

## Seeking for the primary in carcinoma of unknown primary : Can PET -CT scan help ?

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### Introduction

Carcinoma of unknown primary syndrome (CUPS) is labelled when even after the extensive work up in form history, physical examination, laboratory parameters, computed tomography scan and various forms of imaging, the primary site is not identified in a biopsy -proven malignancy.<sup>[1]</sup>

Carcinoma of unknown primary syndrome (CUPS) represents 0.5-9% of the patients with malignant tumors and only 20-27% of primary sites are identified before death.<sup>[2]</sup> Identification of the primary is important from the therapeutic and prognostic point of view. Inability to locate the primary site in CUPS leads to suboptimal cancer therapy which have to a negative impact on the survival. Some studies have reported that although the median survival time of patients with CUPS is less than 1 year, if the primary site is identified and cancer directed therapy started accordingly, the chances of survival can be increased.<sup>[3,4]</sup> However, a large number of primary tumors remains undetected approximately 40% even after a detailed evaluation.<sup>[1]</sup> Positron-emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) or PET combined with computed tomography (PET/CT) is recommended in the diagnostic work up of patients with CUP.<sup>[5]</sup> The rate of detection of the primary site varies; 24.5-41% for the FDG-PET.<sup>[6]</sup> and 22-73% with the FDG-PET/CT<sup>[7]</sup> The efficacy of PET or PET/CT for the detection of primary sites in patients with CUP remains to be determined especially in developing countries like India where there are limited resources and high rate of false positivity due to infectious disease. The present retrospective study aims to determine whether PET/CT had any additional advantage over the conventional diagnostic modalities to identify the primary site.

### Materials and methods

The retrospective data and records of the patients who were referred with the clinical diagnosis of carcinoma of unknown primary. Carcinoma of unknown primary is assigned to those who have biopsy proved malignancy and no primary could be found out even after extensive evaluation in form of history, physical examination, laboratory tests, chest Xray, Computed tomography of chest, thorax, abdomen and pelvis. All the conventional diagnostic work up comes out as negative.

Patients were instructed fasting 8 hours before injecting the radio-pharmaceutical. Whole body PET scan from vertex to mid thigh with contrast enhanced CT (1.5 mm slice thickness) acquired in 3 D mode 60 minutes after intravenous administration of 370 MBq of [<sup>18</sup>F]-2-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) using Siemens Biograph Horizon with time of flight PET-CT scanner. Reconstruction of the acquired data performed so to obtain fused PET-CT images in trans axial, coronal and sagittal views. Semi-quantitative estimation of FDG uptake performed by calculating SUV<sub>max</sub> values, corrected for dose administered and lean body mass.

Primary site of malignancy is defined when additional information was revealed on PET-CT scan imaging. The images were evaluated by both nuclear medicine physician and radiologist. When the FDG uptake site in the PET or PET/CT was confirmed as benign lesion, it was assigned as false positive.

### Results

Total of 54 patients were evaluated (37 males and 17 females). No primary site could be found out in 14 patients (7 were nodal metastasis, 5 bone metastasis, 4 visceral metastasis) hence 40 patients were evaluated in whom we could find out the primary lesion. The median age was 65 years (range 47-86 years). Majority of patients presents with nodal metastasis either cervical lymph nodes (32.5%) or axillary nodes and inguinal nodes 2.5% and 7.5% respectively. After extensive work up and investigations the most common primary site found out to be lung (27.5%) followed by head and neck region (10%) and colorectal (10%). Among 25% patients, no primary site could be made out.

The median standardized uptake value does not vary among the primary site (8.9, 8.6) and metastatic site. Adenocarcinoma were reported in 22 patients and squamous cell carcinoma in 14 patients. The characteristics of the patient are given in table 1.

### Discussion

The identification of the primary site in carcinoma of unknown primary can help in focussed treatment directed according to the primary and hence associated with better outcome. It also helps in optimizing the radiation therapy field design and evaluation of response to the treatment.

Certain reports have stated that in spite of complete diagnostic workup, PET-CT may not add any significant information of either the occult primary site or helps in patients management and the additional value of PET/CT in CUPS patients may be overestimated<sup>[8]</sup>

Wolpert et al. investigated the diagnostic value of PET/CT in 64 patients with Brain metastasis of unknown primary and detected additional lesions suspicious of extracerebral metastases in 27 of 64 patients (42%) mainly in lymph nodes and concluded that PET/CT improves the accuracy of tumor staging by detecting more metastases that resulted in adjustment of therapeutic strategy.<sup>[9]</sup>

In Bakhshayeshkaram et al.'s study which included sixty-two CUP patients, PET/CT revealed additional metastasis in 56.4% (35/62) patients. The most frequent sites were mediastinal, hilar, and retroperitoneal lymph nodes.<sup>[10]</sup>

In the same study of Bakhshayeshkaram et al., they found that the lung was the most frequent primary source of brain metastasis in 4.93% patients<sup>[10]</sup> A study by Gutzeit et al. has shown

that CT alone can detect the primary tumor in 8/45 patients (18%), while this percent was 33% (15/45 patients) when used PET/CT. In another study by Riaz et al. which included 100 patients, the sensitivity, specificity, and accuracy of 18FFDG PET/CT in detection of primary tumor were reported as 80%, 74%, and 78%<sup>[11]</sup>

In a study cohort by Reinert et al. which included 155 patients to detect the effect of PET/CT on clinical management of CUP patients, he concluded that there was no significant differences in estimated overall survival time could be noticed between patients with an identified primary tumor and patients with unidentified primary tumor<sup>[12]</sup>

It has been realized that in only 20 % of patients with CUP, the primary site can be identified after extensive workup. Reason for not able to identify primary site in majority of patients remains unclear. Some common hypothesis suggested spontaneous regression or immune mediated destruction of primary site or very small size of primary tumor<sup>[13,14]</sup> one metaanalysis investigated the diagnostic accuracy of the PET/CT and reported detection rate of 37%<sup>[7]</sup>

The detection rates by PET/CT was not significantly different between patients presenting with cervical metastasis or extracervical metastasis. The most common primary tumors detected were lung, oropharyngeal, and pancreatic cancer.<sup>[15,16]</sup> Histopathological diagnosis and metastatic pattern may suggest a primary site, for example in patients presenting with level II, Level III lymph nodes, the head and neck region should be surveyed, likewise if patients present with poorly differentiated carcinoma and supraclavicular nodes, suspicion for gastrointestinal primary should be raised. Females patients having axillary lymphadenopathy should be evaluated for breast primary and on the other hand if they present with peritoneal malignancy, primary ovarian carcinoma should be suspected first. Men with osteoblastic bone metastasis, evaluation should be done for primary prostate malignancy.<sup>[17]</sup>

Physiological FDG uptake in the lymphoid tissue of the adenoids and Waldeyer's ring and overlap between tumor and physiological FDG uptake, makes it difficult to analyze oropharyngeal malignancies. Likewise focally increased FDG uptake in lung may resemble primary malignancy, its CT scan may indicate the presence of a benign inflammatory or infectious lesion or a pulmonary embolism or infarction.<sup>[18,19,20]</sup>

The majority of unknown primary tumors are not detected, either due to insufficient sensitivity of FDG PET/CT or due to disappearance of the primary tumor. Even then PET/CT is advised to identify or rule out additional metastatic sites, which may have important implications for patient management. This may be important for patients presenting with lymph node metastatic disease only, because M stage, which has important therapeutic and prognostic consequences, is still unknown in these patients. Furthermore a baseline investigation in form of PET/CT is advisable to monitor the therapeutic outcome.<sup>[21]</sup>

Flechter et al. recommended that a baseline FDG PET/CT in patients of carcinoma of unknown primary is beneficial and should be done in work up and a confirmatory biopsy is advisable in view of high false positive results.<sup>[22]</sup>

Four individual studies in patients with carcinoma of unknown primary showed the therapeutic influence of FDG PET/CT and reported a modified therapy in 18.2 -60 % of patients based on FDG PET/CT imaging.<sup>[23,24,25,26]</sup>

Kaya et al, reported that the median overall survival between FDG PET/CT -positive and FDG PET/CT – negative groups was not significantly varied.<sup>[27]</sup> In another study by Fencletal, survival rates of CUP patients with at least one hypermetabolic lesion was reported significantly lower than the other patients with carcinoma of unknown primary.<sup>[28]</sup>

The primary tumor site is often small and tumor with size around and below the spatial resolution of a PET machine may not be picked up unless an intense FDG uptake is present. However even if such a small lesion has a high FDG uptake, partial volume averaging with the surrounding normal tissue may occur, resulting in a considerable decrease in the qualitatively or semi quantitatively perceived FDG uptake. Hence the lesion may incorrectly resemble a benign process, which generally has a lower FDG uptake [standardized uptake value (SUV)<2.5-3.0] than a malignant tumor. Therefore, the technological advances that lead to a higher signal to noise ratio (SNR) and a higher spatial resolution are likely to increase the diagnostic yield of FDG PET/CT in patients with CUP. PET CT systems with Time of flight (TOF) capabilities are commercially available. In TOF PET , the actual time difference in the arrival of the two annihilation protons at the detectors is recorded. The TOF information is incorporated directly into the reconstruction algorithm permitting some combination of faster scanning, improved SNR or improved spatial resolution.<sup>[29]</sup>

Several tumors exhibit a maximum FDG uptake well beyond 60 mins after FDG administration while surrounding normal tissues show a decline in FDG uptake with time [48–50]. Hence lesion to background contrast can be considerably increased at delayed PET imaging leading to increased chances of detecting the primary site. Therefore routine use of delayed PET imaging is recommended in patients with diagnosis of carcinoma of unknown primary.<sup>[30,31]</sup>

The development of fully integrated whole body PET/ MRI system may further hold promising results in diagnosing primary site in carcinoma of unknown primary. A integrated PET/MRI system allows true simultaneous scanning, thereby minimizing the mismatch between functional(PET) and anatomical (MRI) data sets.<sup>[32]</sup> Superior soft tissue resolution of MRI especially in brain, liver and other soft tissue regions and bone marrow and possibility of acquiring a variety of tissue contrasts is an advantage with PET/MRI.<sup>[33]</sup> MRI allows functional tissue information to be obtained , which may help in detection of primary tumor.

An interesting use of molecular technology that allows a large scale gene expression profiling holds a promise in the patients of carcinoma of unknown primary. Several gene expression assays have been validated using samples from the primary tumor or known metastatic sites. Molecular assays is applied that evaluates the expression of multiple tissue type specific gene markers using quantitative reverse transcriptase chain reaction and helps in identifying the primary site.<sup>[34,35]</sup> The integration of molecular technology ,advanced techniques and imaging modalities are expected to play an very important role in the management of patients with CUP

## Conclusion

Carcinoma of unknown primary has been a heterogenous disease and poses a challenge to the oncologist community. Every effort should be made to identify the primary site so that focussed treatment can be done which further improves the chances of survival and better

outcome. FDG PET/CT whole body has come to rescue tool in the patients of unknown primary and can pick up the primary site to guide the further treatment. Further advances in this investigation in form PET/MRI can help in delineating the soft tissue lesions in a carcinoma of unknown primary. The present study tried to find out the common tumors found in these patients and further in a large group of data is needed to reach at a point in favour or against PET/CT.

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Table 1.Characteristics of the diagnosed primary patients

parameters	Patients (n-40)
Sex	
Male	30
female	10
Age	
Median	65 years
range	47-86 years
Site of metastasis	
Sketelal	10 (25%)
Brain SOL	4 (10%)
Cervical node ( I,II,III,IV,V)	13 (32.5%)
Inguinal node	3 (7.5%)
Axillary node	1 (2.5%)
Umblical nodule	1 (2.5%)
Liver SOL	6 (15%)
Omental thickening	2 (5%)

Primary site	
Colorectal	4 (10%)
Breast	2 ( 5%)
Lung	11(27.5%)
Upper GIT	5 (12.5%)
Renal	2 (5%)
Ovarian	2 (5%)
Prostate	3 (7.5%)
Head and neck	4 (10%)
Biliary tract and pancreas	3 (7.5%)
Cervix and vagina	3 (7.5%)
liver	1 (2.5%)
SUX max	
median of the primary	8.9
range	3-24
median for the metastatic site	8.6
range	2.5-23.6