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Diagnostic accuracy of f18-fluorodeoxyglucose positron emission tomography-computed tomography in the evaluation of carcinoma of unknown primary: A single-center study

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ABSTRACT

Background: The term carcinoma of unknown primary (CUP) is not a single disease entity that it can be explicated as the recognition of metastasized tumor, in which the primary origin of the malignancy from an organ or site remains occult. The term refers to a clinical disorder that revolves around and represents a diversified metastatic tumor group, for whom the diagnostic investigations are unable to pinpoint the primary site of the tumor, comprising extensive radiological techniques, invasive endoscopic procedures, and histopathology, many which fail to diagnose the primary site. **Aims and Objectives:** The study was conducted to ascertain the diagnostic accuracy of fluorine-18 labeled fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) in the evaluation of CUP. The secondary objective of the study was to identify rate of the primary malignancies localized on 18F-FDG PET-CT that presents as CUP in local settings. **Materials and Methods:** The prospective and cross-sectional study included patients with CUP who underwent 18F-FDG PET-CT scans between October 2021 and February 2022. The primary site localized on 18F-FDG PET-CT was confirmed through biopsy and histology. False-negative and false-positive patients were ascertained through biopsy and/or follow-up of 6 months. **Results:** Of a total of 63 patients, 57.1% were male, while 42.9% were female with a mean age of 56.27 years. The overall detection rate of primary tumor (PT) site on 18F-FDG PET-CT was 88.8%. Abnormal sites and indicative of primary malignant tumor were correctly detected in 79.36% that were truly positive proven on biopsy. False-negative rate of scan was 4.76%, though malignancy was proven through other investigations or follow-up, while 6.36% had true negative and 9.52% showed false-positive results on the scan. In this study, the calculated diagnostic accuracy of 18F-FDG PET-CT identified as 85.7%, sensitivity 94%, specificity 40%, positive predictive value 89.2%, and negative predictive value 57.1%. **Conclusion:** 18F-FDG PET-CT demonstrated high sensitivity and diagnostic accuracy ascertaining the PT site in patients with CUP in our study population.

Key words: Carcinoma of unknown primary; Positron emission tomography; FDG PET; Diagnostic accuracy

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INTRODUCTION

The term carcinoma of unknown primary (CUP) is not a single disease entity that it can be explicated as the recognition of metastasized tumor, in which the primary origin of the malignancy from an organ or site remains occult. The term refers to a clinical disorder that revolves around and represents a diversified metastatic tumor

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group for whom the diagnostic investigations are unable to pinpoint the primary site of the tumor, comprising extensive radiological techniques, invasive endoscopic procedures, and histopathology, many which fail to diagnose the primary site.[1,2] CUP is one of the ten most commonly encountered diagnosis among the patients evaluated for metastatic cancers, estimating 3–5% of all malignancies. In the population of cancer-related mortality, CUP is considered as fourth most frequent reason. The average age of patients diagnosed as CUP is 60 years.[3,4] In patients with CUP, the average survival rates have been recorded as 10–12 months or 1 year approximately. The localization of primary tumor (PT) site in patients with CUP has consistently been a diagnostic conundrum requiring a wide range of workups. However, the localization of PT site earlier in the diagnostic work up guides the management strategy and helps in selection of specific therapy that may improve the treatment outcome.[5] More than 50% of patients with PT involve more than one site which often represents metastasis.[6] Cup is also known as metastasis of unknown origin.[7,8] The diagnostic procedures used for PT localization comprise radiological methods and histopathology. A few of those tests may be invasive, costly, and time consuming and also many of the times fail to diagnose the primary site. Positron emission tomography-computed tomography scan using fluorine-18 labeled fluorodeoxyglucose (18F-FDG PET-CT) as metabolic marker can identify pathological sites demonstrating increased metabolic rates due to high mitotic frequency, a hallmark of malignant diseases. Due to high lesion to background contrast, small lesions can be identified with higher sensitivity.[9] The whole-body PET-CT scan is a sensitive imaging technique used to provide a non-invasive quantifiable assessment of biochemical as well as physiological processes, while other radiological imaging modalities provide functional or anatomical information. The purpose of this present study was to retrospectively assess the diagnostic accuracy of 18F-FDG PET-CT in the evaluation of CUP.

Aims and objectives

The study was conducted to ascertain the diagnostic accuracy of (18F-FDG PET-CT) in the evaluation of CUP. The secondary objective of the study was to identify rate of the primary malignancies localized on 18F-FDG PET-CT that presents as CUP in local settings.

MATERIALS AND METHODS

The approval of Institutional Ethical Board was obtained from FMH College of Medicine and Dentistry Institutional Review Board under the letter number (FMH-03/12/2021–IRB1048). This was a prospective analysis of patients who were assigned for 18F-FDG PET-CT due to CUP at INMOL Cancer Hospital Lahore throughout October 2021–February 2022. According to European association of nuclear medicine guidelines, PET-CT scan was performed in conformity with the standard head to mid-thigh protocol, for which a minimum of 6 h of fasting was required. The scans were carried out with injected FDG dose of radioactivity in between 250 and 370 Mega Becquerel according to body weight. The approximate time between injection and data acquisition was between 60 and 90 min. The whole body scan after injection of FDG from vertex to feet was obtained by PET-CT scanner (Discovery STE 16 slice CT-scanner with the BGO-PET scanner) with 3 min acquisition for every six to eight bed positions. The CT scan used for anatomical localization and attenuation correction was performed in all patients and acquired earlier from vertex to feet using (120kVp/70mAs). The data were shifted to the process workstation for review in analysis using ADW 4.1 GE software. The data points acquired after quantification was statistically analyzed. The data were entered using IBM-SPSS v-23 software. Sixty-three patients were clinically designed with CUP disease, in which the majority of subjects 36 were male, while 27 were female with average age of 56.27 years (age ranged between 35 and 70 years).

Inclusion criteria

Adult subjects had 18F-FDG PET-CT scan at INMOL Cancer Hospital and patients with evidence of metastasis on histopathology or previous imaging studies. Patients provided consent for inclusion in the study were recruited. Patients with the biopsy-confirmed metastatic lesion were included; however, there were few cases with negative histopathology that was included as they showed radiological evidence of metastatic lesions.

Exclusion criteria

Patients with uncontrolled diabetes or hypertension, allergy to the intravenous contrast agent, pregnancy on urine test, and patients who did not cooperate for the scan (inability to relatively lie still) were excluded from the study.

Interpretation criteria and result analysis

Sites of abnormal FDG uptake corresponding to abnormal CT findings or abnormal focus within the normal viscera demonstrating SUV max greater than liver and/or a value >2.5. The foci with values <2.5 were considered abnormal when corresponding to CT abnormality. The qualitative variables (sexual category, identified unknown primary cancers site on PET-CT scan) were all represented as percentages or frequency, while quantitative variables like ageare represented as (mean ± SD). A Chi-square test was applied. The diagnostic accuracy, sensitivity, and specificity of PET-CT scan in primary malignancy detection were calculated by applying statistical formula by standard two-

by-two contingency table as the histology results were accepted as a gold standard. Accuracy = (TP + TN)/(TP + FP + TN + FN), sensitivity = TP/(TP + FN), and specificity = TN/(TN + FP).

RESULTS

Among 63 patients examined using 18F-FDG PET-CT, 36 (36; 57.1%), patients were men, while 27 (27; 42.9%) were female (mean age 56.27 years; age range 35–70 years). Patients with the biopsy-confirmed metastatic lesion were 40 (63.49%); however, there were 23 cases with negative histopathology (36.5%); however, they underwent 18F-FDG PET-CT as they had radiologically suspected metastatic lesions.

As per age distribution, retroperitoneum was found to be a common PT site in patients below 40 years, while lung followed by head and neck were found to be involved as primary sites in majority of patients above 40 years.

The overall hypermetabolic lesions indicative of PT site were identified in 56 out of 63 patients by 18F-FDG PET-CT scan. Remaining seven patients did not show any hypermetabolic lesions as primary or metastatic disease. Six patients out of 56 showed single site of FDG uptake, considered primary site, did not show any metastatic sites of hypermetabolism (Table 1).

The hypermetabolic lesions indicative of PT site that were proven histopathologically to be malignant were correctly identified in 50 from the total of 63 subjects (79.36%; True positive). The patients with normal PET-CT scans (n=4; 6.36%) who remained disease free on 6 month's follow-up were considered true negative. Three patients (4.76%) in whom PT was not detected by 18F-FDG PET-CT scan turned out to be false-negative as later pathologic evaluation confirmed primary malignant site despite no FDG uptake. In six patients (9.52%), the hypermetabolic lesions identified by PET-CT scan were non-malignant on follow-up biopsy; hence, results were considered false positive.

Histopathology features of primary lesions detected on PET-CT scan

The identified primary lesions on PET-CT scan were; lung 16/50 (32.0%), head and neck 9/50 (18%), lower GIT 3/50 (6%), liver 5/50 (10%), lymphoma 5/50 (10%), kidney 2/50 (4%), breast 2/50 (4%), upper GIT 1/50 (2%), ovary 1/50 (2%) (Figure 1), prostate 1/50 (2%), retroperitoneum 2/50 (4%), and pancreas 3/50 (6%).

Of the 50 patients with localized PT, all had confirmation by biopsy and histopathology. Of these, 33 (66%) were adenocarcinoma, 4 (8%) showed squamous cell carcinoma,

Table 1: Patient demographics

Gender	Frequency (%)
Women	27 (42.9)
Men	36 (57.1)
Mean age years (range)	56.2 (35–70)
Primary site identified by 18F-FDG PET-CT	
Lung	(n=18, 32.1)
Head and neck	(n=11, 19.6)
Liver	(n=5, 8.9)
Lymphoma	(n=5, 8.9)
Lower GIT	(n=4, 7.1)
Pancreas	(n=3, 5.3)
Kidney	(n=3, 5.3)
Breast	(n=2, 3.5)
Retroperitoneum	(n=2, 3.5)
Upper GIT	(n=1, 1.7)
Ovaries	(n=1, 1.7)
Prostate	(n=1, 1.7)
Metastatic sites on F18-FDG PET/CT	
Multiple metastatic sites	(n=35, 55.5)
Thorax	(31.4)
Abdomen	(22.8)
Head and neck	(17.1)
Skeletal metastasis	(14.2)
Lymph nodes	(8.5)
Pelvis	(5.7)
Solitary metastatic site	(n=15, 23.8)
Abdomen	(11.1)
Head and neck	(6.3)
Thorax	(3.1)
Skeletal	(3.1)
No metastatic site	(n=13, 20.6)

among the adenocarcinoma group, the frequency of different primary sites was lung 16 (48.4%), breast 2 (6.0%), renal 2 (6.0%), liver 4 (12.2%) **(**Figure 2**)**, colon 4 (12.2%), prostate 1 (3.0%), pancreatic 2 (6.0%), gastric 1 (3.0%), and ovarian carcinoma 1 (3.0%).

Among the squamous cell carcinoma group, the distribution of the primary site among patients was oropharynx 1 (25.0%), nasopharynx 1 (25.0%), and hypopharynx 2 (50.0%).

Remaining 13 (26%) out of 50 patients in whom 18F-FDG PET-CT detected the PT showed multiple myeloma 4 (30.7%), lymphoma 4 (30.7%), melanoma 1 (7.6%), parotid 2 (15.4%), soft tissue sarcoma 1 (7.7%), and follicular thyroid carcinoma 1 (7.7%).

In our cohort, about 35 patients were having multiple metastatic sites, in which the thorax 31.4% and abdomen 22.8% were found to be the predominant sites of metastasis with head and neck at 17.1% and skeletal metastasis at 14.2%.

Overall calculated diagnostic accuracy in this study was found to be 85.7%, sensitivity 94%, specificity 40%, positive predictive value 89.2%, and the negative predictive value 57.1%.

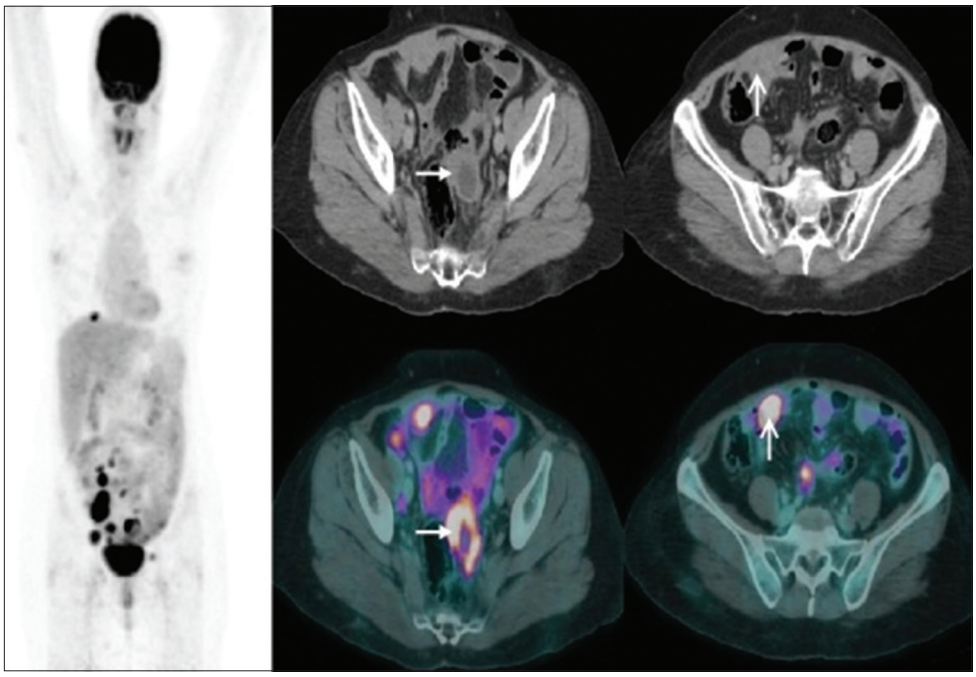

Figure 1: Images showing hypermetabolic ovarian pathology and peritoneal metastasis

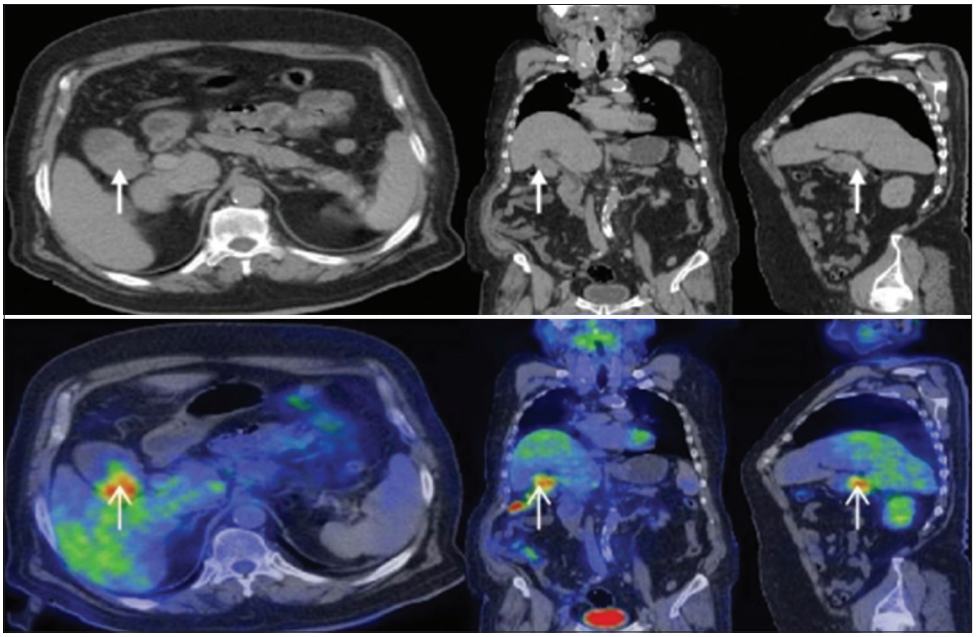

Figure 2: Row-A shows axial, coronal and sagittal computed tomography slices demonstrating gall bladder mass (↗), Row-B shows corresponding axial, coronal and sagittal fused PET-CT images showing hypermetabolic gall bladder mass

DISCUSSION

The psychological impact of the term carcinoma creates panic and anxiety in the patients, which is multiplied many folds if the treatment is delayed due to unknown or occult PT site. There is no single investigation available which may detect PT site with high diagnostic accuracy in patients of CUP. Consequently, multiple investigations are performed to localize the PT with high adverse impact on clinical, psychological, and socioeconomic status of the patients. As mentioned in previously conducted, researches reported that the identification of PT sites by conventional imaging modalities is <30%. The lack of identification of PT may adversely affect patient management.[3-10] 18F-FDG PET-CT has been identified as a useful imaging technique in many published research reports.[11] However, limited published data are available from Pakistan describing the performance

of 18F-FDG PET-CT in CUP. The frequency of malignant disease in our country is different from other regions of the world. CUP rank among the ten most frequently occurring cancers.[12]

The CUP prevalence is robustly dependent on age parameters showing maximum occurrence proportion in older people.[13] Congruent numerical data results were found in this analysis demonstrating majority patients of older group and slight male preponderance. Similar results were found in a previously conducted researches which show greater ratio of male than females.[5]

Notably in this cohort; lung cancer (32.0%) is the most commonly occurring PT site that is, followed by head and neck tumors (18.0%) and liver (10.0%). These results are in agreement with the published data in by Riaz S et al., showing lung as most common PT site followed by head and neck cancer. Overall the most common PT site identified in the cohort of both genders was lung; however, the most common PT site among females was found to be head and neck, while the lungs were most frequently detected PT site among males.

In the evaluation of lung cancer, 18F-FDG PET-CT is known useful modality. For characterization of lung nodule as benign or malignant, 18F-FDG PET-CT is considered highly accurate investigation. The detection rate of metastases in mediastinal nodal site as well as extrathoracic sites is much improved using whole body PET-CT when compared with other imaging techniques such as CT, magnetic resonance imaging (MRI), ultrasound, and bone scan. Published data have shown that PET-CT provides better sensitivity and specificity as compare to contrast-enhanced CT (CE-CT) and MRI in patients of head and neck cancer degree of FDG uptake is useful in detection of nodal involvement even in radiologically small volume or size insignificant lymph nodes in CE-CT. Distant metastatic evaluation in head and neck cancer is equally significant due to its high impact on patient survival. For the evaluation and identification of distant metastatic disease CE-CT of the thorax, liver ultrasound and bone scanning do not improve management strategy of patients in a significant proportion to be considered for routine use in staging. The ability of PET-CT to undergo whole-body evaluation in single imaging session from the head to mid-thigh affects clinical management of patients by identifying distant sites of metastases.[14] In all women with presumed CUP, the routine use of mammography is controversial even the breast cancer detection in patients with CUP has potential benefit despite the fact that mammography is non-invasive and quick test that it has comparatively low breast cancer detection rate.[15]

The overall diagnostic accuracy was found to be 85.7% in this study which is consistent with the published data showing diagnostic accuracy within the range of 83–87%.[2-16] In our study, the sensitivity was calculated as 94%, specificity as 40%, PPV 89.2%, and the NPV 57.1%. The positive hypermetabolic lesions indicative of malignant tumors on the PT site which was histopathologically proved to be malignant were correctly identified in 50 from the total of 63 sufferers (True positive; 79.36%). This detection rate corresponds to the studies in the literature which reported the rate of detection between ranges of (57–77%).[5-17] The specificity calculated in our study is concordant with some previously published researches showing specificity within the range of 44–66%.[17,18] Low specificity in our study though has been documented in some previously publish researches also is attributable to small sized study population. Another contributory factor may be the inclusion criteria that allowed recruitment of those patients who have high suspicious of malignant disease on the basis of radiology as well thus inflammatory and other benign diseases have been recruited causing false positive scans.

Among the imaging methods, CT and MRI are broadly performed for diagnostic workup of CUP. Given their lack of potential to identify the metabolic status, they may be insufficient to identify most of the cancer sites, as well as metastatic spread. The most obvious fact behind using 18F-FDG PET-CT is that typically cancerous cell shows an increased level of metabolic activity hence, ensuring increased uptake than other normal tissues showing high lesion to background contrast which makes it a highly sensitive technique of imaging for localization of malignant lesions. In contrast to CT alone, PET-CT being hybrid technique is a much better imaging technique in detection of malignant lesions for accurate staging. CE-CT part of PET-CT study provided additional morphological details and helped detection and characterization of enhancing small sized lesions.

Moreover, the contrast agent used in CT of PET-CT is of additive value in 18F-FDG PET negative lesions. Furthermore, in patients with PT of unidentified origin, 18F-FDG PET-CT scan could identify additional metastasis hence, modifying the stage of disease and can direct oncological treatment; hence, it can be hypothesized that PT detection at an early stage will optimize treatment planning rendering additional diagnostic CT unnecessary. PET-CT scan using 18F-FDG as radiotracer may be used as the foremost or first-line imaging modality for CUP diagnosis.[15-19] Further benefits of 18F-FDG PET-CT include cost reduction, saving time that would be wasted in conducting unfruitful investigations and directing sites of biopsy with maximum yield. True negative results

were found in 6.36% patients normal PET-CT scans and remained disease free in follow-up; hence, results were considered true negative.

There were three (4.76%) false-negative patients, in which the PT site was not identified by 18F-FDG PET-CT scan; however, these patients were pathologically confirmed to be malignant. The final diagnosis in these patients was neuroendocrine tumor of pancreas, renal cell carcinoma, and prostate carcinoma. Despite of highest detection rate of PT sites using 18F-FDG PET-CT scan, various kinds of tumor may persist enigmatic likewise, as mentioned in a research conducted by Alberini et al., based on the fact that increased glucose utilization with excessive levels of FDG uptake was identified within the high-grade epithelial tumors, but the low-grade tumor was scarcely depicted due to low FDG uptake. Moreover, 18F-FDG radiotracer used in PET-CT can best assist in tracing macroscopic disorder, but, most of the time, it is not possible to identify very small lesions due to limited resolution of technology.[20]

Limitations of the study

Our study has limitation that it included patients with negative histopathology but showed radiological evidence of metastatic lesions.

CONCLUSION

18F-FDG PET-CT demonstrated high sensitivity and diagnostic accuracy in localizing the PT site in patients with CUP in our study population.

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Authors' Contributions:
UBZ- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **MNY-** Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **SDH-** Design of study, statistical analysis and interpretation; **HR-** Review manuscript; **RB-** Review manuscript; **NN-** Literature survey and preparation of figures; **AS-** Coordination and manuscript revision.

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