Contrast-enhanced [18F] fluorodeoxyglucose-positron emission tomography-computed tomography as an initial imaging modality in patients presenting with metastatic malignancy of undefined primary origin

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ABSTRACT

Background: To evaluate the advantages of contrast enhanced F-18-fluorodeoxyglucose (FDG) positron emission tomography-computed tomography (PET-contrast enhanced CT [CECT]) when used as an initial imaging modality in patients presenting with metastatic malignancy of undefined primary origin (MUO). **Materials and Methods:** A total of 243 patients with fine needle aspiration cytology/biopsy proven MUO were included in this prospective study. Patients who were thoroughly evaluated for primary or primary tumor was detected by any other investigation were excluded from the analysis. Totally, 163 patients with pathological diagnosis of malignancy but no apparent sites of the primary tumor were finally selected for analysis. The site of probable primary malignancy suggested by PET-CECT was confirmed by biopsy/follow-up. **Results:** PET-CECT suggested probable site of primary in 128/163 (78.52%) patients. In 30/35 remaining patients, primary tumor was not detected even after extensive work-up. In 5 patients, where PET-CECT was negative, primary was found on further extensive investigations or follow-up. The sensitivity, specificity, positive predictive value and negative predictive value of the study were 95.76%, 66.67%, 88.28% and 85.71% respectively. **Conclusions:** F-18 FDG PET-CECT aptly serves the purpose of initial imaging modality owing to high sensitivity, negative and positive predictive value. PET-CECT not only surveys the whole body for the primary malignancy but also stages the disease accurately. Use of contrast improves the diagnostic utility of modality as well as help in staging of the primary tumor. Although benefits of using PET-CECT as initial diagnostic modality are obvious from this study, there is a need for a larger study comparing conventional methods for diagnosing primary in patients with MUO versus PET-CECT.

Keywords: Contrast enhanced computed tomography, fluorodeoxyglucose positron emission tomography-computed tomography, malignancy of undefined primary origin, probable primary, unknown primary

INTRODUCTION

Malignancy of undefined primary origin (MUO) is metastatic malignancy identified on the basis of a limited number of tests, without an obvious primary site, before comprehensive investigation.[1] Carcinoma of unknown primary (CUP) is defined as metastatic epithelial or neuroendocrine malignancy identified

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on the basis of final histology, with no primary site detected despite a selected initial screen of investigations, specialist review, and further specialized investigations as appropriate.[1] Among the newly diagnosed cancer cases, CUP account for 3–5%.[2] It is seventh to eighth most common cause of malignancy and fourth most common cause of cancer-related death in males and females.[3] The conventional pretreatment evaluation includes history, physical examination (including pelvic and rectal examination), complete blood counts, biochemistry, urine analysis, occult fecal blood test, serum tumor markers, histopathology review of biopsy material with use of immunohistochemistry, mammography in females, computed tomography (CT) of chest, abdomen and pelvis, and any other relevant tests.[2] However, these tests are expensive, time-consuming, and invasive.[4]

Conventional modalities identify the site of primary in only 20–27% of cases.[5] In rest of the cases, primary site is not found during the patient's lifetime. The life expectancy is very short with a median survival of only 6–9 months.[3] The occult primary is usually refractory to the systemic therapy. However, the prognosis of patients with unknown primary tumor is significantly improved when the histology and the site of the primary tumor are known.[6] The detection rates of unknown primary by fluorodeoxyglucose (FDG) positron emission tomography (PET) have been described to vary between 8% and 57% in the various literature with an overall rate of about 39%[2,7,8] and when using CT for anatomical localization, the detection rates increased up to 73%.[9] As hospital policy, we routinely evaluated patients with pathological diagnosis of MUO with contrast enhanced F-18-FDG PET-CT PET-CECT. Hence, we postulate that FDG PET-CT that has maximum sensitivity amongst the presently available imaging modalities may be used as initial screening investigation for MUO and CECT may further increase our confidence in reporting the primary site.

MATERIALS AND METHODS

This prospective study included 243 patients with fine needle aspiration cytology (FNAC)/biopsy proven MUO who were referred to PET-CT department for evaluation of the primary tumor. A thorough clinical history was elicited, and physical examination was done. Those patients, who were thoroughly evaluated for primary or primary tumor was detected by any other investigation, were excluded from the analysis. The patients were followed-up for a minimum period of 6 months. Those patients who were lost to follow-up, or died before the final diagnosis could be established were excluded from the study. A total of 163 patients amongst the 243 patients was included in the final analysis.

Scan protocol

The patients were fasting for 4–6 h prior to the scan. The blood glucose level <150 mg/dl was ensured. All the patients underwent whole body PET-CECT with standard protocol on philips medical systems (Cleveland), Inc. (Cleveland, Ohio, 44143 USA) with time of flight imaging and 64 slice CT scanner. After 60 min of intravenous (IV) administration of 185–245 MBq of F-18-FDG, emission data were acquired for 10–12 bed positions, typically from the vertex to mid thigh (lower extremities were included if melanoma was suspected or presentation was with inguinal nodal metastasis). The PET acquisition time was usually 1.30 min/field of view (FOV); patients with weight >80 kg were examined at 1.45 min/FOV. Delayed imaging of a particular region was done in case of any diagnostic dilemma.

Sixty four-slice CECT was used for attenuation correction, anatomical correlation, and diagnostic purpose. CT scans in all patients were performed craniocaudally using 120 kVp with a weight-based protocol for determining tube current (mA). Patients were positioned on the scanning table with their arms raised to reduce the beam-hardening artefacts, unless the site of primary was suspected to be in head and neck region. In those patients where gastrointestinal (GI) primary was suspected, oral contrast was given as well (100-mL diatrizoate sodium [gastrovideo] contrast material with an iodine concentration of 249.64 mg/mL diluted up to a total volume of 1000 mL). A total volume of 100 mL of the IV contrast agent omnipaque/visipaque with an iodine concentration of 350 mg/mL was injected using a power injector at a flow rate of 2 mL/s, followed by 40 mL of saline at same flow rate.

Image reconstruction and interpretation

The PET images and CT images were separately reconstructed using row action maximum likelihood algorithm iterative reconstruction technique and displayed in transaxial, sagittal, and coronal planes. Fusion software was used to fuse the images accurately that was then viewed on the Philips extended brilliance workstation displaying maximal intensity projection images, PET images, CT images and fused PET-CT images. Maximum standardized uptake values were automatically generated by the software. The study was reviewed independently by two experienced nuclear medicine physicians and a radiologist.

Follow-up

The positive scan diagnosis was confirmed by biopsy from suggested site/sites of probable primary tumor. The cases where biopsy was inconclusive or negative for the primary malignancy and also where PET-CECT was unable to diagnose the site of the primary tumor; further investigations like triple endoscopies with blind biopsies were performed. When all available investigations could not detect primary, these patients were treated as confirmed CUP cases and were followed-up for a minimum of 6 months.

Data analysis

A case was considered as "true positive" when the PET-CECT identified site of primary that was subsequently confirmed by histopathology, "false-positive" when site of primary identified by PET-CECT study was not confirmed by histopathology. Case was considered "true negative" when neither the PET-CECT was able to detect primary nor was it found on further investigations/follow-up of 6 months. "False negative" cases

constituted those cases, wherein PET-CECT did not reveal the site of primary, but was subsequently detected on further work-up/follow-up. Further sensitivity, specificity, positive predictive value and negative predictive values were calculated with 95% confidence intervals.

RESULTS

Out of total 163 patients, 102 were male and 61 were female with age ranging from 30 to 70 years.

These patients were divided into four groups depending on the mode of presentation as follows [Table 1]:
- Lymph nodal metastases
- Visceral metastases
- Skeletal metastases
- Others.

Group I: Nodal metastases

Totally, 56 patients presented with nodal metastatic disease. These were further divided into two groups: (a) Cervical nodal and (b) extra cervical nodal metastases.

Subgroup Ia: Cervical nodal metastases

Totally, 35 patients had cervical nodal metastases at presentation. They were further subdivided into two groups: Upper cervical nodal metastases (22/35) and supraclavicular nodal metastases (13/35).

Ia. (1) Upper cervical nodal metastases

Of 22 patients who presented with upper cervical nodal metastases, PET-CECT was able to detect primary in 14 patients (nasopharynx [4], tonsil [4], vallecula [2], supraglottis [1], tongue [1], esophagus [1], Burkitt lymphoma [1]). The nasopharynx [Figure 1] and tongue were the most common site of primary tumors, and squamous cell carcinoma was the most common histology. In 4 patients (tonsil [2], tongue [1], vallecula 1]) the site of primary identified on PET-CECT was found to be nonspecific inflammation on biopsy, hence were considered false-positive. PET-CECT was unable to detect the site of primary in 8/22 patients. These patients underwent extensive work-up for detection of site of primary and were followed-up for 6 months; but the primary remained unknown.

Ia. (2) Supraclavicular nodal metastases

A total of 13 patients presented with supraclavicular nodal metastases. PET-CECT suggested probable primary in 10 patients (lungs [3], nasopharynx [1], thyroid [1], rectum [1], cystic duct [1], heart [1], peritoneal [1], pancreas [1]). In patient with suspected thyroid primary, ultrasonography-guided FNAC failed to show any evidence of malignancy, hence it was considered as false-positive. PET-CECT was not able to localize the site of primary in 3/13 patients. They were subjected to further investigations for the detection of site of primary and also were followed-up for 1-year, but the primary was not found.

Subgroup Ib: Extra cervical nodal metastases

Total 21 patients presented with extra cervical nodal metastases (axillary [4], mediastinal [2], paraesophageal [1], retroperitoneal[12] and inguinal [2]). PET-CECT suggested probable primary in 17/21 cases (esophagus [1], lung [1], stomach [4], pancreas
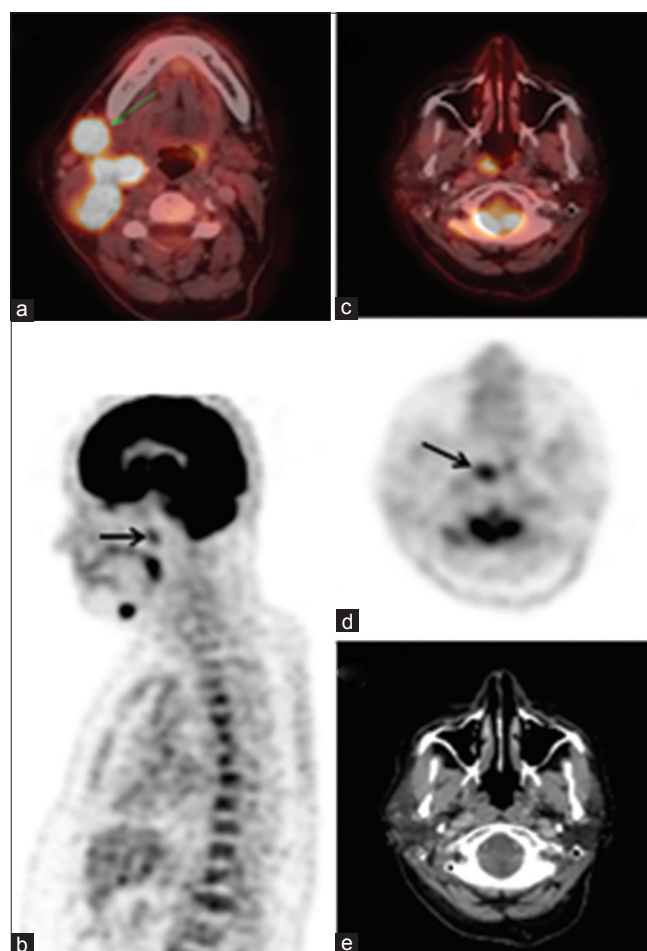

Figure 1: Positron emission tomography-contrast enhanced computed tomography (PET-CECT) in 51-year-old lady with right cervical adenopathy of the squamous origin. (a) Transaxial fused PET-computed tomography (CT) section showing fluorodeoxyglucose (FDG) avid enlarged right cervical lymph nodes, (b) sagittal view of maximum projection intensity image showing focus of increased FDG uptake in nasopharynx suggestive of probable primary tumor (arrow), (c and d) transaxial fused PET-CT and FDG PET sections (arrow) showing increased FDG uptake in right side of nasopharynx, (e) transaxial CT image showing no corresponding abnormality in nasopharynx. Biopsy from the right side of nasopharynx-primary squamous cell carcinoma

Table 1: Various modes of presentation

Mode of presentation	No of cases
Lymph nodal metastases	
Cervical nodal	35
Extracervical nodal	21
Visceral metastases	
Hepatic	24
Brain	07
Omental, peritoneal deposits	06
Skeletal metastases	28
Others	42
Total	163

[1], sigmoid colon [1], testis [1], ovary [2], lymphoma[4] and cholangiocarcinoma [2]). However, suspected case of primary in esophagus turned out to be candidal esophagitis. In two cases, where stomach was suggested as primary, biopsy showed inflammatory changes (one nonmalignant ulcer and the other chemical reactive gastritis, likely drug induced). Similarly, the FDG uptake in common bile duct also showed nonspecific inflammation in histopathology. These four cases were considered false-positive. Again in about 4/21 patients, PET-CECT was unable to detect the site of primary, hence were extensively evaluated. Since the work-up turned out to be negative, they were followed for a year, but the primary was not found.

Group II: Visceral metastases
Subgroup IIa- Hepatic metastases
A total of 24 patients presented with hepatic metastases. PET-CECT suggested probable primary in 20/24 cases (hepatocellular carcinoma [HCC] [5], cholangiocarcinoma [2], appendix [2], descending colon [1], pancreas [5], gall bladder [1], ovary [1], duodenum [1], ileum[1] and appendix [1]). All sites of primary were found to be true positive except for suggested primary in duodenum, which turned out to be neutrophilic duodenitis. In 2 patients where HCC was the suggested primary, FDG PET showed no focal abnormal FDG uptake. However, CECT was helpful in characterizing the disease on the basis of its enhancement pattern. Similarly, in 2 patients, there was no focal abnormal FDG uptake in the whole body, but CECT showed enhancing suspicious lesion in ileum and appendix. On the basis of strong clinical suspicion, elevated serum 5-hydroxyindoleacetic acid (HIAA) levels and a suspicious mass on CECT, they were taken for surgery and carcinoid tumor was found on postsurgery histopathological specimens. PET-CECT could not locate the site of primary in 4/24 patients. Amongst these 4 patients, 1 patient had elevated serum chromogranin and urine serum 5-HIAA levels. Panendoscopy was nondiagnostic, hence patient was put on long acting somatostatin analogs. After 2 months duration she presented to the emergency department with intestinal obstruction, for which she underwent laparotomy. An ileal mass was found for which resection anastomoses was done, and the histopathology showed neuroendocrine tumor. In other 3 patients, despite of extensive work-up and follow-up, the site of primary remained unknown.

Subgroup IIb – Brain metastases
Totally, 7 patients presented with brain metastases [Figure 2]. PET-CECT was able to identify the site of primary in all patients (lung [5], thyroid [1] and HCC [1]), which were confirmed with biopsy and proved to be true positive.

Subgroup IIc – Omental and peritoneal deposits
Six cases presented with omental and peritoneal deposits, histology being poorly differentiated adenocarcinoma. PET-CECT could detect the site of primary in three cases-ovary and stomach [Figure 3] that were confirmed on biopsy. Site of the primary tumor remained unknown in the remaining 3 patients, even after extensive work-up and follow-up.

Group III: Skeletal metastases
Total 28 patients presented with skeletal metastases [Figure 4]. PET-CECT was able to detect the site of primary in 22/28 cases (lungs [10], prostate [4], kidney [1], ureter [1], cervix [1], retroperitoneal sarcoma [1], spindle cell tumor [1], breast [1], stomach[1] and cholangiocarcinoma [1]). Out of these, 4 patients (kidney, retroperitoneal sarcoma, stomach, and one lung case) were found to be falsely positive. PET-CECT could not detect the primary malignancy in 6/28 patients. However, two amongst these 6 patients had elevated serum prostate specific antigen level in the borderline range and hence were taken for transrectal ultrasound guided biopsy. Histopathology showed adenocarcinoma and hence these cases were categorized under false negative. Rest 4 patients underwent extensive work-up for detection of site of primary and were followed-up for more than 1-year; but primary remained unknown.

Group IV: Others
Total 42 patients with presentations other than mentioned above were included in this category. Twenty-eight patients presented with undiagnosed masses (pulmonary mass [23], abdominal mass [3], presacral mass[1] and anterior mediastinal mass [1]). Other presentations were pulmonary nodules, malignant pericardial effusion, malignant pleural effusion, malignant ascitis, lump in left chest wall, lump in right arm, swelling in the submandibular region and nonspecific constitutional symptoms. PET-CECT was able to detect the site of primary in 35/42 patients, most commonly in the lung. In one case where PET-CECT suggested thyroid as probable primary, FNAC failed thrice to show any evidence for malignancy. In 7/42 cases, PET-CECT failed to detect the site of primary. Out of these, in 2 patients, primary site was detected on follow-up, one in esophagus who later presented with dysphagia and other in pulmonary mass, which showed an increase in size. The primary could not be located in other 5 patients after extensive work-up and follow-up.

Amongst total 163 patients included in the study, PET-CECT suggested the probable site of the primary tumor in 128 (78.5%) patients. However, out of these, 113 (88.3%) patients were confirmed as true positive. The most common site of primary was lung and second most common was in head and neck region. PET-CECT findings were falsely positive for the site of primary in 15/126 (11.7%) cases. The most common site falsely reported as the site of primary was in head and neck region. PET-CECT could not localize the site of primary in about 35/163 (21.47%) patients. Out of these, the primary site was detected on further work-up in five cases, and the sites of primary remained unknown in rest of the 30 cases despite an extensive work-up and follow-up of >6 months. Results of the study are depicted in Table 2.

The sensitivity, specificity, positive predictive value and negative predictive value of the study were 95.76%, 66.67%, 88.28% and 85.71% respectively in detection of the primary site in patients presenting with MUO.
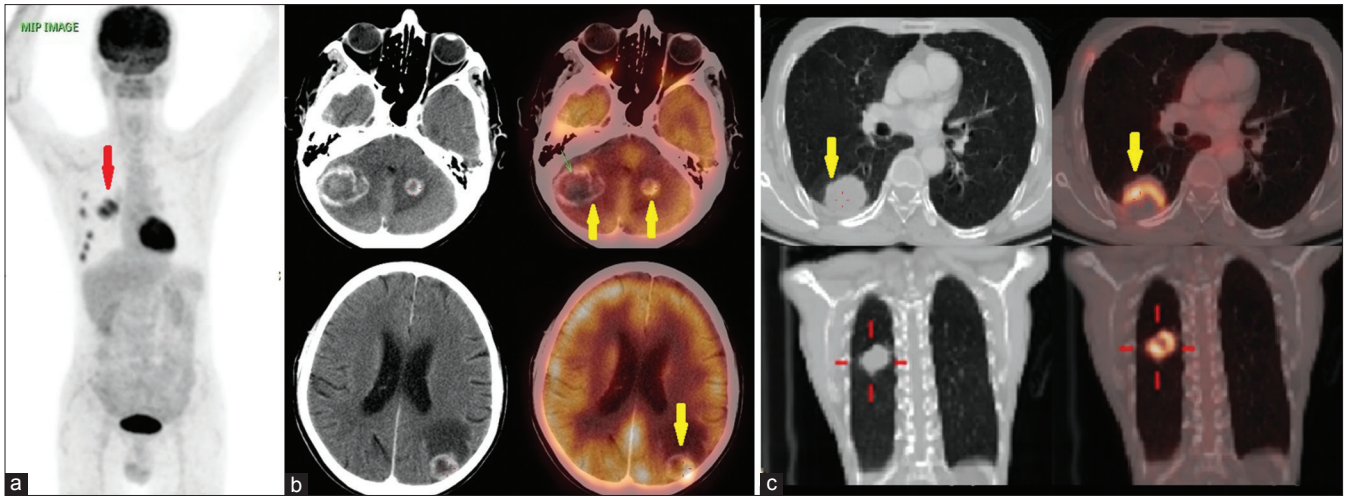
Figure 2: Positron emission tomography-contrast enhanced computed tomography (PET-CECT) in 46-year-old male with multiple brain metastases. (a) Maximum intensity projection image showing focal fluorodeoxyglucose (FDG) uptake in the right chest (red arrow). Multiple foci of FDG uptake seen linearly in the right chest were due to fracture of ribs. (b) Transaxial computed tomography (CT) and fused PET-CECT images showing FDG uptake in an enhancing lesion in the left cerebellum, left parietal cortex and a non-FDG avid lesion in the right cerebellum (yellow arrows). (c) Transaxial and coronal CT and fused PET-CECT images showing FDG uptake in a mass in right lower lobe. histopathological examination–bronchogenic adenocarcinoma
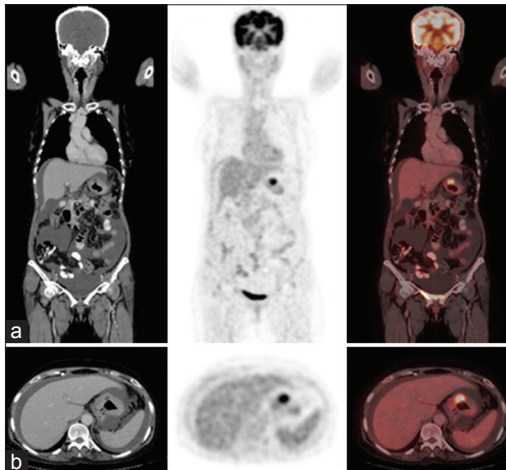

Figure 3: Positron emission tomography-contrast enhanced computed tomography (PET-CECT) in a 61-year-old lady with malignant ascites. (a) Coronal CECT, fluorodeoxyglucose (FDG) PET and fused PET-computed tomography (CT) sections and (b) transaxial CECT, FDG PET and fused PET-CT sections showing intense FDG uptake in a hypodense lesion in thickened wall of fundus of stomach. Biopsy of the lesion confirmed adenocarcinoma of the stomach

DISCUSSION

It is largely seen that conventional imaging modalities detect the site of unknown primary in only 20–27% of cases in a lifetime.[5] The conventional imaging modalities, which are primarily based on anatomical evidence of the increase in size, asymmetry, anatomical distortion and contrast enhancement have good image resolution. However, when it comes to detection of early mitotic, metabolic, receptor level or genetic changes in tumor; they significantly lag behind. Further, relatively poor contrast resolution of these modalities makes them unsuitable for detection of unknown primary that may not be enhancing very significantly compared to surrounding normal tissues. In contrast, molecular imaging is able to detect

Table 2: Unknown primary site detected by PET-CECT vs. Biopsy findings

	PET-CECT+ve	PET-CECT −ve	Total
Biopsy+ve	113	5	118
Biopsy −ve	15	30	45
TOTAL	128	35	163

+ve: Positive, -ve: Negative

very early mitotic, metabolic, receptor level or genetic changes in tumor with high contrast resolution. Especially FDG PET imaging over the last decade and more has proven this beyond doubt. As compared to PET or CT alone; FDG PET-CT has been shown to have better sensitivity and specificity for detection of various tumors.[10-12]

Dong *et al.*,[13] in their meta-analysis of patients of CUP, have shown the sensitivity of FDG PET-CT to be 81% and specificity of 82%. A recent meta-analysis by Kwee and Kwee[9] showed that FDG PET-CT is able to detect 37% of primary tumors in patients with CUP, with high sensitivity and specificity of 84%. Kwee *et al.*[14] in their review article emphasized that if FDG PET/CT fails to detect a primary tumor, other diagnostic procedures are also likely to fail and that FDG PET-CT should be used as a first line imaging modality in all patients with metastatic disease rather than using it after other diagnostic procedures have failed to identify a primary tumor. Hence, we analyzed those patients with MUO in whom FDG PET-CT was used as the initial modality for finding primary site and excluded cases that were thoroughly investigated before performing FDG PET-CT. As per our hospital policy, we use diagnostic CECT while acquiring CT component of FDG PET-CT. This further increased the sensitivity for detection of unknown primary in our patients.

As said earlier, study population was divided into four groups on the basis of site of metastatic disease at the time of presentation.
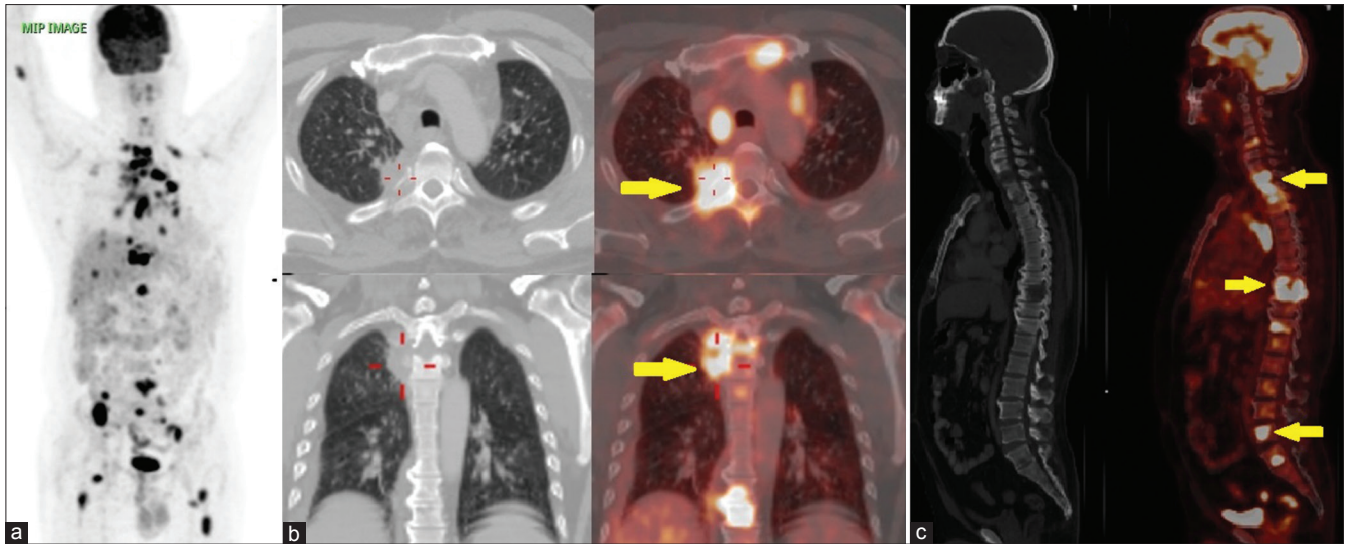
Figure 4: Positron emission tomography-contrast enhanced computed tomography (PET-CECT) in 56-year-old male with multiple skeletal metastases. (a) Maximum intensity projection image shows involvement of multiple lymph nodes, liver and bones with probable primary in the right lung. (b) Transaxial and coronal computed tomography (CT) and fused PET-CECT images showing fluorodeoxyglucose (FDG) uptake in a mass in the apical segment of right upper lobe with infiltration of the chest wall and erosion of adjacent bones. (c) Sagittal CT and fused PET-CECT images showing FDG uptake in multiple lytic lesions involving the vertebrae. histopathological examination–adenocarcinoma of the lung

In patients with nodal metastases, majority of patients presented with cervical nodal metastases. Squamous cell histology was the most common subtype found in these patients that is in concordance with the literature.[15] Only 7/56 patients showed poorly differentiated carcinoma on histology. Nasopharynx was the most common true positive primary site detected in patients presenting with cervical nodal metastases. By and large, upper cervical level nodal level (level I-III) involvement was associated with primary mainly in head and neck region. In four cases that were false-positive on PET-CECT, the primary was thought to be in the oropharyngeal region. This may be due to physiologically increased FDG uptake in the oropharyngeal region that makes the differentiation from a malignant lesion difficult. Similar findings were noted by Fukui *et al.*[16] who suggested that oropharynx is a difficult area to evaluate due to high physiological FDG uptake in the adenoids, waldeyers lymphoid tissue and due to overlap between tumor and physiological FDG uptake. Very often necrotic neck nodes are disregarded by PET-CT due to less FDG avidity whereas the presence of central necrosis in neck nodes is considered as a reliable sign of node metastasis at CECT. Addition of CECT to PET-CT increases the specificity, owing to complex anatomy and vascularity in head and neck region. High physiological uptake in the brain also limits the intracranial lesion detectability. To avoid it, CECT images of the brain should be viewed separately.

The common histology, which was observed in patients presenting with supraclavicular nodal metastases was adenocarcinoma. It was interesting to see that the site of primary in these patients was located below head and neck region. This is consistent with previous findings by others authors where it was found that lower cervical and supraclavicular nodes are usually associated with infraclavicular primary.[2] Also, it is common to find cervical metastases of nonsquamous cell histology to have primary located outside head and neck in areas like lung, GI or urogenital system.[2]

In patients presenting with hepatic metastases, HCC was diagnosed as a true primary in five cases. Amongst these five cases, no focal abnormal FDG uptake was seen in liver in two cases [Figure 5]. However, CECT was diagnostic and helped in delineating the tumor with its characteristic enhancement pattern in the arterial phase. Similarly, the carcinoid in ileum and appendix was also detected on the basis of enhancement on CECT as there was no abnormal FDG uptake. It is a well-known fact that well differentiated HCC and well-differentiated neuroendocrine tumors do not concentrate FDG. But for CECT, it would have been difficult to detect them on the basis of FDG PET alone. Similarly, cystic liver metastases or small metastatic lesions can show absent or only modest FDG uptake. CECT helps in characterizing the faintly FDG-avid lesions, which can be otherwise missed on PET-CT.

Amongst our cases wherein lung was the probable site of primary detected on PET-CECT, one case was false-positive (tuberculosis). Lung is one of the most frequently reported sites for false-positive findings on FDG PET/CT.[9] In our study, CECT helped in accurate localization and characteristic pattern analysis of the lesion showing increased FDG uptake, which, in part, may be responsible for reducing the rate of false-positive results in our study. In one patient who presented with malignant pericardial effusion, FDG PET did not show significant abnormal FDG uptake in lung, however CECT findings suggested lung as the possible primary site; which was confirmed as mucinous bronchoalveolar carcinoma of lung on biopsy. Moreover, CECT helps in excluding local invasion and thus assessing the proximity to vital structures and tumor resectability.

The sensitivity of PET-CECT was on a higher side in our study compared to previous studies. This can be attributed to various reasons. Patients referred to us did not undergo conventional work-up, hence possibility of detection of primary in this MUO patients was high. Further, as seen in cases of HCC, mucinous bronchoalveolar carcinoma and carcinoid, CECT helped detecting primary that would have been missed on FDG PET or PET-CT scan without contrast. Further CECT is modality of choice in 'T' staging of many of the solid tumors. Hence in those cases where primary tumor was confirmed with biopsy, complete staging of the tumor was already done by PET-CECT, saving time and cost for the patient although this aspect was not analyzed in the present study. Further, the scans were performed on state of the art PET-CT machine with time of flight technology, which also helped in improving our sensitivity.

The oral contrast helped in better visualization of GI tract leading to increased confidence for reporting CECT. This was primarily important to avoid false-positive interpretation due to physiological FDG uptake in bowel. Megibow *et al.*,[17] in their study showed that oral contrast material provides clear visualization of the bowel wall and has a synergistic effect by enhancing the mucosa, thus creating a gradient of attenuation and resulting in the improvement of the quality of the image. In combination with IV contrast material, low density oral contrast material has been shown to provide excellent distension and visualization of mural features in the GI tract. The small sized omental and peritoneal metastatic deposits, which may demonstrate faint FDG avidity to no FDG avidity can be identified with the help of CECT. In cases of attenuation artifact due to contrast in our study, we analyzed the nonattenuation corrected images for analysis, though their number were very few.
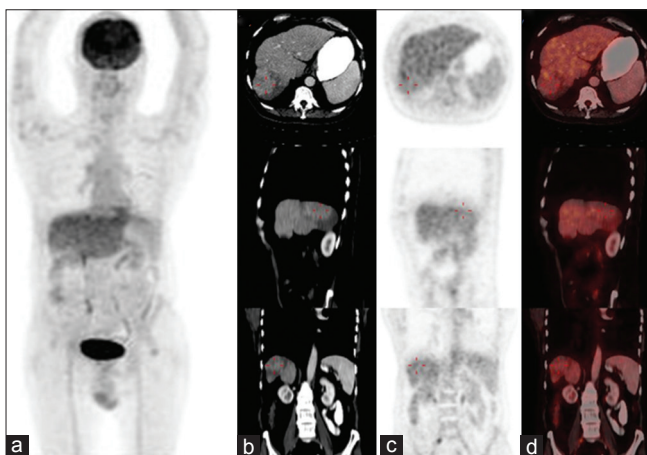
As compared to the sensitivity, specificity of FDG PET-CECT in our study for detection of unknown primary was only 66.67%. This may be primarily due to the fact that FDG is metabolic tracer and not a tumor specific imaging agent. The uptake of FDG in benign infective and inflammatory processes is proven beyond doubt.[18,19] Hence, we recommend that all patients in whom FDG PET-CECT is suggestive of probable primary; it should be confirmed with a biopsy and histopathological examination. The FDG PET-CECT seems to have high negative predictive value (>80%). Thus, we propose an algorithm [Figure 6] for its use as first diagnostic test for evaluation of patients with MUO rather than doing at the last. Although the cost analysis was not a part of the study, it seems logical to subject patient to single test with high sensitivity, positive and negative predictive value first than a battery of multiple tests, which may be invasive, time-consuming, with low yield and ultimately prove costly as well.

This study is unique in two ways that we included only naive patients who were not evaluated by conventional methods and secondly, as we routinely use CECT, we were able to study the contrast enhancement pattern of various tumors, which increased the sensitivity of our study and our confidence level in reporting the diseases. However, the usefulness of CECT over CT as part of FDG PET study is not well analyzed. A recent study by Brendle *et al.*[20] in GI FDG uptake concluded that PET-CECT provides an additional benefit especially in detecting GI malignancy, however due to considerable false negative rate even with CECT, did not recommend its routine use.

CONCLUSION

FDG PET-CECT appears to be one stop shop as an initial noninvasive diagnostic modality in patients with MUO. It allows whole body survey for the detection of site of primary and distant metastases with high sensitivity. It is useful for guiding biopsy of probable sites of the primary tumor. Addition of CECT improves the detection of non-FDG avid tumors like
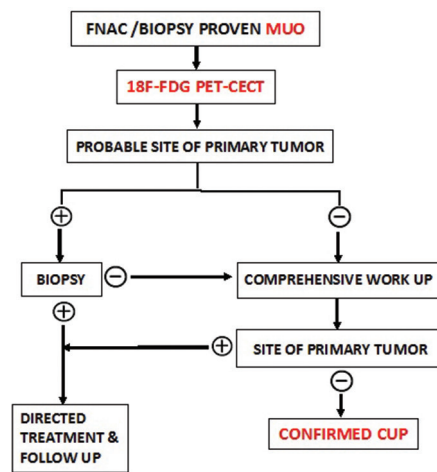

Figure 5: Positron emission tomography-contrast enhanced computed tomography (PET-CECT) in a 63-year-old male with neuroparenchymal metastasis, biopsy from which showed metastatic adenocarcinoma. (a) Maximum intensity projection image with no focal abnormal FDG uptake, (b) CECT sections showing hypodense lesion in segment VI and VII of liver (c) corresponding fluorodeoxyglucose (FDG)-PET sections showing no focal abnormal FDG uptake in liver, (d) fused PET-CECT sections. CECT imaging features were suggestive of hepatocellular carcinoma, which was confirmed on biopsy

Figure 6: Diagnostic algorithm for patients detected with malignancy of undefined origin

HCC, neuroendocrine tumors, bronchoalveolar carcinoma, etc., In our opinion, only those patients with MUO where PET-CECT is unable to detect primary, should be subjected to further extensive work-up. However, this needs to be confirmed in larger patient population with cost analysis.

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