Navigating the Unknown: Evaluating the Role of FDG PET-CT in Detecting Primary Tumors in Cancer of Unknown Primary- A Five Years Institutional Perspectives in Bangladesh

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ABSTRACT

Objective: To evaluate the clinical usefulness of 18F FDG PET-CT whole body imaging for identifying primary tumors in patients with cancer of unknown primary (CUP).

Methods: A total of 108 patients with an unidentified primary etiology were referred for whole body FDG PET-CT scan from 2019 to 2023 at the Institute of Nuclear Medical Physics, Savar. Visual examination and semi-quantitative analysis (standardized uptake value, SUV) were used to analyze PET-CT images. The utility of FDG PET-CT was evaluated based on formal clinical follow-up findings and histopathological data.

Result: The study analyzed 108 cancer patients with CUP aged 19–80 years (mean age: 56.70 ± 13.42 years; males: 65.7%, females: 34.3%). Comorbidities included diabetes (22.2%), hypertension (24.1%), and others. Metastases were frequently detected in cervical lymph nodes (33%), bones (19.4%), and liver (13.9%). Whole-body FDG PET-CT scans identified the primary site in 25% of cases, primarily in the lungs (13.9%), with histopathological confirmation. Histopathology revealed adenocarcinoma (55.6%), squamous cell carcinoma (22.2%), and poorly differentiated carcinoma (11.1%). Pre-scan treatment varied, with 59.3% receiving no prior treatment, while others underwent chemotherapy, radiotherapy, or surgery. The mean SUV was 9.43 ± 11.61.

Conclusion: The FDG PET-CT whole-body scan, a non-invasive and sensitive imaging modality, achieved a 25% success rate in identifying primary tumors, enhancing tumor staging, treatment planning, and prognostic accuracy.

Keywords: Carcinoma of Unknown Primary, CUP, 18F FDG PET-CT, Hybrid imaging

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INTRODUCTION

Cancer of unknown primary (CUP) is a rare yet challenging oncological entity, accounting for approximately 3–5% of all malignancies worldwide. It is defined by the presence of metastatic disease without an identifiable primary tumor despite comprehensive diagnostic evaluations, including imaging, endoscopy, and biopsy (1,2). The prognosis for patients with CUP is generally poor, as the inability to identify the tumor origin limits personalized treatment strategies. CUP often requires a balance between empiric treatment and a search for the primary site, both of which can be resource-intensive and emotionally taxing for patients (3,4).

Traditional diagnostic techniques, such as CT, MRI, and histopathological evaluations, have limited sensitivity in CUP cases, particularly when the tumor is small or in an anatomically obscure location (5). Fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) has emerged as a potential game-changer in this context. This imaging modality combines metabolic and anatomical information, enabling the detection of hypermetabolic foci that might represent primary tumors or metastatic lesions (6).

FDG PET-CT has shown promise in identifying the primary tumor in 20–40% of CUP patients, making it a valuable diagnostic tool for guiding biopsies, treatment planning, and prognostication (7,8). Moreover, its whole-body imaging capability facilitates comprehensive staging, critical for the appropriate management of CUP (9). However, the accuracy of PET-CT in CUP varies depending on factors such as tumor histology, size, and FDG avidity, as well as the presence of inflammatory conditions that can mimic malignancy (10).

In developing countries like Bangladesh, the adoption of FDG PET-CT is relatively new. Resource constraints and limited access pose significant challenges to its widespread use (11). This study aims to evaluate the utility of FDG PET-CT in detecting primary tumors and staging CUP in a five-year cohort at a single institution in Bangladesh. The findings may help refine the diagnostic approach to CUP in resource-limited settings.

PATIENTS AND METHODS

A retrospective observational study was conducted from 2019 to 2023 at the Institute of Nuclear Medical Physics, Savar, Bangladesh. A total of 108 patients diagnosed with CUP were included. Inclusion criteria encompassed patients with metastatic disease confirmed by biopsy but with no identified primary tumor after routine investigations. Whole-body FDG PET-CT scans were performed using standard imaging protocols. FDG uptake was analyzed visually and semi-quantitatively using standardized uptake values (SUV). Clinical data, including demographics, comorbidities, and previous treatments, were collected. Metastatic patterns and primary tumor detection rates were recorded. Histopathology confirmed FDG PET-CT findings. Descriptive statistics were used to summarize demographic and clinical data. SUV values were analyzed to assess their correlation with primary tumor sites and metastatic lesions.

RESULTS

The study included 108 patients aged 19 to 80 years (mean: 56.7 ± 13.4 years). Most participants were male (65.7%), and the mean age of male patients was 59.48±1.5 and for females mean age was 53.86±1.9.

Table 1: Age and sex distribution of the patients

Age group	Male Frequency (%)	Female Frequency (%)
19-44 years	9 (8.3)	7 (6.5)
45-64 years	35 (32.4)	25 (23.1)
65-80 years	27 (25.0)	5 (4.6)
Mean age ± SD	56.7±13.4 Y	
Median age	57 Y	

Among the patients 59.3% got no treatment before FDG PET-CT scan. A 20 % patients had either chemotherapy or radiotherapy, 4% patients had both before PET Scan. Surgery was performed in 11% patients and surgery with chemo or radiotherapy was done in only 5% patients.

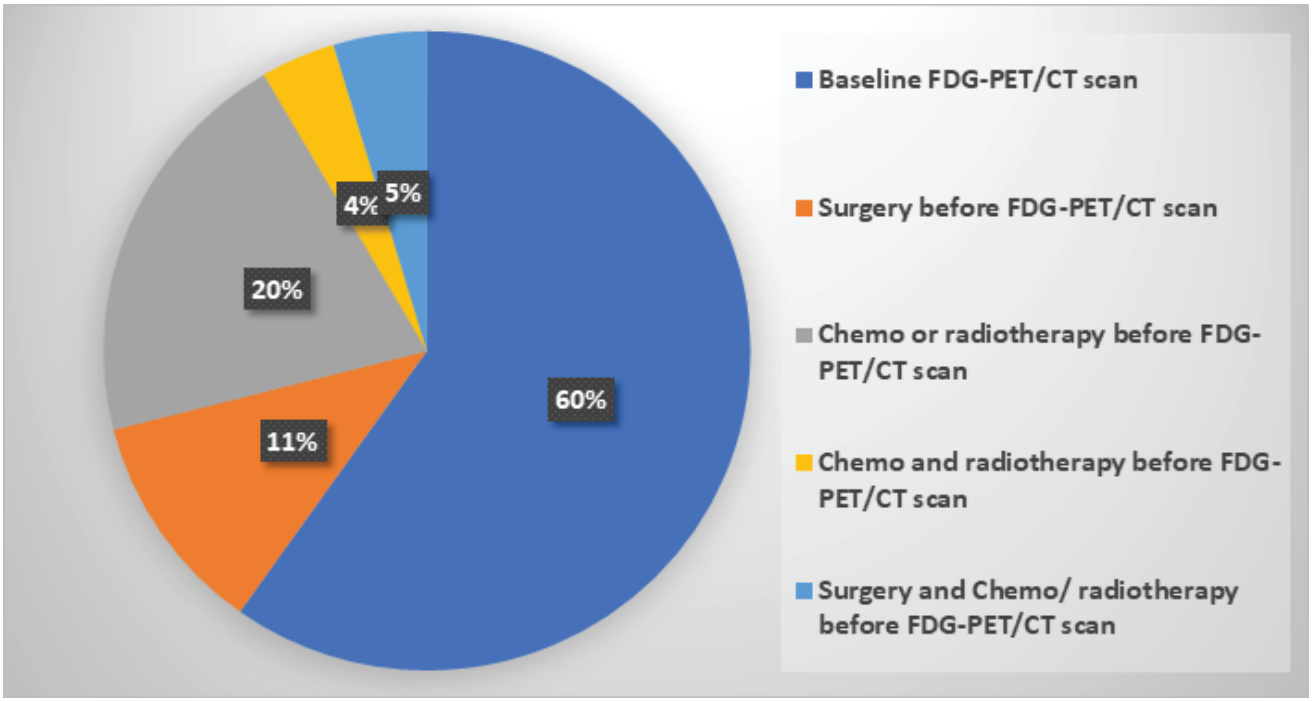

Figure 1: Baseline PET-CT imaging and treatments received by the patients

Among the patients in this study, 22.2% had Diabetes Mellitus, 24.1% had hypertension, 3.7% had cardiovascular disease, 2.8% had bronchial asthma,0.9% had IGT,0.9% had hypothyroidism and 1.9% had HBV infection.

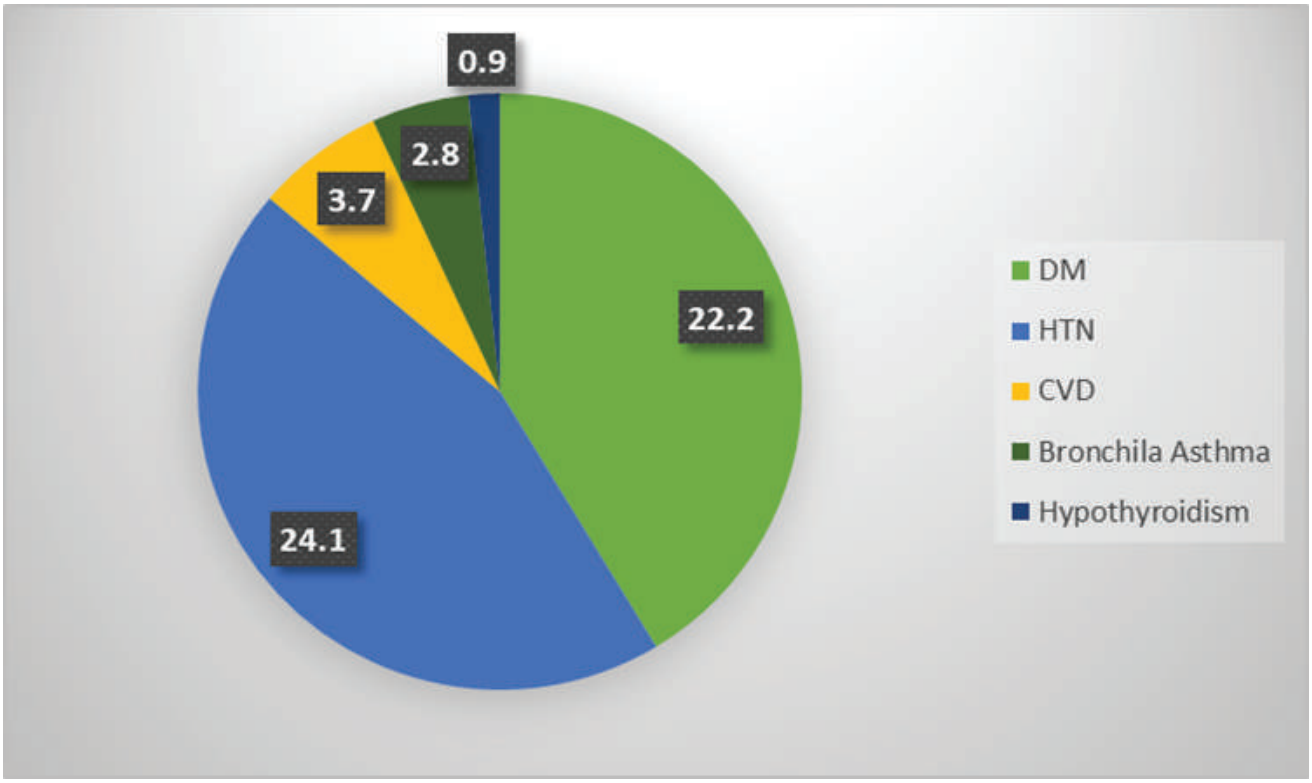

Figure 2: Distribution of co-morbidities among the patients

Metastatic lesions were detected in cervical lymph nodes (33%), bones (19.4%), and liver (13.9%). Less frequent metastatic sites included the thyroid gland, brain, and umbilicus.

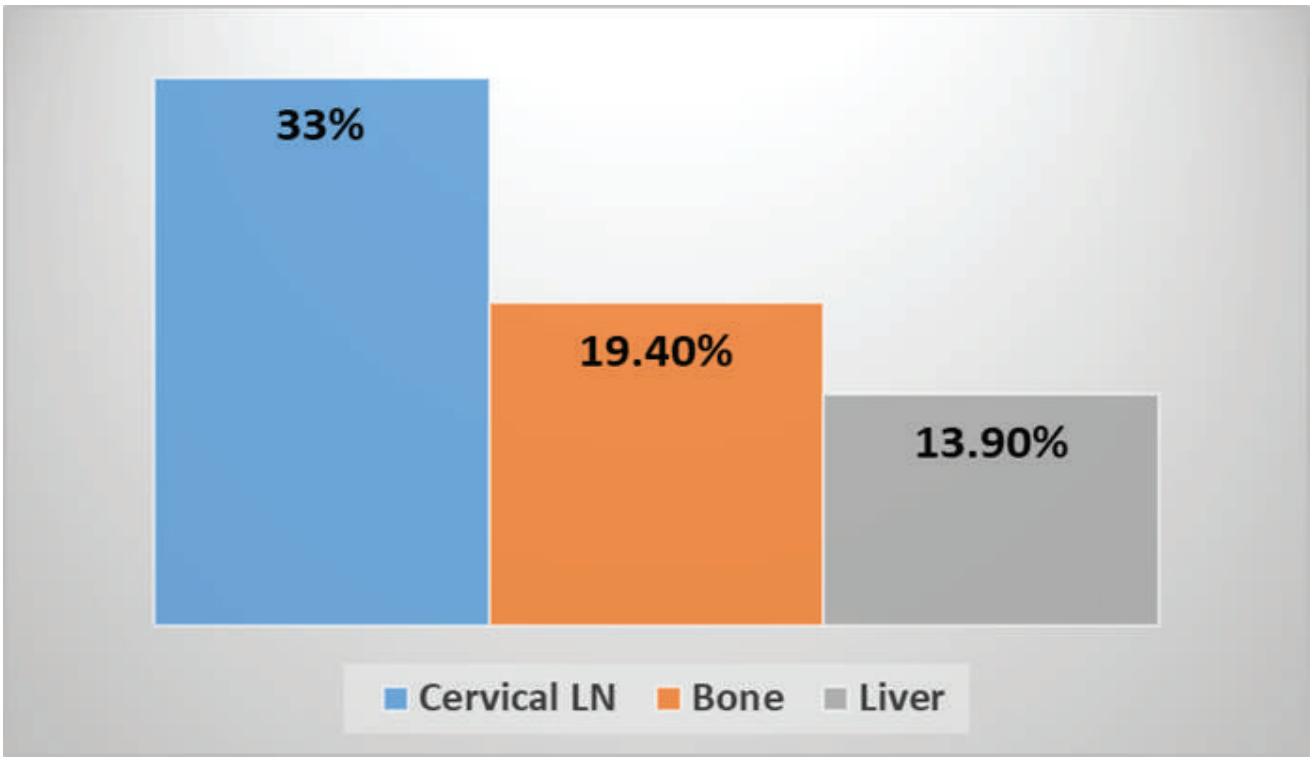

Figure 3: Distribution of known metastatic sites among the patients

In 70% of cases other new metastatic sites were evident in the PET-CT imaging, including the submandibular gland, supraclavicular lymph node, inguinal lymph node, abdominal lymph node, axillary lymph node, adrenal gland, brain, breast, lungs, chest wall, omentum, peritoneum, mediastinal mass.

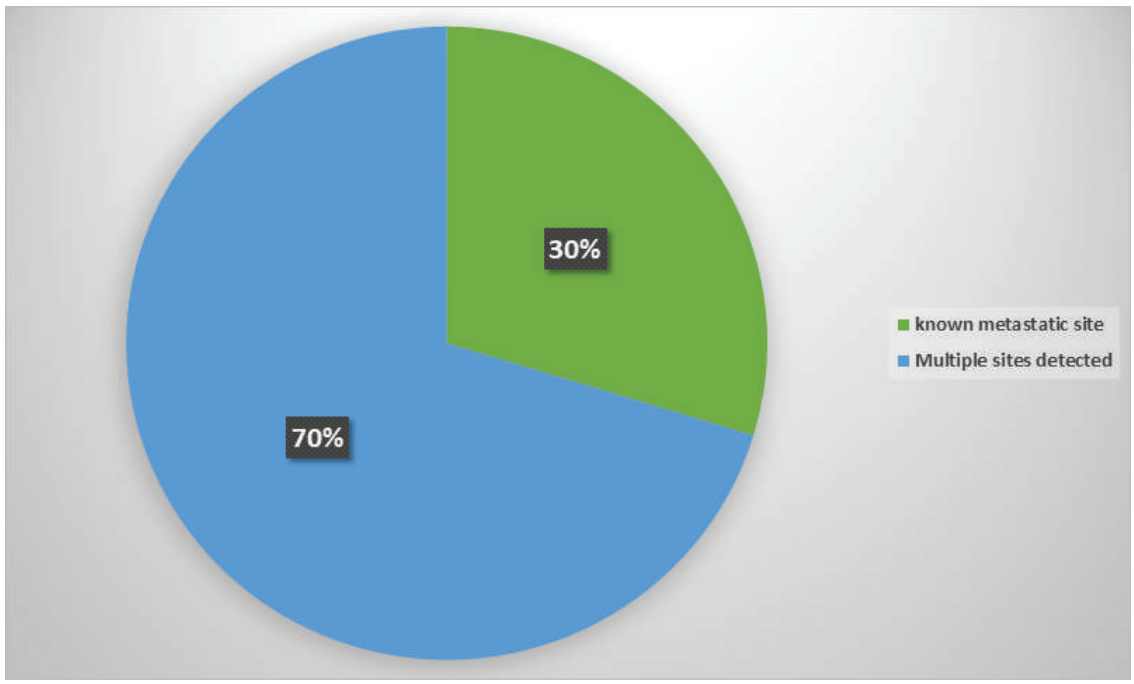

Figure 4: Known metastatic site and other multiple sites detected in PET-CT.

FDG PET-CT successfully identified the primary tumor in 25% of cases. The lungs were the most common site (13.9%), followed by the thyroid, gastrointestinal tract, and pancreas.

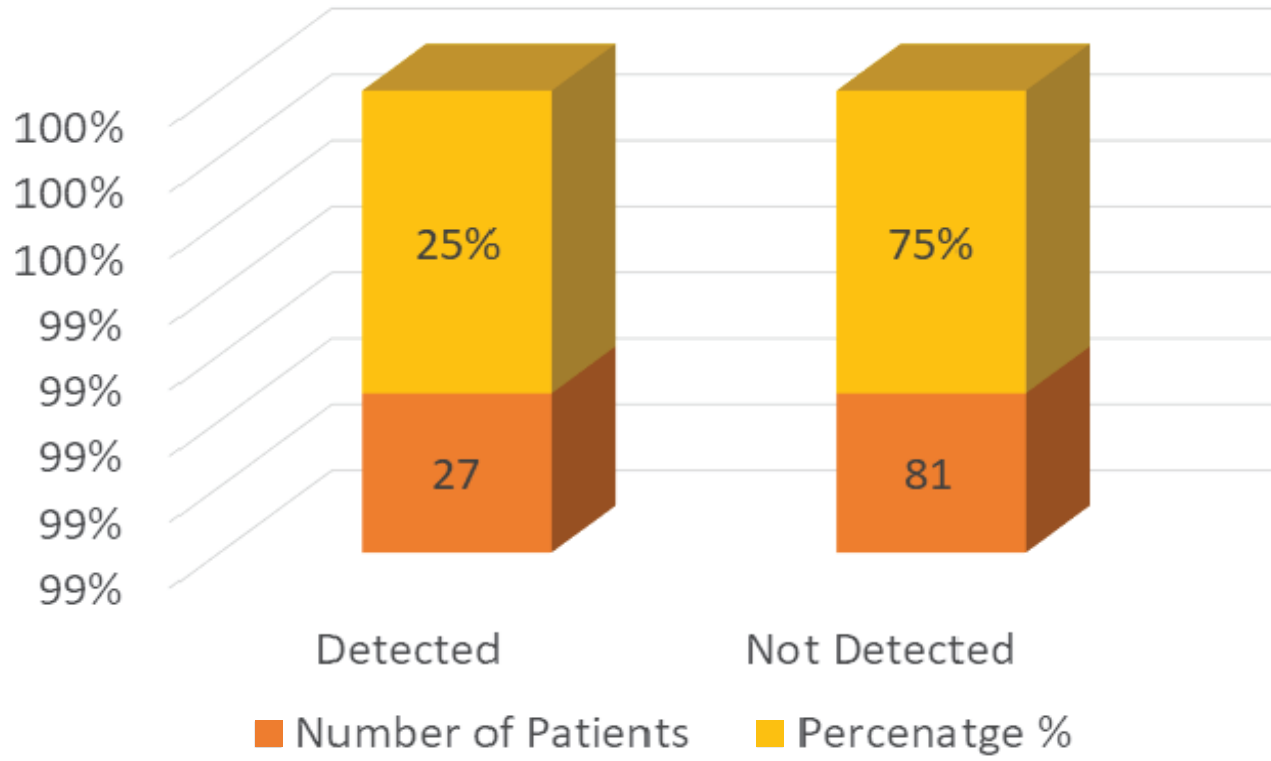

Figure 5: Distribution of primary sites detected by FDG PET-CT

Among these primary sites, the most frequent site of FDG uptake was the lungs (13.9%). The remaining sites in this study were the tonsil, thyroid gland, esophagus, stomach, rectum, pancreas, GE junction and recto-vesical pouch.

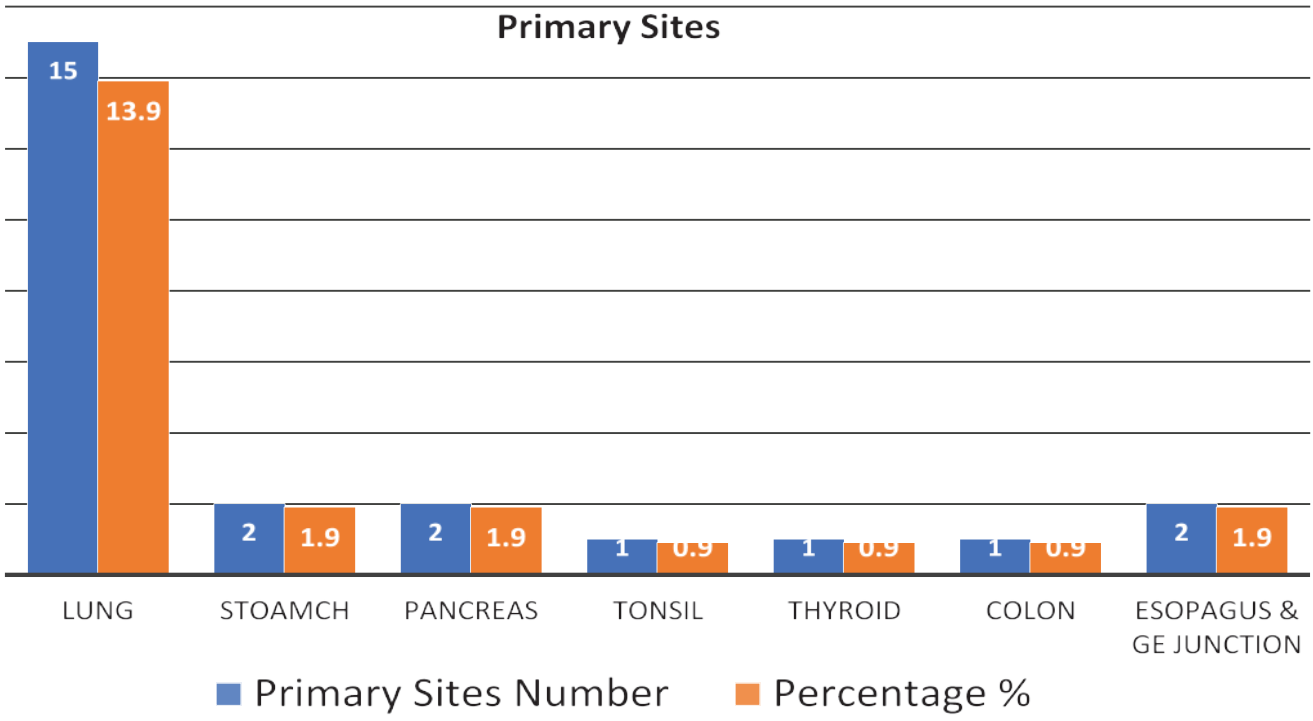

Figure 6: Distribution of organs of primary sites detected by FDG PET-CT

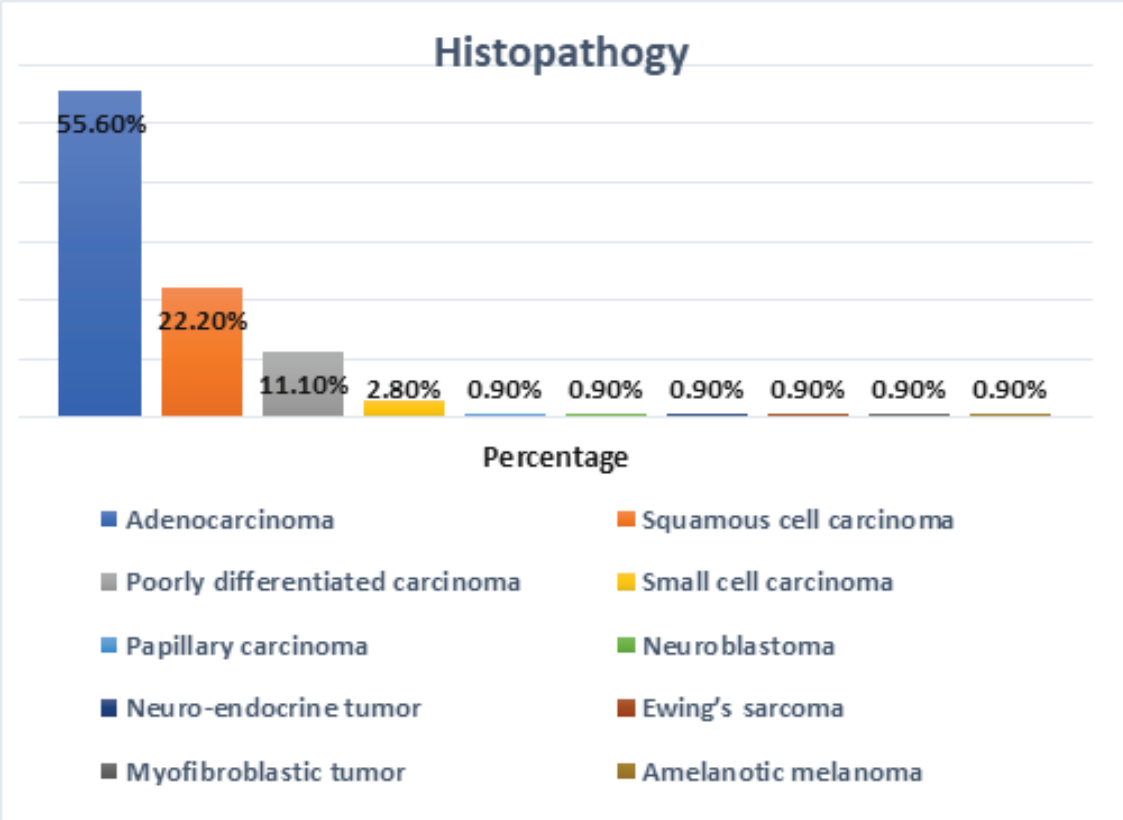

Figure 7: Distribution of histopathology among the patients

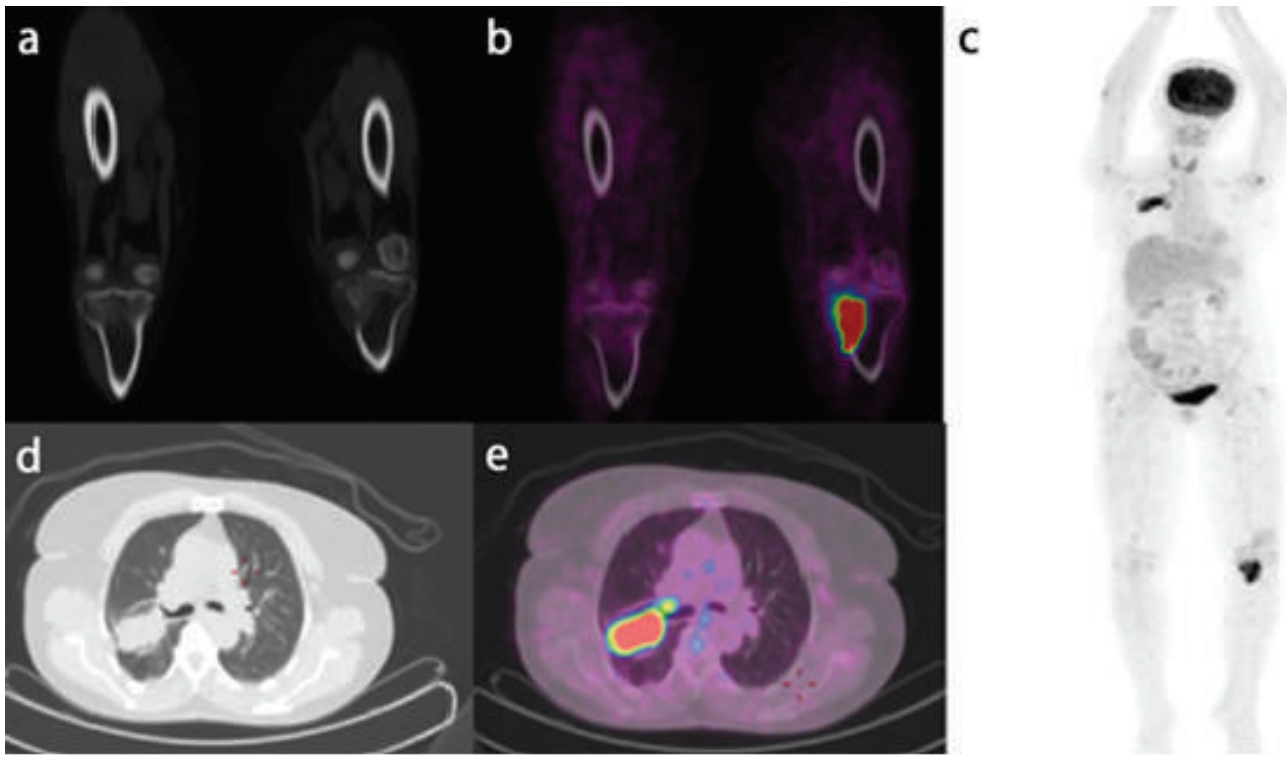

Figure 8: The FDG PET-CT MIP (c), together with axial (a, b, d, e) PET-CT views, revealed a metastatic lesion in the left tibia (Known metastatic site). A soft tissue density mass in the right upper posterior lung (e) was identified and confirmed as primary adenocarcinoma through histopathological examination.

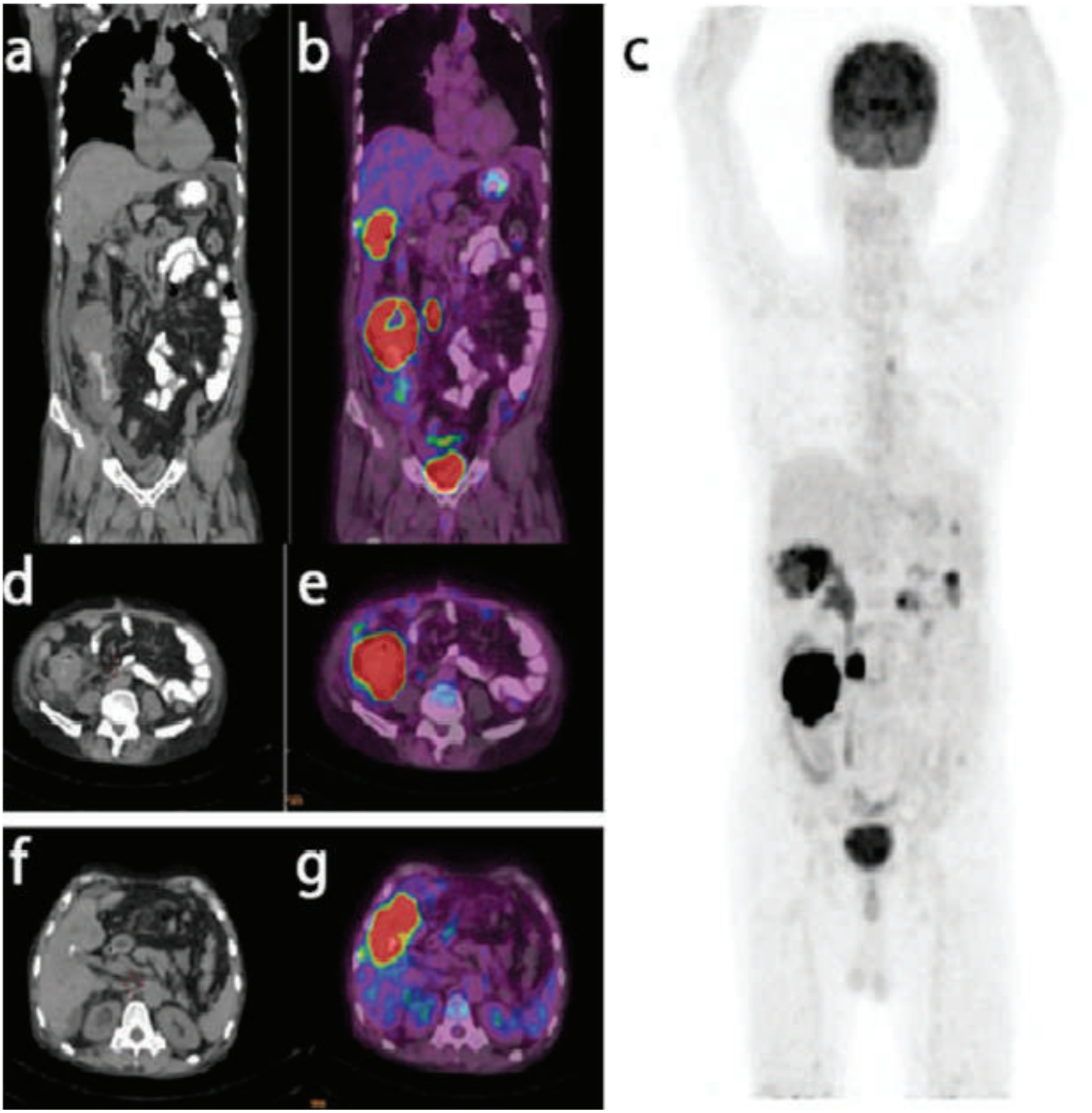

Figure 9: FDG PET-CT MIP (c), along with axial (d, e, f, g) and coronal (a, b) PET-CT images, showing a metastatic hepatic mass. A complex mass originating from the ascending colon was noted (e), identified as primary adenocarcinoma based on histopathology.

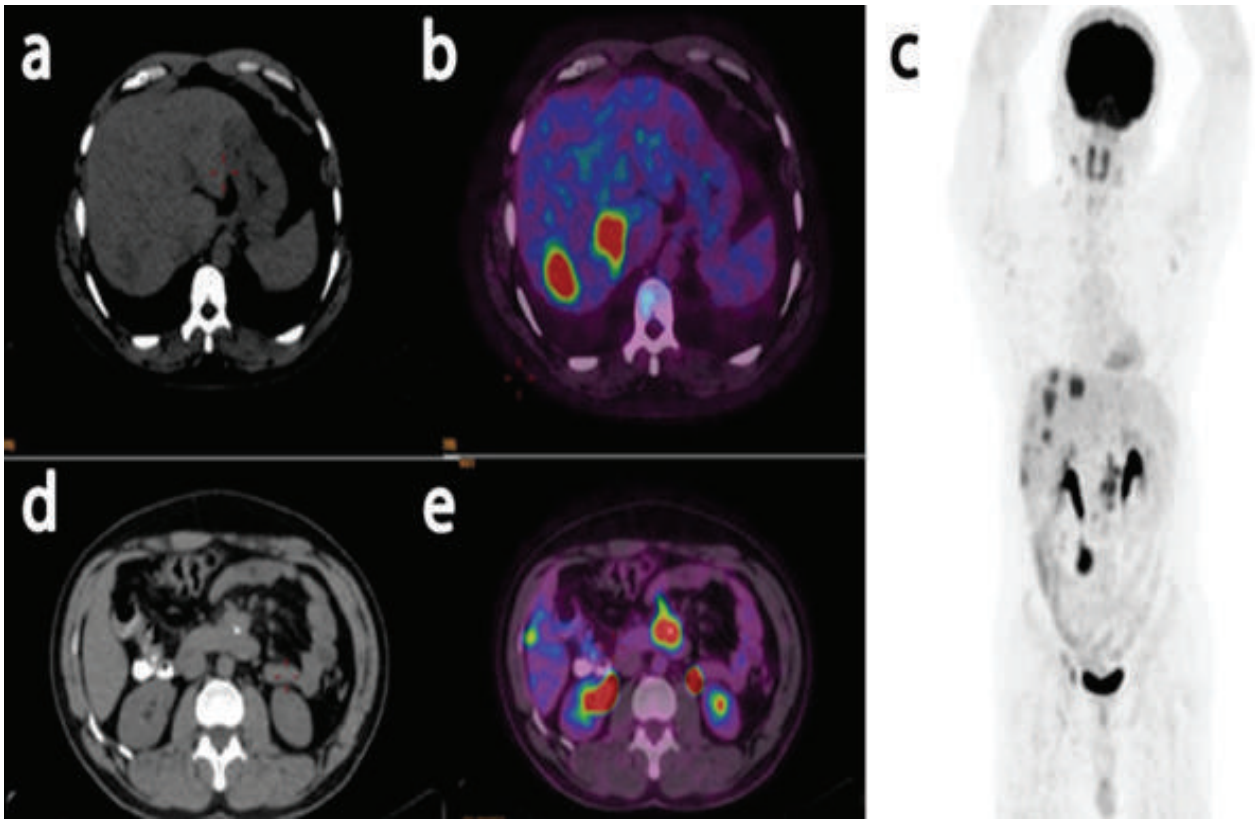

Figure 10: FDG PET-CT MIP (c), along with axial (a, b, d, e) PET-CT images, showing multiple metastatic lesions in the liver. There was a soft tissue density hypermetabolic mass in the body of the pancreas (e), identified as primary adenocarcinoma based on histopathology.

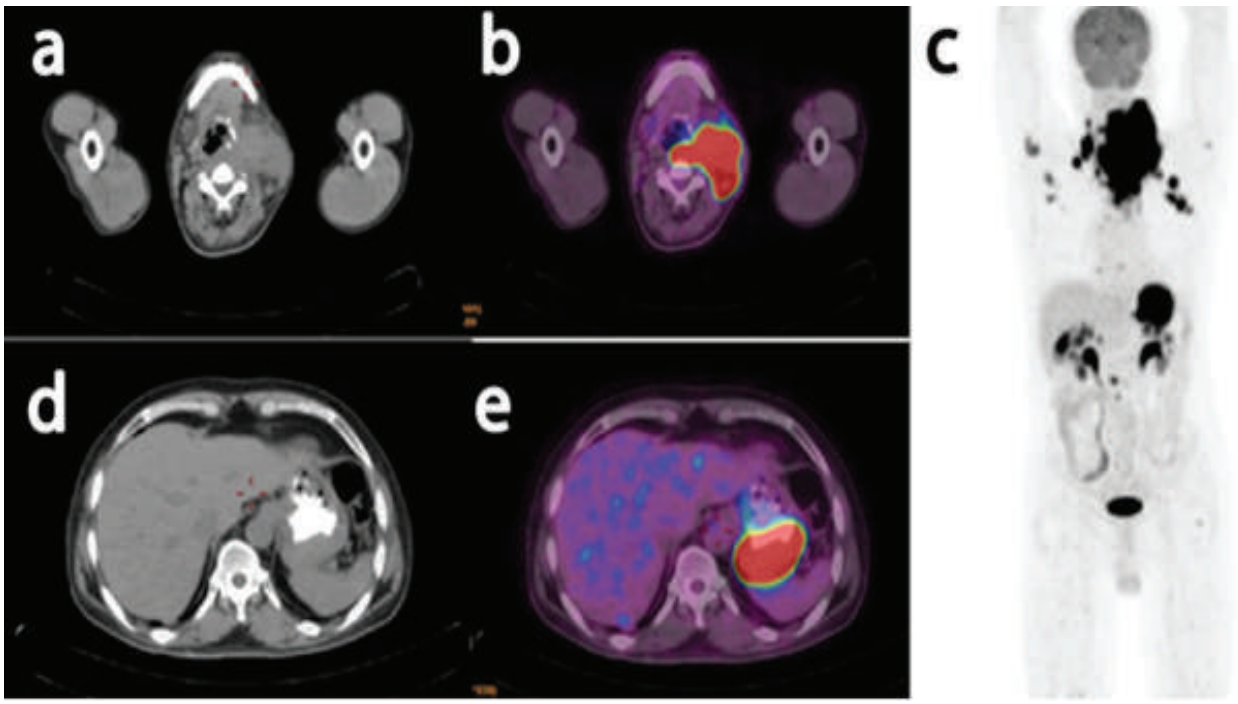

Figure 11: The FDG PET-CT MIP (c), along with axial (a, b, d, e) PET-CT views, shows multiple metastatic lymph nodes in the bilateral cervical, axillary, and supraclavicular regions. A hypermetabolic soft tissue mass in the stomach was identified (e) and confirmed as primary adenocarcinoma through histopathological analysis.

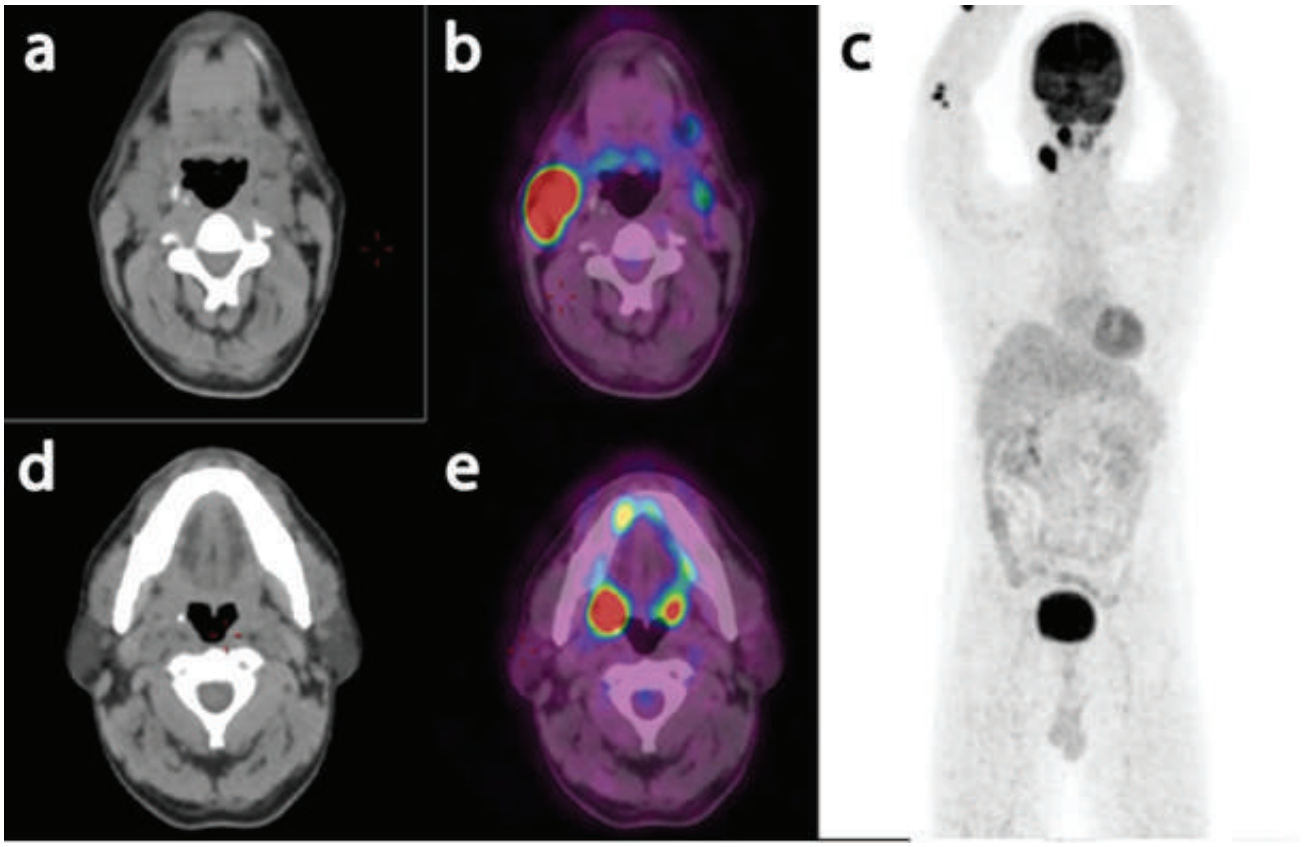

Figure 12: FDG PET-CT MIP (c) and axial (a, b, d, e) PET-CT images showing metastatic left cervical lymph nodes (b). A focal hypermetabolic soft tissue density area in the right tonsillar region (e) was confirmed as primary Squamous cell carcinoma through histopathology.

DISCUSSION

This study highlights the critical utility of FDG PET-CT in diagnosing and managing cancer of unknown primary (CUP), achieving a primary tumor detection rate of 25%. This aligns with global studies, which report detection rates ranging between 20% and 40%, influenced by variations in patient cohorts, imaging protocols, and technological advancements (7, 12). Unlike traditional imaging modalities such as CT or MRI, which rely solely on identifying anatomical abnormalities, PET-CT leverages the metabolic characteristics of cancer cells. Its ability to detect hypermetabolic foci provides an edge in identifying elusive tumors, particularly in cases where structural changes are minimal or absent (13, 15).

The identification of the lungs as the most frequent primary site (13.9%) depicted in Figure 6 corroborates prior research, which frequently associates lung malignancies with CUP, especially in cases presenting with cervical lymphadenopathy (14). These findings emphasize the importance of comprehensive thoracic evaluation in CUP patients, even when clinical or radiological evidence of lung involvement is absent. FDG PET-CT's ability to detect small, deep-seated, or metabolically active tumors in anatomically challenging locations reinforces its superiority over conventional imaging.

Additionally, PET-CT identified other less common primary sites, including the tonsil, thyroid gland, and gastrointestinal tract. The diversity of primary tumor locations underscores the diagnostic complexity of CUP and the necessity of advanced imaging techniques to guide clinical decision-making. The detection of the false primary in one case, where the colon was misidentified due to benign or inflammatory FDG uptake, highlights the importance of correlating PET-CT findings with histopathological confirmation (18, 19). This case illustrates the challenges of interpreting FDG avidity, as non-malignant conditions can mimic malignant activity.

In this study, PET-CT demonstrated its capability to

comprehensively evaluate metastatic disease. The most frequently involved sites are cervical lymph nodes, bones, and liver (Figure 3), which align with global findings on CUP metastatic patterns (16). These insights are invaluable in guiding diagnostic biopsies, determining disease burden, and planning systemic therapies. PET-CT also revealed metastases in less common locations, such as the thyroid gland, umbilicus, and brain. Such findings highlight its utility in uncovering occult or unexpected metastatic sites, which are often overlooked in routine imaging but are critical for accurate disease staging and treatment planning (17).

The ability of PET-CT to provide both metabolic and anatomical data ensures that it serves as a comprehensive tool for disease assessment. By visualizing hypermetabolic activity, it overcomes the limitations of traditional imaging in detecting small, necrotic, or metabolically inactive lesions, particularly in challenging anatomical regions like the mediastinum, retroperitoneum, or omentum (15).

Histopathological analysis remains the gold standard in CUP diagnosis and treatment planning. In this study, adenocarcinoma was the predominant histological subtype (55.6%), followed by squamous cell carcinoma (22.2%) and poorly differentiated carcinoma (11.1%). (Figure 7) This aligns with existing literature, which identifies adenocarcinomas as the most frequent histological subtype in CUP patients (20). The predominance of adenocarcinoma also reflects the challenges of CUP, as these tumors often lack distinguishing clinical features, necessitating advanced imaging and molecular diagnostics for precise identification.

In resource-constrained environments like Bangladesh, FDG PET-CT presents a non-invasive and integrative diagnostic approach that can bridge gaps in cancer diagnostics. Its ability to simultaneously detect primary tumors and stage disease and guide biopsy significantly reduces diagnostic delays, which are common in low-resource settings. However, financial constraints and limited availability of PET-CT scanners remain major barriers to widespread adoption. Addressing these challenges through subsidies, public-private partnerships, or mobile imaging units could significantly enhance access to this technology.

The findings of this study reinforce the need for multidisciplinary collaboration in CUP management. While FDG PET-CT provides valuable insights, it should not replace histopathological evaluation but rather complement it. This integrative approach ensures that diagnostic accuracy is maintained while minimizing the risks of misdiagnosis or unnecessary interventions.

Despite its advantages, the 25% detection rate for primary tumors highlights the limitations of FDG PET-CT. False negatives can occur due to low FDG avidity tumors, necrotic regions, or small lesions below the resolution of current PET-CT technology. (10). Future advancements in molecular imaging, such as incorporating novel tracers or biomarkers, hold promise for improving diagnostic accuracy.

Additionally, standardization of imaging protocols and interpretation criteria is essential to reduce variability in detection rates. Comparative studies investigating the efficacy of PET-CT combined with advanced imaging modalities, such as PET-MRI or novel radionuclides, may offer further insights into optimizing CUP diagnosis.

CONCLUSION

FDG PET-CT is a valuable diagnostic tool for detecting primary tumors and staging cancer of unknown primary. While it successfully identified the primary site in 25% of cases, its limitations underscore the need for histopathological correlation and careful clinical interpretation. The findings suggest that FDG PET-CT can enhance diagnostic precision and treatment planning, particularly in resource-limited settings. Further studies should explore strategies to improve its accessibility and diagnostic yield.

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