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Pivotal role of PET/CT in characterization of occult metastasis with undetermined origin

Ashraf Anas Zytoon[1]* , Elsayed Elmekkawy Elsayed[1], Amr Ibrahim Nassar[1] and Koji Murakami[2]

Abstract

Background: The purpose of this multicenter diagnostic accuracy test study was conducted to assess the role of positron emission tomography/computed tomography in the detection of primary tumor in cases of metastasis of undetermined primary site, to estimate its capability in detecting additional lesions as well as evaluating disease burden and staging. This multicentric diagnostic accuracy test study included 175 patients with pathologically proven, radiologically, and/or clinically suspected metastatic lesions of undetermined primary site. Clinical, surgical, and histopathologic findings and correlative imaging modalities were used to assess the results of PET/CT; the accuracy of PET/CT was expressed in terms of sensitivity and specificity, positive and negative predictive values.

Results: The study included 175 patients; PET-CT-positive lesions suggestive of primary malignant tumors were detected in 105 out of 175 patients. These lesions were pathologically proven to be malignant (true positive) in 100/175 patients (57.1%). Five out of 175 patients (2.9%) proved to be falsely positive after pathologic assessment; 70 out of 175 patients (40%) were negative for detection of primary malignancy all over the body by PET/CT (true negative) with no false negative results. PET/CT achieved a sensitivity of 100%, and specificity of 93.3% in detection of unknown primary tumor location.

Conclusion: PET/CT is an effective modality for early detection of the primary tumor site in patients with cancer of undetermined primary (CUP) which facilitates early selection of appropriate treatment protocols that will improve patients' prognosis.

Keywords: Cancer of unknown primary, Metastasis of undetermined primary, Positron emission tomography, Primary tumor detection

Background

Cancer of unknown primary (CUP) is defined as the presence of histologically proven metastatic disease for which the site of origin cannot be identified at the time of diagnosis. CUP 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]. The reasons cancer presents as CUP remains unclear; one hypothesis is that the primary tumor either regresses after seeding the metastases or remains too small to be detected [2].

Diagnostic procedures which are used for primary tumor detection include a combination of various radiological modalities, specific signs and symptoms, histological results, and laboratory abnormalities. Some of these tests can be expensive, time-consuming, and invasive. Furthermore, in the majority of patients these tests may eventually fail to detect a primary tumor. Clearly, there is a need for an alternative, noninvasive imaging modality with a high diagnostic yield. Combined positron emission tomography and computed tomography PET/CT, using the radiotracer 18F fluoro-2-deoxyglucose (FDG), can be an excellent problem-solving tool in patients with CUP [3]. 18F-FDG PET/CT hybrid imaging has gained wide application in the diagnosis, staging, and follow-up of cancer patients. The

* Correspondence: ashradio@gmail.com
[1]Radiodiagnosis Department, Faculty of Medicine, Menoufia University, Menoufia, Egypt
Full list of author information is available at the end of the article

degree of 18F-FDG uptake in tumor tissues is a valuable indicator in the prognostic stratification of cancer patients [4].

The rationale for using the radiotracer FDG for PET/CT imaging is the fact that the vast majority of malignant tumors exhibit an increased glucose metabolism (Warburg effect). In contrast to CT and conventional magnetic resonance imaging (MRI), FDG PET/CT has high lesion-to-background contrast, which makes it more sensitive imaging modality for the detection of malignant lesions [5]. It can be hypothesized that detection of a primary tumor will optimize treatment planning, which in turn will improve patients' outcome [6].

The hardware combination of anatomy and function has been the true evolution in imaging. It is evident that apart from additional costs, potential savings are associated with PET/CT as a result of avoiding additional imaging examinations or invasive procedures and by helping clinicians make the optimum treatment decisions [7]. PET/CT is better than CT alone for detection of malignant lesions for accurate staging. It can change the strategy of treatment according to its findings [8]. Furthermore in patients with unknown primary tumor (UPT), PET/CT could detect additional metastases, modifying the stage of the disease and thus influence the oncological treatment and thus optimize the management plan of those patients [9].

This multicenter study was conducted to assess the role of PET/CT in detection of primary tumor in cases of metastasis of cancer of unknown primary site, to estimate its capability in detecting additional lesions as well as evaluating disease burden and staging.

Methods
Patients
Our multicenter diagnostic accuracy test study was carried on 175 patients (110 men and 65 women, aged between 13 and 86 years) with pathologically proved, clinically, laboratory, or radiologically suspected metastatic lesions of unknown primary site; they were referred for localization of primary tumor site.

Inclusion criteria
Inclusion criteria were as follows: patients having at least one biopsied metastatic lesion, patients with radiologically suspected metastatic lesion(s), and/or elevated tumor markers.

Exclusion criteria
Exclusion criteria were as follows: uncontrolled diabetes, allergy to intravenous contrast, pregnancy, inability to cooperate with the scan process (inability to lie relatively still for 1–2 h and to lie supine for 30–60 min).

Data collection and analysis were done with approval of the research ethics committee, and written informed consent was obtained from each patient after the nature of the procedures had been fully explained.

FDG PET/CT study
Combined PET/CT scan was performed using Biograph True Point 64 and Biograph Sensation 16 PET-CT (Siemens Medical Healthcare, Erlangen, Germany). The integrated CT system is a 64- and 16-multi-slice scanner. The acquisition of co-registered CT and PET images were performed in one session. Adequate patient preparation rules were strictly followed. Patients were instructed to fast except for glucose-free hydration for 4–6 h before injection of 18F-FDG. The scan was performed 45–60 min (average 55 min) after IV injection of 0.1 millicurie/kilogram [mCi/kg] (3.7–4.5 MBq/kg body weight) with maximum dose of 18 mCi/kg of 18F-FDG. The blood glucose levels were checked in all patients before FDG injection, and no patients showed a blood glucose level of more than 140 mg/dl. The patients were examined in supine position. A whole-body examination was performed starting from skull vault to the feet.

The PET component of the combined imaging system had an axial view of 16.2 cm (per bed position) with an interslice spacing of 3.75 mm in one bed position. The transaxial field of view and pixel size of the PET images reconstructed for fusion were 58.5 cm and 4.57 mm, respectively, with a matrix size of 128 × 128 and 4.5 mm spatial resolution. To avoid artifacts caused by the urinary tract, patients were asked to drink 500 ml tap water or sugar-free green tea 30–60 min prior to image acquisition, and to void just before the start of acquisition. This is to ensure a negative oral contrast within the small bowel and to promote 18F-FDG excretion from the kidneys. No urinary bladder catheterization was used.

A PET scan was performed with several bed positions (12 to 14) depending on the height of the patient, with an axial field of view of approximately 15 cm per bed position with an in-plane spatial resolution of 4 mm covering the same field of view as with CT. The acquisition time of emission data was 2 min per bed position in the three-dimensional mode. The total examination time ranges between 24 and 28 min. Our protocol was adequately satisfied the minimal imaging requirement even though 2 min per bed position is a short acquisition time, relying upon enough injection dose and high sensitivity of Siemens PET camera. The PET section thickness was 3.4 mm. The images were loaded onto a workstation, and attenuation corrections were performed using the CT data. Attenuation-corrected PET images were reconstructed with an ordered-subset

expectation maximization iterative reconstruction algorithm.

According to previous recommendation guidelines; CECT data as part of the combined PET/CT examination provide additional information and support lesion detection and characterization. Furthermore, CT contrast agents are of additional value in 18F-FDG PET-negative tumors, so CE PET/CT, even if it involves extra cost, can provide fully diagnostic morphologic and functional data in a single session that could change the clinical management plan and rendering additional diagnostic CT unnecessary [10–12].

Thus, a fully diagnostic CT scan was done using the following parameters: 350 mA, 120 kV, 0.5-s tube rotation time, slice thickness 5 mm, 8 mm table feed and 3 mm incremental reconstruction. IV contrast administration of 120 mL of a low-osmolarity iodinated contrast agent (Ultravist 300®, Bayer, Germany) and negative oral contrast agent (water) for bowel was used.

PET images and CT images were fused, displayed, reconstructed, and viewed on workstations (Syngo Multimodality Workplace, Siemens Medical Solutions, AZE Virtual Place Version 3.0035; Azemoto, Tokyo, Japan), which provided multi-planar reformatted PET, CT, and fused PET/CT images with linked cursors as well as maximum intensity projection (MIP) PET images in video mode.

Data interpretation and image analysis

In women of reproductive age, FDG PET/CT imaging was done within a week before or a few days after the menstrual flow phase to avoid any misinterpretation of pelvic FDG PET/CT images [13]. PET/CT images were interpreted in consensus by experienced dual board-certified radiologist/nuclear medicine consultants, one dual board-certified radiologist/nuclear medicine specialist, and one consultant radiologist.

All images were qualitatively and quantitatively interpreted by three dual-qualified consultant radiologists with more than 20 years experience and one dual-qualified specialist radiologist with more than 5 years experience. The presence of abnormal FDG uptake was indicated when accumulation of the tracer was moderately to markedly increased compared to the uptake in normal structures or surrounding tissue, visual in all three planes with the same co-ordinates (x, y, z), with the exclusion of physiological bowel, vessel, and urinary activity. The criterion for malignancy was [18F] FDG hypermetabolism at the site of pathological changes on CT or marked focal hypermetabolism at sites suggestive of malignancy despite absence of signs of pathology at those sites on CT. The distribution of pathological lesions, a prior knowledge of the pattern of spread of different tumors, and the patient's history were taken into consideration. Quantitative evaluation using standard uptake value (SUV) according to this formula: SUV = (μCi/gram in tissue)/(total μCi injected) body weight. Max. SUV value of more than 3 was considered significant as a reliable predictive value for predicting malignancy. This method of PET/CT SUVmax was selected as a relative minimum cut-off value for best optimal sensitivity and accuracy and was relied upon the average SUVmax results of the previous studies [14–16].

During the statistical analysis, patients were categorized based upon the PET/CT results and the final diagnosis. PET/CT results were compared with the final diagnosis. According to the diagnosis of the primary site of malignancy, "primary detected" was classified as true positive (TP) only when it was confirmed histologically during the follow-up. If the finding was confirmed as benign, or if the patient was without any signs of malignancy during the follow-up, the diagnosis was classified as false positive (FP). "Primary unknown" means an evaluation that was classified as true negative (TN) if neither FDG PET 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 by FDG PET, but was proven histologically or by follow-up using other imaging studies, the finding was classified as being false negative (FN).

Clinical, surgical, and histopathologic findings and correlative imaging modalities were used to assess the results of FDG PET/CT. All detected primary malignancies were hypermetabolic on PET, for all such cases, the final diagnosis was obtained from the medical records, including pathologic reports by biopsy or operation as well as clinical/radiological follow-up. The data gathered during the histopathological examination and clinical follow-up was considered as the reference standard and defined as the final diagnosis. Ultrasonography, mammography, bronchoscopy, endoscopy-colonoscopy, and biopsy were performed as diagnostic tests for patients with suspicion of primary focus in the follow-up period after PET/CT.

Metastatic lesions with increased tracer uptake comparable to surrounding normal tissues were deemed positive for metastatic spread. Conversely, nodular lesions with no detectable tracer uptake were deemed negative for metastatic spread, even if they are identified on the CT portion. This method of PET/CT image analysis was derived from the results of previous studies [17–19].

A diagnosis of the primary malignancy site was classified as true positive (TP) when it was confirmed histologically during the follow-up. If it was confirmed as benign or if the patient was without any signs of malignancy during the follow-up, the diagnosis was classified

as false positive (FP). It was classified as true negative (TN) if neither FDG PET 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 by FDG PET, but was proven histologically or by follow-up using other imaging studies, the finding was classified as being false negative (FN).

Histopathological evaluation
Biopsy/operation specimens were histopathologically evaluated by using standard histomorphometric techniques. All specimens were sliced, routinely processed, stained with hematoxylin eosin, examined microscopically, and interpreted by an experienced pathologist in oncologic pathology.

Statistical analysis
For the sample size, based on past review of literature, Kwee et al. showed the specificity of PET/CT to range from 73 to 100% [3] and the prevalence of carcinoma of unknown primary tumors (CUP) ranges from 0.5 to 9% of all patients with malignant neoplasms according to Le Chevalier et al. [20]. Sample size has been calculated at 80% power and 95%CI, and it is estimated that 180 patients would be required. Sample size (*n*) based on

$$\text{Specificity} = Z21 - \alpha/2 \times \text{SP} \times (1 - \text{SP})L2 \times (1 - \text{Prevalence})$$

where *n* = required sample size, *S* = anticipated specificity, *α* = size of the critical region (1 − *α* is the confidence level), z1 − *α*/2 = standard normal deviate corresponding to the specified size of the critical region (*α*), and *L* = absolute precision desired on either side (half-width of the confidence interval) of specificity. In this study, 5 patients were dropped out and were unable to do PET/CT examination: inability to cooperate with the scan process "inability to lie relatively still for 1–2 h and to lie supine for 30–60 min due to severe bone pain" (2 patients), allergy to intravenous contrast (2 patients), diabetic patients with uncontrolled blood glucose levels (1 patient).

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY). Numerical and categorical data were presented as number or proportion and percentage. All values are presented as median and range. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy with 95% confidence intervals (CI) were calculated by using standard statistical formulas by standard 2 × 2 tables. The positive predictive value (PPV) of PET-CT-guided biopsy was calculated by determining the percentage of biopsies from primary sites detected by PET-CT scan that showed histopathological evidence of malignancy. A confidence level of less than 0.05 was considered to be statistically significant. The sensitivity, specificity, accuracy, and detection rate of PET/CT in detecting primary malignancy were calculated using the following statistical formulae. Sensitivity = TP/(TP + FN), specificity = TN/(TN + FP), and accuracy = (TP + TN)/(TP + FP + TN + FN) [21].

Results
Patient characteristics
This diagnostic accuracy test study included 175 patients (110 men and 65 women), aged between 13 and 86 years with mean age of 55.1 ± 14.5 years presenting with pathology-proved, clinically, laboratory, or radiologically suspected metastatic lesions of cancer of unknown primary site.

The location of metastasis upon presentation was as follows; 22.8% nodal metastasis (2.9% supraclavicular, 11.4% cervical, 5.6% inguinal, 2.9% abdominal), 17.1% liver metastasis, 11.4% bone metastasis, 8.6% lung metastasis, 5.7% brain metastasis, 5.7% malignant pleural effusion, 2.9% patients had peritoneal nodules and malignant ascites, 2.9% anterior abdominal wall metastasis, 14.3% multiple metastatic sites, 8.6% systemic symptoms and clinical suspicion of occult malignancy including anorexia, progressive weight loss, fever of undetermined origin, and elevated tumor markers (Table 1). Among those 175 patients included in the study, 48.6% of our patients had histopathology-proved metastatic lesion (20% had poorly differentiated carcinoma, 17.1% had adenocarcinoma, 5.7% had squamous cell carcinoma, 2.9% had clear cell tumor, and 2.9% had large cell carcinoma), and the remaining 51.4% had clinical and radiological suspicion of the presence of a malignancy (Table 2).

PET-positive lesions suggestive of primary malignant tumors were found in 105 out of 175 patients. The reported locations of primary tumor were as follows; 45 (25.7%) in the thorax {40 (22.8%) lung and 5 (2.9%) pleura}, 20 (11.5%) in GIT {15 (8.6%) lower GIT and 5 (2.9%) upper GIT}, 6 (3.4%) pancreatic, 5 (2.9%) in the breast, 15 (8.6%) in the ovary, 10 (5.7%) in head and neck "pharyngeal", 2 (1.1%) in the kidney, and 2 (1.1%) in the prostate (Table 3, Fig. 1).

These lesions were pathologically proven to be malignant (TP) in 100 of 175 patients (57.1%). Five patients out of 175 patients (2.9%) proved to be falsely positive (FP) after pathologic assessment. Two (1.1%) patients presented with regional cervical lymphadenopathy. PET/CT suggested primary nasopharyngeal and thyroid neoplasm. Nasopharyngeal endoscopic biopsy and thyroid fine-needle biopsy (FNB) were free from malignancy. The other three patients (1.8%) presented with regional mesenteric lymphadenopathy 2 (1.1%) as well as peritoneal nodules 1 (0.7%), and PET/CT suggested primary

Table 1 The location of metastasis on presentation

Variable	Location of metastasis on presentation	%
Location of metastasis on presentation	Lymph nodes	22.8
	Hepatic focal lesions	17.1
	Osseous lesion	11.4
	Pulmonary nodules	8.6
	Pulmonary nodules and mediastinal LNs	5.7
	Brain	5.7
	Malignant pleural effusion	5.7
	Pleural effusion and osseous lesion	5.7
	Systemic symptoms (anorexia, progressive weight loss)	5.7
	Peritoneal nodules and malignant ascites	2.9
	Anterior abdominal wall mass	2.9
	Hepatic focal lesions and osseous lesions	2.9
	Fever of unknown origin and fits	2.9

gastric, colonic, and ovarian neoplasm. Endoscopic and US-guided biopsy were found to be negative for tumor tissue at histopathological examination.

In total, 70/175 (40%) patients were diagnosed by PET/CT as negative for detection of the primary malignancy all over the body (TN) with no false negative results. So PET/CT in detection of unknown primary had a sensitivity of 100% (95% CI 96.38 to 100.00%) and specificity of 93.33% (95% CI 85.12 to 97.80%), positive predictive value (PPV) of 95.24% (95% CI 89.56 to 97.90%), negative predictive value (NPV) of 100%, and accuracy of 97.14 (95% CI 93.46 to 99.07%) (Fig. 2).

Discussion

CUP is a heterogeneous group of metastatic malignancies, in which a primary tumor could not be detected despite thorough diagnostic evaluation. Early identification of primary tumor may enable more specific and effective treatment, thus leading a longer mean survival time for CUP patients [22]. In less than 30% of CUP patients, a primary site is identified by conventional imaging modalities. Failure to identify the primary tumor site may negatively affect patient management as tailored chemotherapeutic regimens and targeted agents have been increasingly developed over the last decade for a number of solid tumors [23]. The use of 18F-FDG, a glucose analog is based on the fact that cancer cells generally have a higher level of metabolic activity than normal tissues resulting in its increasing uptake [24].

The results of our study showed that FDG PET/CT was able to detect 57.1% of primary tumors in CUP patients with sensitivity of 100.00% (95% CI 96.38 to 100.00%) and specificity of 93.33% (95% CI 85.12 to 97.80%), positive predictive value of 95.24% (95% CI 89.56 to 97.90%), negative predictive value (NPV) of 100%, and accuracy of 97.14% (95% CI 93.46 to 99.07%) indicating that it is an effective study and demonstrating the advantage of metabolic information in the search for a malignancy.

Table 2 Results of biopsy obtained from metastasis

Variable		%
Biopsy from metastasis (*n* = 175)	No biopsy taken	51.4
	Biopsy taken	48.6
Method of obtaining biopsy from metastasis (*n* = 85)	Aspiration cytology	17.1
	Excision biopsy	14.3
	Needle biopsy	14.3
	US-guided biopsy	2.9
Histopathological result of biopsy taken from metastasis (*n* = 85)	Poorly differentiated carcinoma	20
	Adenocarcinoma	17.1
	Squamous cell carcinoma	5.7
	Clear cell tumor	2.9
	Large cell carcinoma	2.9

Table 3 The sites of primary tumors detected by PET-CT and the methods of obtaining biopsy to confirm/exclude their malignant nature
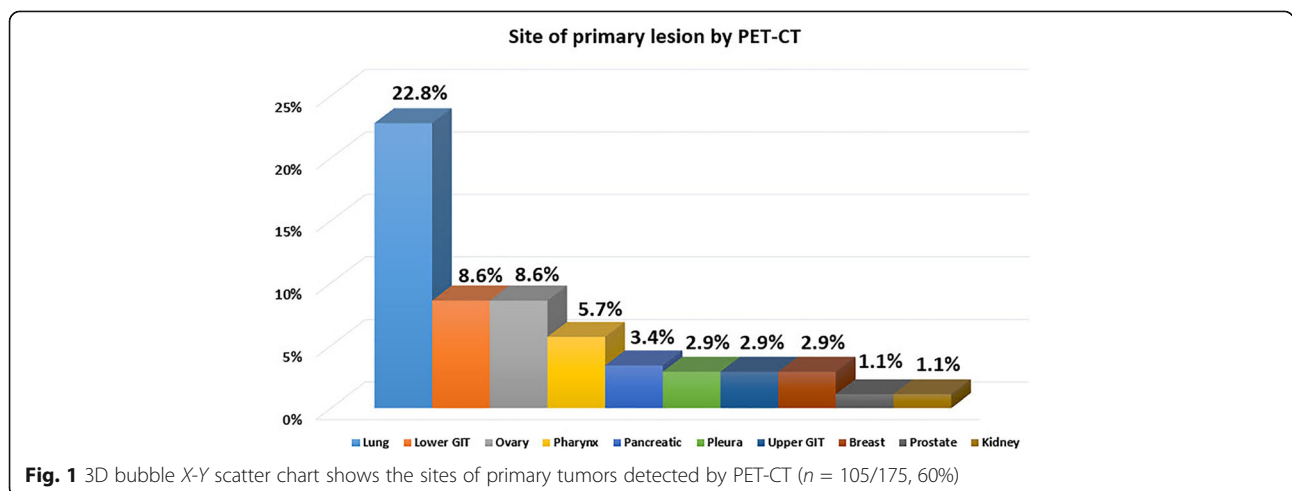
Variable		%
Detection of primary lesion by PET-CT (*n* = 175, 100%)	Primary lesion detected by PET-CT	60.0
	No primary lesion detected by PET-CT	40.0
Site of primary lesion by PET-CT (*n* = 105, 60%)	Lung	22.8
	Lower GIT	8.6
	Ovary	8.6
	Pharynx	5.7
	Pancreatic	3.4
	Pleura	2.9
	Upper GIT	2.9
	Breast	2.9
	Prostate	1.1
	Kidney	1.1
Method of obtaining biopsy from primary lesion detected by PET-CT (*n* = 105, 60%)	CT-guided biopsy	22.8
	Endoscopic biopsy	17.0
	Bronchoscopic biopsy	8.6
	Needle biopsy	2.9
	Nephrectomy	2.9
	Transrectal US biopsy	2.9
	US-guided biopsy	2.9

According to our results, FDG PET/CT was able to identify the primary sites in 100 out of 175 patients (57.1%) presenting with either pathologically proved or clinically suspected malignancy. These results were pathologically confirmed (true positives), and the most prevalent location of primary tumors detected by FDG PET/CT was the lung, which is consistent with the previous literatures [22, 25] (Fig. 3).

Gutzeit et al. studied 45 patients with tumor metastasis from unknown primary site by PET/CT, obtaining a detection 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 57%. Our study supports these results with a detection rate of 57.1% in our study [26, 27].

Bruna et al. reported a detection rate of primary tumor of 38% with comparable sensitivity and specificity of 93% and 77% respectively, while Fencl et al. reported a sensitivity of 62.0% and specificity of 81.9%. The relatively lower sensitivity in this study showed that 50% of patients in those series were at an advanced stage of
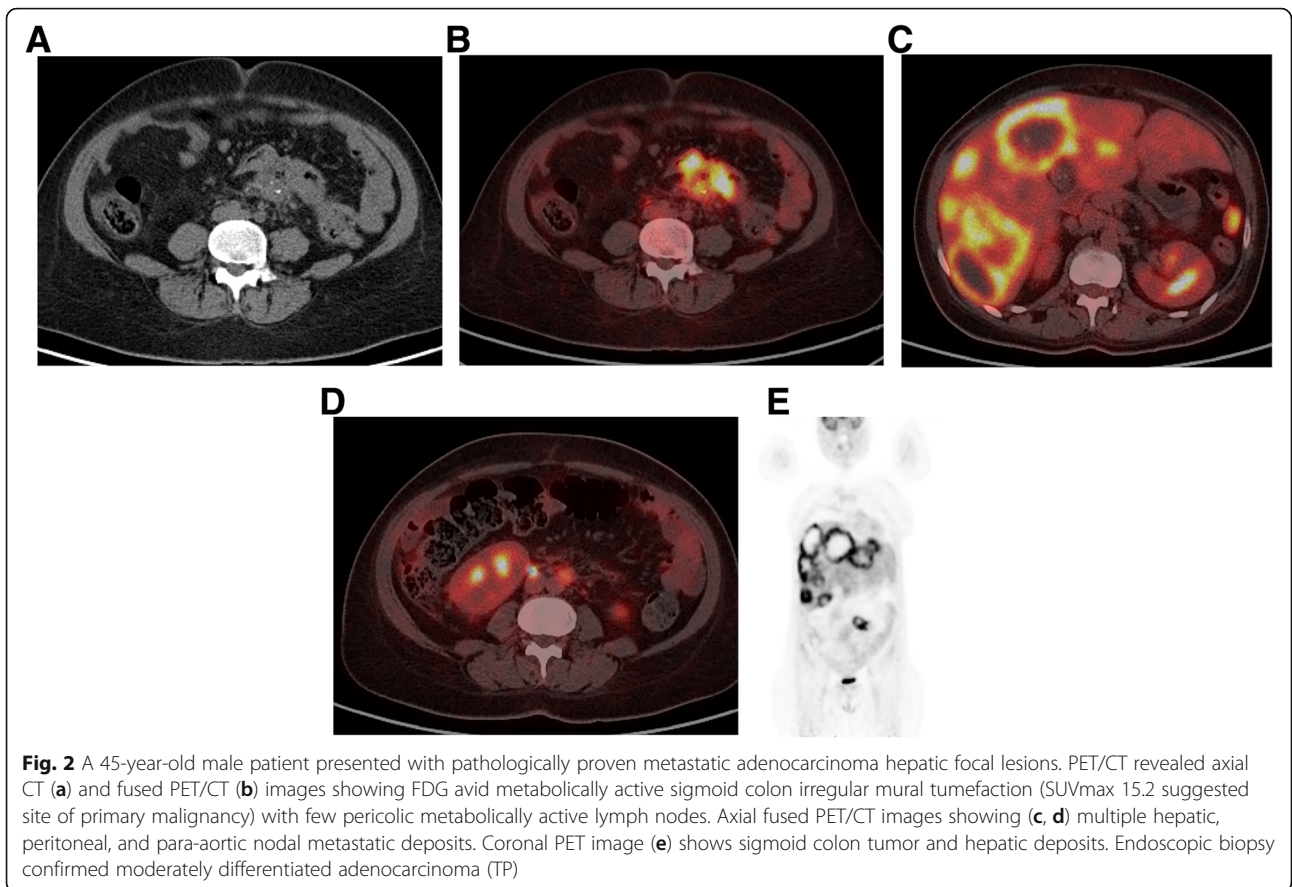

Fig. 1 3D bubble *X-Y* scatter chart shows the sites of primary tumors detected by PET-CT (*n* = 105/175, 60%)

Fig. 2 A 45-year-old male patient presented with pathologically proven metastatic adenocarcinoma hepatic focal lesions. PET/CT revealed axial CT (**a**) and fused PET/CT (**b**) images showing FDG avid metabolically active sigmoid colon irregular mural tumefaction (SUVmax 15.2 suggested site of primary malignancy) with few pericolic metabolically active lymph nodes. Axial fused PET/CT images showing (**c**, **d**) multiple hepatic, peritoneal, and para-aortic nodal metastatic deposits. Coronal PET image (**e**) shows sigmoid colon tumor and hepatic deposits. Endoscopic biopsy confirmed moderately differentiated adenocarcinoma (TP)

disease and presented with multiple hypermetabolic lesions [28, 29].

Kwee et al. made another meta-analysis including 11 studies and reported that the detection rate of PET/CT was 22–73% in patients with CUP, sensitivity of FDG PET/CT in detection of primary tumor ranged from 55 to 100%, and specificity ranged from 73 to 100%. These variable diagnostic yields might be due to different patient inclusion criteria and the extent of the diagnostic workup in different studies [3] (Fig. 4).

PET/CT identified focal FDG uptake was indicative of primary tumor in 105/175 patients. Of those, five
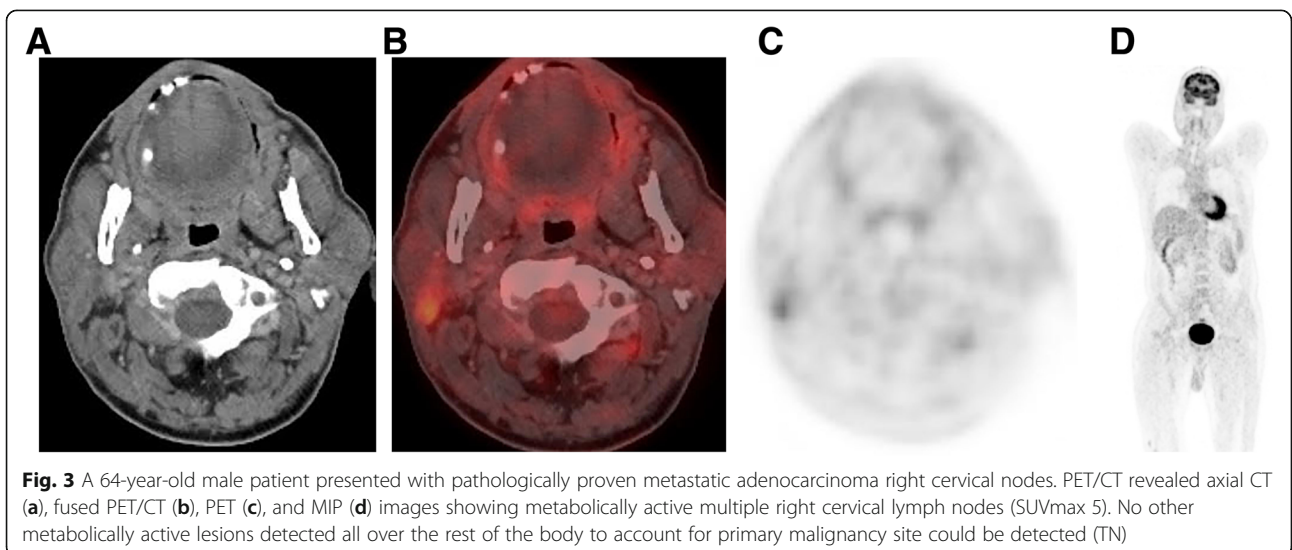

Fig. 3 A 64-year-old male patient presented with pathologically proven metastatic adenocarcinoma right cervical nodes. PET/CT revealed axial CT (**a**), fused PET/CT (**b**), PET (**c**), and MIP (**d**) images showing metabolically active multiple right cervical lymph nodes (SUVmax 5). No other metabolically active lesions detected all over the rest of the body to account for primary malignancy site could be detected (TN)

patients out of 175 patients (2.9%) proved to be falsely positive (FP) after pathologic assessment and confirmed as non-malignant (no signs of cellular atypia). These results can be explained by the reason that normal physiological uptake of FDG is common, especially in the head and neck, urinary and gastrointestinal systems, skeletal and cardiac muscles, lymph nodes, bone marrow, and healing bones. Therefore, findings from these areas can mimic cancers, and benign processes such as infection, inflammation, and granulomatous diseases (i.e., sarcoidosis, tuberculosis) are known to cause false-positive results. This may be due to increased glucose utilization and FDG uptake caused by increased cellular metabolism in inflammatory lesions; thyroid uptake is incidentally identified on 18F-FDG PET imaging with a frequency of almost 4%, with a diffuse uptake pattern in roughly half of cases and a focal pattern in the remainder that represents chronic thyroiditis, multinodular goiter, or Graves' disease [30, 31].

Moderate physiological FDG uptake is noted in the liver, spleen, GI tract, and salivary glands. Uptake in the cecum and right colon tends to be higher than in the remainder of the colon due to the presence of glucose-avid lymphocytes [32]. Other sites of physiological FDG activity can be confused with malignancy. Examples include activity within brown fat, adrenal activity, uterus, and ovaries [33]. In premenopausal women, endometrial uptake of FDG varies cyclically and is increased both at ovulation and during the menstrual phase of the cycle with mean SUV values of 3.5–5 [34]. Benign ovarian uptake of FDG in premenopausal women can be associated with ovulation [33]. Thus, histopathologic examination of FDG PET/CT-positive lesions should be performed [35, 36] (Fig. 5).

In his study about the unknown primary tumor (UPT), Saidha et al. concluded that in 15–25% of cases, the primary site cannot be identified by PET/CT even on postmortem examination. PET/CT depicted histologically verified primary tumors in approx. 61% in patients presenting with cervical lymph node metastases from unknown primary tumors, and 40% in those with extra cervical disease presentation. In this study, PET/CT detection of additional metastases in 14.2% influenced change in management plan and modifying the stage of the disease and oncological treatment in about 50% of cases [9]. In our study, no primary tumor could be detected in 70 out of 175 patients (40%). In 30 patients (17.1%), PET/CT has detected more metastatic sites that modified the treatment plan. These negative results can be explained by facts that the biological behavior of the primary tumor may be different from those of the tumor cells in the metastatic regions, and metastases may show higher FDG uptake levels than in the primary tumor; in low-grade epithelial tumors, FDG uptake can be low or absent, and the size of primary lesion may be small beyond the resolution power of FDG PET/CT (especially
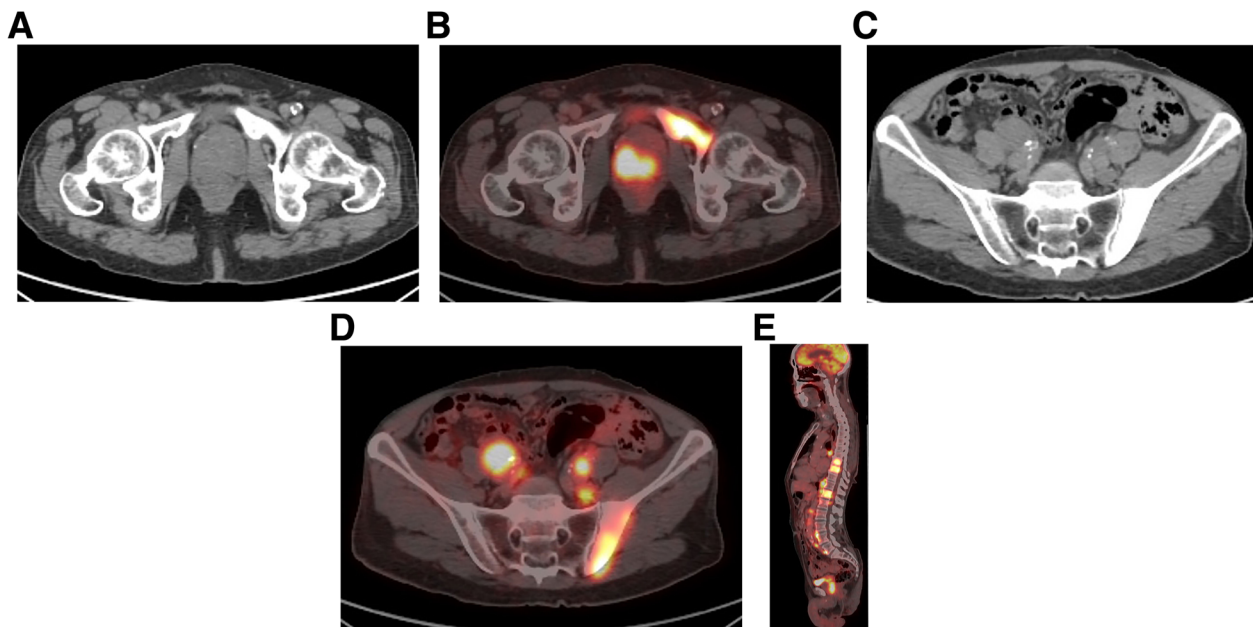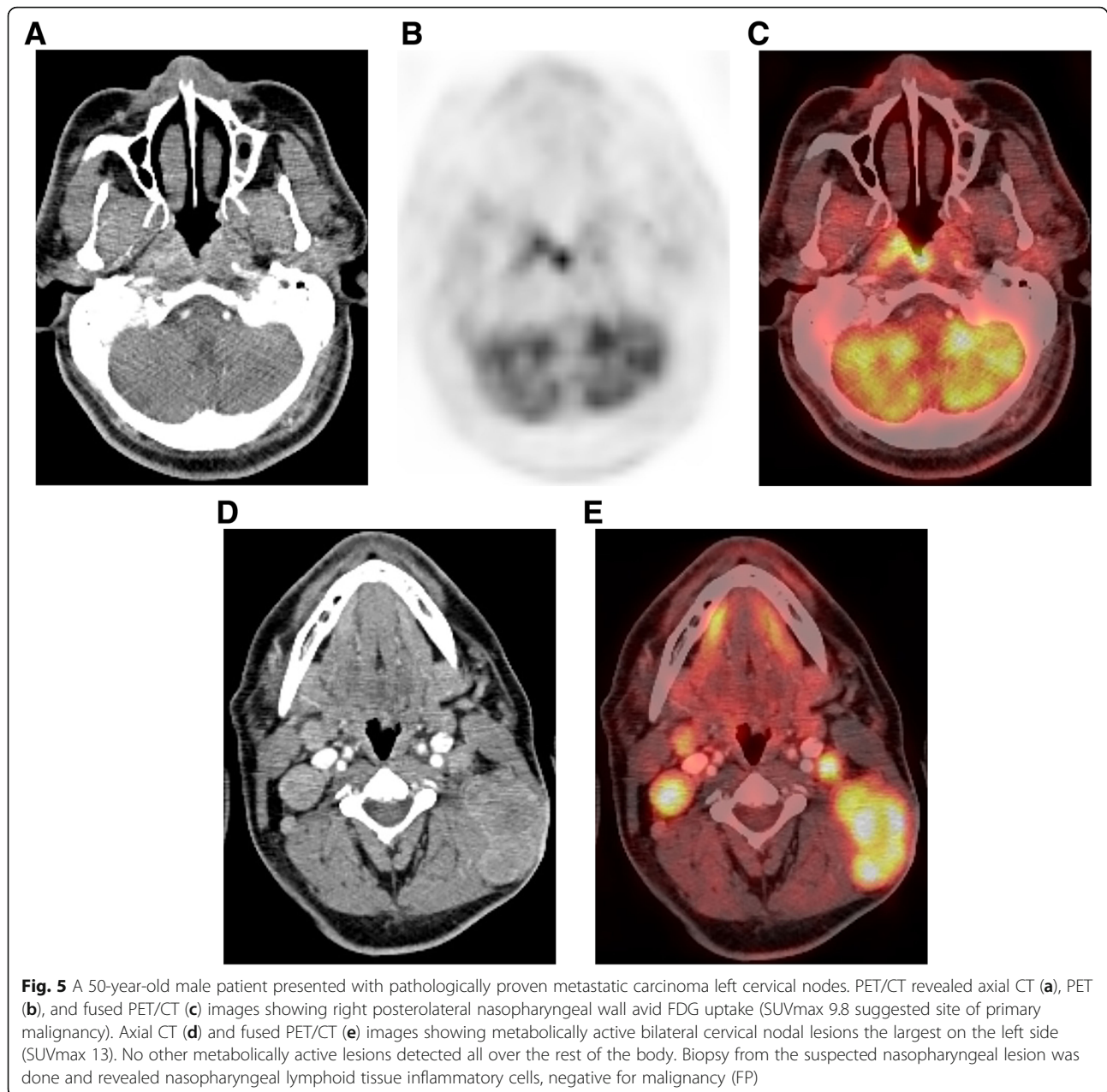

Fig. 4 A 71-year-old male patient presented with pathologically proven metastatic carcinoma left supraclavicular lymph node. PET/CT revealed axial CT (**a**) and fused PET/CT (**b**) images showing FDG avid metabolically active prostatic lesion (SUVmax 17.1 suggested site of primary malignancy) as well as left pubic ramus metastatic deposit. Axial CT (**c**) and fused PET/CT (**d**) images showing metabolically active left iliac bone and iliac nodal metastatic deposits (SUVmax 16.65). Sagittal fused PET/CT (**e**) image showing metabolically active multiple osseous metastatic deposits. Transrectal US prostatic biopsy confirmed prostatic adenocarcinoma (TP)

Fig. 5 A 50-year-old male patient presented with pathologically proven metastatic carcinoma left cervical nodes. PET/CT revealed axial CT (**a**), PET (**b**), and fused PET/CT (**c**) images showing right posterolateral nasopharyngeal wall avid FDG uptake (SUVmax 9.8 suggested site of primary malignancy). Axial CT (**d**) and fused PET/CT (**e**) images showing metabolically active bilateral cervical nodal lesions the largest on the left side (SUVmax 13). No other metabolically active lesions detected all over the rest of the body. Biopsy from the suspected nasopharyngeal lesion was done and revealed nasopharyngeal lymphoid tissue inflammatory cells, negative for malignancy (FP)

within the abdomen, pelvis, and head and neck, which are anatomically complicated areas) [29]. The smallest primary tumor detected in this study was in the nasopharynx 1.5 × 0.5 cm. Also the primary tumor may vanish after seeding the metastasis due to its angiogenic incompetence which leads to marked apoptosis or because it may have regressed spontaneously [22, 36]. Our recommendation for 18F-FDG low uptake neoplasm is to perform delayed phase PET/CT (Dual Time Point PET/CT), Gallium-PSMA PET/CT (for prostatic cancer), and close follow-up re-imaging PET/CT study; otherwise, CECT, MRI, and tumor markers could be of great benefit.

This study has strengths which include its high diagnostic accuracy test study, and the specificity of PET/CT in the detection of the primary tumor in patients with metastasis of unknown origin (MUO) is relatively low, although the sensitivity, accuracy, and detection rate were found to be high. Furthermore, PET/CT is noninvasive and may lead to the detection of other metastatic foci by scanning the entire body in a single session, while also guiding treatment. Despite its higher costs when compared to other methods, based on the abovementioned advantages, PET/CT offers advantages as the first-line diagnostic tool in the detection of the primary tumor in patients with MUO (Fig. 6).
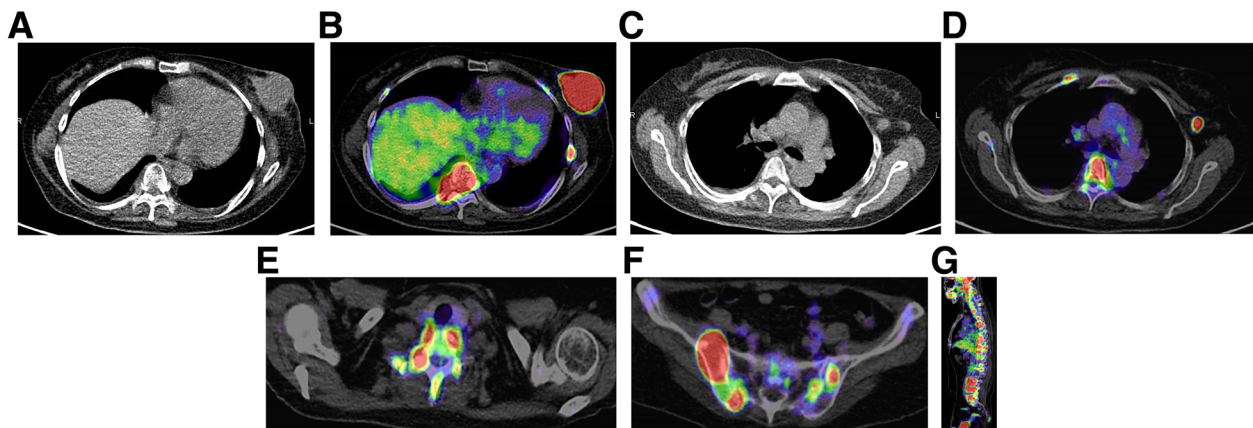
Fig. 6 A 58-year-old female patient presented with pathologically proven metastatic carcinoma left axillary lymph nodes. PET/CT revealed axial CT (**a**) and fused PET/CT (**b**) images showing avid FDG uptake metabolically active left breast lesion (SUVmax 12.8 suggested site of primary malignancy) with left axillary lymph node spread axial CT (**c**) and fused PET/CT (**d**) images. Axial (**e**, **f**) and sagittal (**g**) fused PET/CT images showing diffuse bone metastasis. Biopsy from the left breast lesion confirmed invasive ductal carcinoma (papillotubular type) (TP)

Unfortunately, we could not analyze the therapeutic benefits of our imaging outcome for the patients with proven metastatic disease that could practically be associated with the localization of the primary sites as this demands a vast medical team of oncologists, surgical oncologists, oncology radiologists, and medical statisticians to collect and analyze the essential data from the imaging data and its impact regarding therapy, and it would be the topic of the upcoming study for further assessment of the critical value of PET/CT results upon patient management.

Conclusion

FDG PET/CT is an effective modality for early detection of the primary tumor site in CUP patients which facilitates early selection of appropriate treatment protocols that will improve patients' prognosis.

Abbreviations

MUO: Metastasis of unknown origin; PET/CT: Positron emission tomography/computed tomography; CUP: Cancer of undetermined primary; FDG: 18F fluoro-2-deoxyglucose; MRI: Magnetic resonance imaging; UPT: Unknown primary tumor; SUV: Standard uptake value; TP: True positive; FP: False positive; TN: True negative; FN: False negative; FNB: Fine-needle biopsy; NPV: Negative predictive value

Authors' contributions

AAZ has substantial contribution to the conception of the study, design of the study, acquisition, analysis of the data, interpretation of data, creation of the final work, study revision, and accuracy and integrity of the submitted manuscript. EEE has substantial contribution to the conception of the study, design of the study, interpretation of data, study revision, and accuracy and integrity of the submitted manuscript. AIN has substantial contribution to the design of the study, acquisition of the data, interpretation of data, creation of the final work, and the submitted manuscript. KM has substantial contribution to the conception of the study, acquisition of the data, interpretation of data, and integrity of the submitted manuscript. All authors have read and approved the manuscript.

Author details

[1]Radiodiagnosis Department, Faculty of Medicine, Menoufia University, Menoufia, Egypt. [2]Radiology Department, School of Medicine, Juntendo University, Tokyo, Japan.

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