even a third opinion was solicited	FDG hypermetabolism at the site of pathological changes on CT or marked focal hypermetabolism at sites suggestive of malignancy (liver parenchyma, bone marrow) despite absence of signs of pathology at those sites on CT	A diagnosis of the primary site of a malignancy was classified as true positive only when it was confirmed histologically. If the finding was not confirmed histologically, the diagnosis was classified as false positive. An evaluation was classified as true negative if neither FDG-PET/CT nor histological findings or clinical follow-up (including subsequent imaging tests) determined the site of the primary. When the site of the primary was not identified, but was proven histologically, the finding was classified as false negative
Nassenstein et al. [13], 2007	NR	Two different reading teams, each consisting of a radiologist and a nuclear medicine physician	Contrast-enhancing mass on CT or focally increased FDG uptake on PET	"Full medical history was available for all patients"
Fleming et al. [14], 2007	NR	One of three neuroradiologists	An SUV level greater than 2.5 was considered consistent with abnormal, hypermetabolic activity in primary, regional and distant disease	Each site of increased PET metabolic activity was compared with operative histopathology records
Bruna et al. [15], 2007	NR	NR	NR	-"Follow-up" -Histology (n = 7) -Complimentary examination (n = 3), among which were CT of the abdomen and pelvis (n = 2)
Wartski et al. [16], 2007	AC and nAC	Two experienced nuclear medicine physicians, independently	Increased FDG focal uptake indicative of a primary tumor in the head and neck and/or chest regions	FDG-PET/CT results were correlated to the patient's medical record concerning pathological results and treatment. A FDG-PET/CT result was considered as a true positive when an FDG focus matched the primary tumor found during the second panendoscopy, a false positive when the increased FDG focal uptake did not match panendoscopy results and a false negative when the second panendoscopy detected malignant lesions with no corresponding increased FDG focal uptake
Ambrosini et al. [18], 2006	NR	Three nuclear medicine physicians in consensus	NR	-PET/CT findings were subsequently confirmed by surgery or biopsy of the primary tumor -Gastroscopy and 3-month follow-up in one patient
Fakhry et al. [20] 2006	NR	Two nuclear medicine physicians	NR (visual interpretation)	Histology and/or clinical follow-up >6 months in all patients

Table 6 (continued)

Study and year	Evaluated images	Interpreter(s) of FDG-PET/CT	Criteria for positivity	Reference standard
Pelosi et al. [22], 2006	NR	Two nuclear medicine physicians in consensus	NR	The FDG pathological findings, suspected for primaries, were further investigated with other imaging examination, biopsy and/or surgery and clinical follow-up (minimum follow-up of 3 months after the FDG-PET/CT study)
Nanni et al. [26], 2005	NR	Three skilled nuclear medicine physicians; in case of discrepancy, the FDG-PET/CT interpretation was reached by consensus	NR	-FDG-PET/CT findings were subsequently confirmed by surgery or biopsy of the primary tumor -Gastroscopy in one patient
Freudenberg et al. [27], 2005	NR	Two experienced nuclear medicine physicians in consensus (FDG-PET) and two radiologists (CT)	-FDG-PET: regions of focally increased tracer uptake (a maximum SUV of >2.5 was considered to represent malignancy in otherwise equivocal findings) -CT: contrast-enhancing masses or asymmetries typical of malignancies	Histopathology (n=14) and clinical follow-up ≥9 months (n=7) with subsequent panendoscopy with biopsy of the most probable tumor sites (n=7), ultrasound (n=7), CT (n=6), MRI (n=6), diagnostic tonsillectomy (n=4) and additional biopsies (n=4)
Gutzeit et al. [29], 2005	AC and nAC	A nuclear medicine physician and a radiologist, both with 2 years of PET/CT experience	Contrast material-enhanced mass on CT or focally increased glucose metabolism with a SUV exceeding 2.5 on FDG-PET	-All potential sites of the primary tumor depicted by FDG-PET/CT were histologically verified -Axillary lymph node dissection in one FDG-PET/CT-negative patient -Endoscopy and biopsy of the esophagus in one FDG-PET/CT-negative patient

AC: attenuation-corrected images
nAC: non-attenuation-corrected images
CT: computed tomography
FDG-PET: ^{18}F-fluoro-2-deoxyglucose positron emission tomography
FDG-PET/CT: ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography
PET: positron emission tomography
PET/CT: positron emission tomography/computed tomography
NR: not reported
SUV: standardized uptake value

Diagnostic performance

The results of the 11 included studies are presented in Tables 8 and 9, and Figs. 1, 2 and 3. Primary tumor detection rates ranged from 22 to 73%, with an overall detection rate of 37% (162/433) (Table 8). The most commonly detected location of the primary tumor by FDG-PET/CT was the lung, 33% (Fig. 1). The most common locations of false-positive FDG-PET/CT findings were the lung and the oropharynx, both 15% (Fig. 2). The most common cause of false-negative FDG-PET/CT findings was breast cancer, 27% (Fig. 3). Sensitivity and specificity of FDG-PET/CT in primary tumor detection ranged from 55% to 100% and from 73% to 100%, with pooled estimates of 84% (95% CI 78–88%) and 84% (95% CI 78–89%), respectively (Table 8). The included studies were statistically heterogeneous in their estimates of sensitivity (P=0.0001), but homogeneous in their estimates of specificity (P=0.2114).

A Spearman correlation coefficient of -0.201 (P=0.554) between the logit of sensitivity and logit of 1-specificity did not suggest the presence of a threshold effect. No significantly increased RDORs were observed in any of the subgroup analyses according to

Table 7 Quality assessment of the 11 included studies

Study and year	Quality items												% of maximum score
	1	2	3	4	5	6	7	8	9	10	11	12	
Fencl et al. [12], 2007	-	+	+	+	+	+	-	-	-	+	+	+	67
Nassenstein et al. [13], 2007	-	-	-	+	-	+	-	-	-	+	+	+	42
Fleming et al. [14], 2007	-	+	-	-	+	-	-	-	-	+	+	+	42
Bruna et al. [15], 2007	-	+	+	+	-	-	-	-	-	+	+	+	50
Wartski et al. [16], 2007	-	-	-	+	+	+	+	+	-	+	+	+	67
Ambrosini et al. [18], 2006	-	-	-	-	-	-	+	-	+	+	+	+	42
Fakhry et al. [20] 2006	-	+	+	+	-	-	-	-	-	+	+	+	50
Pelosi et al. [22], 2006	+	-	+	+	-	-	-	-	-	+	+	+	50
Nanni et al. [26], 2005	+	-	+	-	+	-	+	+	+	+	+	+	75
Freudenberg et al. [27], 2005	-	-	+	+	+	+	+	-	-	+	+	+	67
Gutzeit et al. [29], 2005	-	-	-	-	+	+	+	+	-	+	+	+	58

completeness of diagnostic workup before FDG-PET/CT, location of metastases of unknown primary, administration of CT contrast agents, type of FDG-PET/CT images evaluated and way of FDG-PET/CT review (Table 9).

Discussion

CUP represents a heterogeneous group of metastatic tumors for which no primary site can be detected following a thorough medical history, careful clinical examination and extensive diagnostic workup [1, 2]. Attempts to identify the primary tumor in patients with CUP are are often time consuming, expensive and ultimately unsuccessful [1, 2]. The results of this study indicate that, overall, FDG-PET/CT is able to detect 37% of primary tumors in patients with CUP, and sensitivity and specificity are reasonably high (both 84%). Sensitivity, however, was heterogeneous across studies. Subgroup analysis could not clarify the observed heterogeneity. It should be noted, however, that results from our subgroup analysis may not be conclusive because of the relatively small number of included studies. Furthermore, it was not possible to perform subgroup analysis according to the number of CT detector rows and CT slice width due to incomplete reporting of included studies. Future studies are required to further investigate potential sources of heterogeneity.

The results of this systematic review should be interpreted carefully, since the methodological quality of the included studies was moderate. Several methodological shortcomings were identified, of which spectrum bias, bias due to the use of an inadequate reference standard and verification bias may seriously have affected the results. According to Pavlidis et al. [1, 2], the precise clinical definition of CUP should refer to patients who present with histologically confirmed metastatic cancer in whom medical history, physical examination, full blood count, basic

Table 8 Diagnostic performance of FDG-PET/CT in primary tumor detection

Study and year	Primary tumor detection rate (%)	Sensitivity (%)		Specificity (%)	
		Value	95% CI	Value	95% CI
Fencl et al. [12], 2007	22	55	38–70	75	62–85
Nassenstein et al. [13], 2007	28	100	74–100	85	69–94
Fleming et al. [14], 2007	73	94	73–99	100	61–100
Bruna et al. [15], 2007	38	93	70–99	77	57–90
Wartski et al. [16], 2007	34	93	69–99	73	48–89
Ambrosini et al. [18], 2006	53	100	84–100	95	76–99
Fakhry et al. [20] 2006	32	70	40–89	75	47–91
Pelosi et al. [22], 2006	35	83	66–93	87	73–94
Nanni et al. [26], 2005	57	100	76–100	89	57–98
Freudenberg et al. [27], 2005	57	86	60–96	100	65–100
Gutzeit et al. [29], 2005	33	88	66–97	89	73–96
Pooled estimate	37	84	78–88	84	78–89

Table 9 Results of subgroup analysis

Parameter	Value	No. of studies	Relative diagnostic odds ratio (1 vs. 2)		
			Value	95% CI	P-value
Completeness of diagnostic workup before FDG-PET/CT	1. Complete	2	1.93	0.22–17.28	0.5072
	2. Incomplete	9			
Location of metastases	1. Cervical	6	0.38	0.02–9.55	0.4765
	2. Extracervical	2			
Administration of CT contrast agents	1. Intravenous and oral	3	2.42	0.32–18.15	0.3347
	2. Not reported	7			
Evaluated FDG-PET/CT images	1. AC and nAC	3	0.36	0.06–2.09	0.2187
	2. AC only or NR	8			
Way of FDG-PET/CT review	1. Reported blinding	3	1.18	0.10–13.54	0.8766
	2. No reported blinding	8			

AC: attenuation-corrected images
nAC: non-attenuation-corrected images
NR: not reported

biochemistry battery, urinalysis, stool occult blood testing, immunohistochemistry with specific markers as well as imaging technology with chest X-ray, CT of the chest abdomen and pelvis or mammography and MR imaging in certain cases have failed to detect the primary tumor. However, only two studies [22, 26] (18%) included patients who fulfilled these criteria. In the other nine studies [12–16, 18, 20, 27, 29], diagnostic performance of FDG-PET/CT might have been overestimated because of (possible) incomplete diagnostic workup. Furthermore, only five studies [12, 15, 20, 22, 27] applied an adequate reference standard of histology and follow-up in all patients. Consequently, in the other six studies [13, 14, 16, 18, 26, 29], diagnostic performance of FDG-PET/CT might have been overestimated. Other methodological flaws include an inadequate description of selection criteria in seven studies [13, 16, 18, 22, 26, 27, 29] (64%), the possibility that FDG-PET/CT formed part of the reference standard (incorporation bias) in five studies [13, 15, 18, 20, 22] (46%), inadequate description of the execution of FDG-PET/CT in six studies [14, 15, 18, 20, 22, 26] (55%), inadequate description of the reference standard in six studies [12–15, 20, 22] (55%), possible interpretation of FDG-PET/CT while knowing the results of the reference standard (test review bias) in eight studies [12–15, 18, 20, 22, 27] (73%) and possible interpretation of FDG-PET/CT without knowledge of the histological nature of the metastases of unknown primary in nine studies [12–15, 16, 20, 22, 27, 29] (82%).

Lung, oropharyngeal and pancreatic carcinoma were the most frequently detected primary tumors by FDG-PET/CT

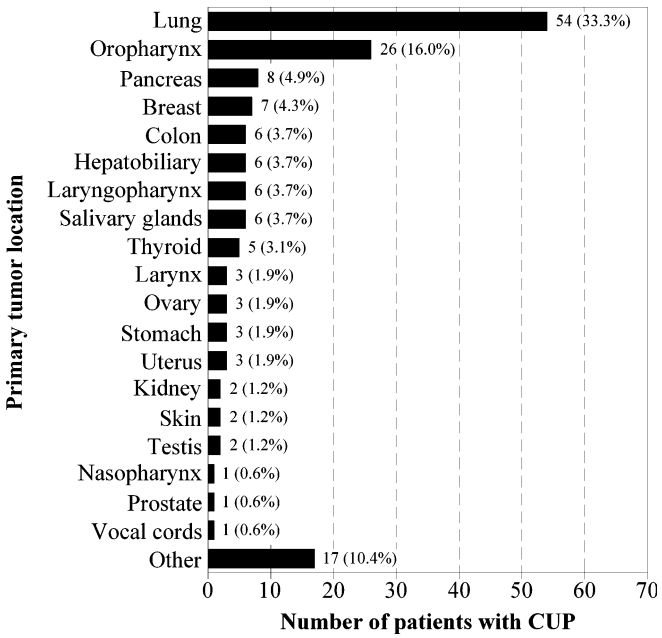

Fig. 1 Locations of primary tumours detected by FDG-PET/CT

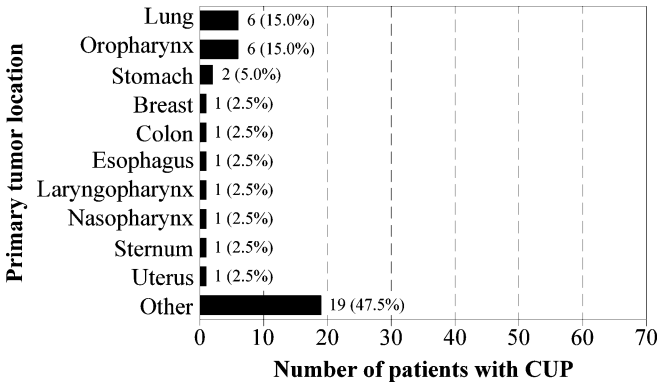

Fig. 2 Locations of false-positive FDG-PET/CT findings

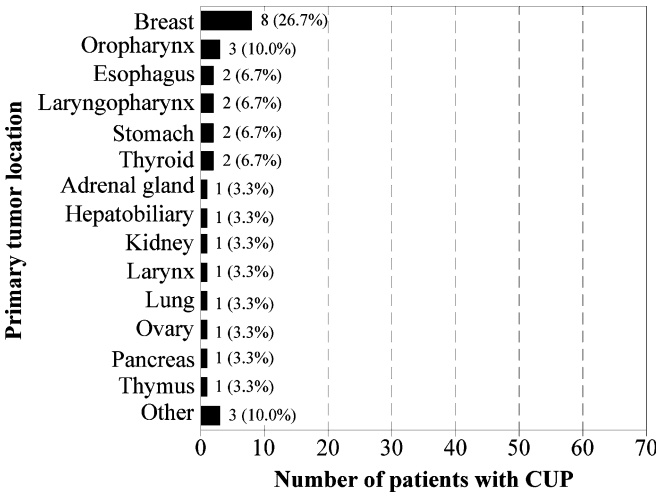

Fig. 3 Locations of false-negative FDG-PET/CT findings

in this meta-analysis (33%, 16% and 5%, respectively). This is partly in line with previous autopsy studies in patients with CUP [31–34], which have shown that the most common locations of the primary tumor are the lung and the pancreas. The high detection rate of oropharyngeal carcinoma by FDG-PET/CT in this meta-analysis, however, is discrepant with the results of autopsy studies [31–34]. This finding can by explained by the fact that 4 of 11 included studies [13, 16, 20, 27] exclusively investigated patients with cervical metastases of unknown primary, whose primary tumors are most frequently located in the oropharynx [5, 35]. Indeed, these four studies [13, 16, 20, 27] comprised 69% of all oropharyngeal carcinomas detected by FDG-PET/CT in this meta-analysis. The most commonly reported locations of false-positive FDG-PET/CT results were the lung and the oropharynx (both 15%). Causes of false-positive results may be FDG uptake in benign conditions with increased glycolysis (e.g., one false-positive FDG-PET/CT finding in the lung proved to be a pulmonary infarction [29]), high physiological FDG uptake (e.g., muscle FDG uptake) and failure to evaluate both attenuation-corrected and non-attentuation-corrected images to minimize the chance of misinterpreting (FDG-PET/CT) artifacts as pathologic (only three of the included studies [12, 16, 29] explicitly stated that both attenuation-corrected and non-attentuation-corrected images were evaluated) [36–38]. Breast cancer was the most common cause of false-negative FDG-PET/CT results (27%). This may be explained by the fact that small (<1 cm) and slow-growing, low-grade (breast) cancers with low or no FDG uptake (e.g., tubular carcinoma and noninvasive cancers such as ductal or lobular carcinoma in situ) may be overlooked on FDG-PET/CT [39].

FDG-PET alone has been thoroughly investigated for primary tumor detection in patients with CUP; meta-analyses on FDG-PET reported primary tumor detection rates ranging between 24.5% and 43%, sensitivities ranging between 87% and 91.9%, and specificities ranging between 71% and 81.9% [4–6]. An advantage of FDG-PET/CT over FDG-PET alone is more accurate localization of foci with increased FDG uptake, and this may reduce the problems of physiological FDG uptake being misinterpreted as pathological and false localization of disease. In addition, tumors with low or no FDG uptake, or tumors of a size below the spatial resolution of FDG-PET, may be depicted by the CT component of FDG-PET/CT. Recently introduced combined FDG-PET/CT scanners with a 64-section multidetector CT component and less than 2.5-mm collimation may detect small primary cancers in the lungs or oropharynx earlier [40] and are clearly superior to FDG-PET/CT alone. Furthermore, the additional anatomic data obtained using FDG-PET/CT may increase the accuracy of FDG-PET-directed biopsies. Another advantage of FDG-PET/CT is the use of the CT images for attenuation correction of the PET emission data, which reduces whole-body scanning times from 45 min to 30 min or less. This approach also provides low-noise attenuation correction factors, compared with those from standard PET transmission measurements using an external radiation source, and eliminates bias from emission contamination of postinjection transmission scans [7, 8]. On the other hand, a disadvantage of CT-based attenuation correction may be misclassification of regions containing high concentrations of CT contrast medium with high-density bone (CT contrast agents have high atomic numbers relative to the atomic number of bone, and as the concentration of a contrast agent increases, its corresponding CT number will fall within the CT number range for bone), which results in overcorrection for photon attenuation, consequently leading to an overestimation of FDG uptake in the contrast-enhanced region [41, 42]. Three of the included studies [13, 27, 29] directly compared FDG-PET/CT and (CT-based attenuation-corrected) FDG-PET alone. In all three studies [13, 27, 29], FDG-PET/CT was able to detect a few more primary tumors than FDG-PET alone, but these differences were not statistically significant. Therefore, FDG-PET/CT has not yet been proven to be diagnostically superior to FDG-PET alone. More studies directly comparing FDG-PET/CT and FDG-PET alone are required to prove the assumed advantage of FDG-PET/CT over FDG-PET alone.

Whole-body MR imaging may be an alternative to FDG-PET/CT [43]; it does not require the operator to work with a potentially harmful radiotracer, the safety profile of MR contrast agents is favorable compared with that of iodinated contrast with CT [44], and the costs for a whole-body MR imaging examination (about 575 euros) are approximately two times less than that of a whole-body FDG-PET/CT examination (about 1,123 euros) [45]. In 1998, Eustace et al. [46] showed the potential of whole-body MR imaging in primary tumor detection in four patients with CUP, using a short-tau-inversion-recovery sequence. However, to our knowledge, no other reports on the diagnostic performance

of whole-body MR imaging in unknown primary tumor detection have been published since then, while (both anatomical and functional whole-body) MR technology has continued to evolve [47, 48].

Identification of the primary tumor in patients with CUP enables accurate tumor staging, which allows optimizing treatment planning; this, in turn, may improve patient prognosis. On the other hand, it should be realized that FDG-PET/CT is an expensive examination, and false-positive FDG-PET/CT findings may result in unnecessary additional invasive diagnostic procedures, which have associated morbidities and costs [49]. In general, it appears that patients with CUP have a limited life expectancy, with a median survival of approximately 6–9 months [1, 2], but a median survival of 23 months has been reported for patients with CUP and an identified primary tumor subsequently treated with specific therapy [50]. Similarly, one study [51] reported that the 3-year survival rate for patients with cervical metastases and occult oropharyngeal primary tumors was 100% after treatment, while the patients with cervical metastases in which a primary tumor was not detected showed a survival rate of 58%. Only four studies included in this systematic review reported the therapeutic impact of FDG-PET/CT; in these four studies, FDG-PET/CT modified therapy in 18.2–60% of patients [15, 16, 20, 22]. Although one study [12] reported that the survival rate of CUP patients with at least one hypermetabolic lesion was significantly lower ($P<0.0279$) than that of the remaining CUP patients, none of the included studies reported FDG-PET/CT-modified patient outcomes. Therefore, the additional value of FDG-PET/CT to patients with CUP and its cost-effectiveness should be further investigated; the currently presented data can be used to perform such an analysis.

In conclusion, although included studies were of moderate methodological quality and their results were heterogeneous, the results of this systematic review and meta-analysis indicate that FDG-PET/CT can be a useful method for unknown primary tumor detection. Future studies are required to prove the assumed advantage of FDG-PET/CT over FDG-PET alone and to further explore causes of heterogeneity.

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