




Effect of Whole-body [18F]Fluoro-2-deoxy-2-d-glucose Positron Emission Tomography in Patients with Suspected Brain Metastasis

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Abstract

Background and Purpose [18F]Fluoro-2-deoxy-2-d-glucose (FDG) positron emission tomography/computed tomography (PET/CT) has a promising role in the workup and management of carcinoma of unknown primary (CUP). We have evaluated the effect of whole-body FDG PET/CT in assessing the patients presented with suspected brain metastasis (CUP-BM) on brain magnetic resonance imaging (MRI) or computed tomography (CT).

Materials and Methods This retrospective study included FDG PET/CT of 50 patients (24 males, mean: 58 ± 12.2 years old) with a CUP-BM diagnosis based on MRI and CT imaging. The final diagnosis of primary brain neoplasm (BP) or brain metastases (BM) was based on FDG PET/CT findings and/or histopathology (HPE).

Results On FDG PET/CT, 52% (26/50) of patients did not have any systemic lesion apart from a brain lesion. Out of these, 50% (13/26) had HPE confirmation of primary brain neoplasm (BP). FDG PET/CT identified multiple systemic lesions apart from brain lesions in the remaining 48% (24/50) of patients. They were categorized as the brain metastases (BM) group. The primary lesions were located in the lungs ($n = 20$), kidneys ($n = 1$), prostate ($n = 1$), esophagus ($n = 1$), and tongue ($n = 1$).

Conclusion FDG PET/CT could suggest a diagnosis of BM based on the presence of systemic lesions. It also provides an easily accessible peripheral site for biopsy and systemic disease burden in a single scan. FDG PET/CT's up-front use in suspected CUP-BM on CT and/or MRI could differentiate the BM from BP in most cases and avoid brain biopsy in the BM group.

Keywords

- ▶ FDG PET/CT
- ▶ brain metastases
- ▶ carcinoma of unknown primary

Introduction

Cancer of unknown primary (CUP) is a heterogeneous group of cancers, so-called when a biopsy unveils malignancy; however, the primary origin could not be established.¹ A provisional diagnosis of the CUP remains a diagnostic and therapeutic challenge, and an accurate diagnosis may result in better survival.² The worldwide prevalence of proven CUP is ~2 to 3% of all cancers diagnosed.^{3,4} The conventional diagnostic approach identifies a primary site in approximately one-third of the patients. However, the primary site remains unrevealed in a large number of patients, even on autopsy.⁵ The overall prognosis of the patient is miserable. In a large study (18,911 patients) by Hemminki et al, dismal survival of 17% at 12 months and a median survival of 3 months was noted in extranodal cases.⁶

Out of all CUP patients presenting with suspected brain metastases (CUP-BM) on imaging poses a unique difficulty as the brain biopsy is not straightforward. CT and MRI remain the primary brain imaging modalities, and contrast-enhanced MRI is the standard for diagnosing BP and BM.⁷ Advanced MRI techniques could distinguish BM from BP, lymphoma, and abscess. The best means of differentiation involves evaluating the peritumoral edema of the lesions. However, imaging is not able to reliably predict the histology of a BM.⁸ The paramount aspect of management is distinguishing between primary brain neoplasm (BP) and brain metastases (BM). The European Association of Neuro-Oncology recommends a thorough physical examination, CT of the chest/abdomen, and mammography. If these are negative, FDG-PET/CT is suggested.⁷

FDG-PET/CT could evaluate the primary mass, loco-regional lymph nodes, and distant metastases in a single study. Due to the inherent advantage of metabolic imaging, PET is more sensitive than CT for identifying even nonenlarged pathologies.⁹ The preponderance of FDG-PET/CT over diagnostic CT is documented in prospective trials.^{10,11} It has an undebatable role in CUPS, as shown by various meta-analyses.¹²⁻¹⁴ However, only a few studies are available exploring FDG PET-CT's role in CUP-BM and have shown good diagnostic performance.¹⁵⁻¹⁸

We hypothesize that excluding extracranial lesions in the patient with suspected BM will make a firm diagnosis of BP. Our study aimed to investigate whole-body FDG PET/CT's role in differentiating BM and BP based on the brain lesion and extracranial findings.

Materials and Methods

Patient Population

We did a retrospective analysis of the patient who underwent FDG PET/CT between Jan 2017 to Dec 2019. Out of 78 patients, based on the exclusion criteria, 28 were excluded. A total of 50 patients were included in the final analysis (→ Fig. 1). The neurosurgery or neurology departments referred patients for a routine assessment of the brain lesions.

Patients Recruitment

All the patients who presented with suspected BM on contrast-enhanced CT or MRI (CECT/CEMRI) of the brain were included in the study. The time interval between brain CECT/CEMRI and FDG PET/CT was less than 1 month.

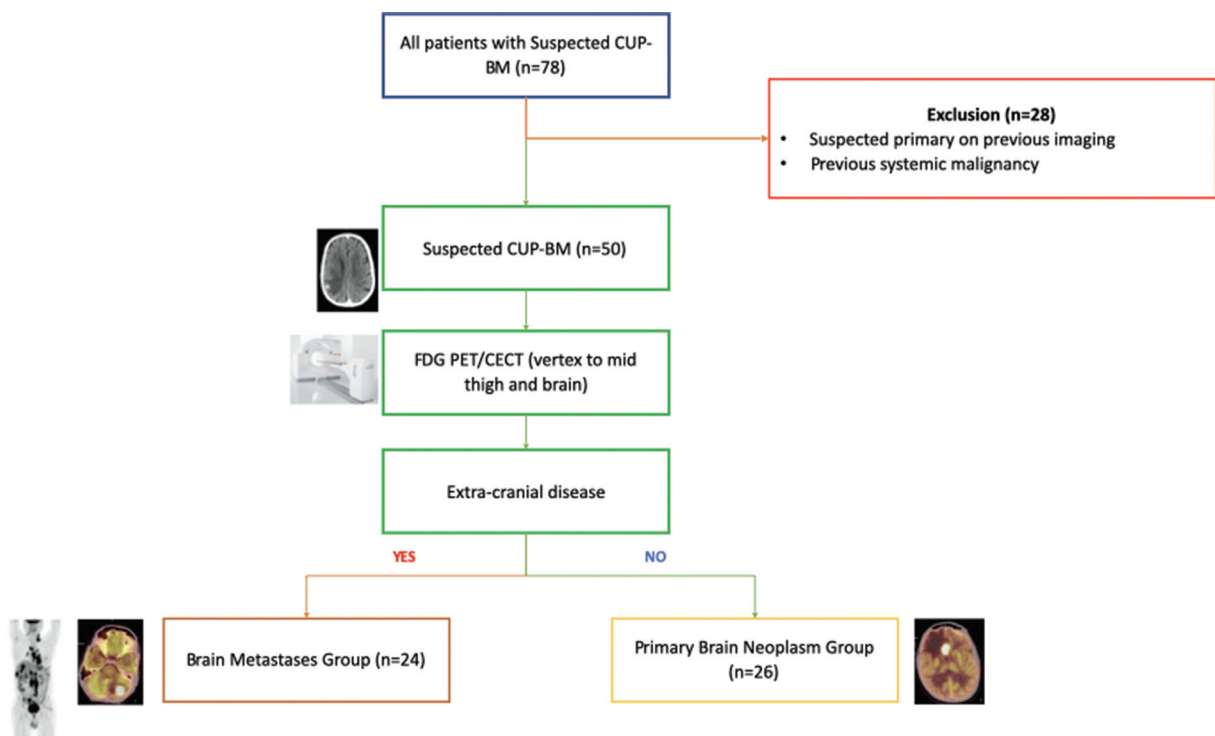


Fig. 1 Figure showing recruitment of the patients in the study.

Inclusion Criteria

- All patients with suspected BM (based on CT/MRI) were included in the study.

Exclusion Criteria

- Patients with a suspicious or proven extracranial primary malignancy from previous imaging or investigations.
- A patient who has a history of previous malignancy (treated or untreated).
- Suspicion of a benign systemic disease is a possible explanation for brain lesions such as tuberculosis.

It was a retrospective study on anonymized data, and all investigations and procedures were done as part of the standard of care. The ethical committee's permission was not required.

FDG PET-CT Imaging

All patients underwent FDG PET/CT scans according to a standard protocol. Patient preparation, image acquisition, image reconstruction, and processing were made per recommendations.¹⁹ After fasting for at least 6 hours, a measurement of blood sugar was done. The patients were instructed to stay in a warm, quiet, dark room lacking distractions and asked to keep their movements minimum before the study and following radioisotope injection. Intravenous injection of FDG was done (dose ~100 microcuries per kg body weight) followed by a saline flush in all patients with fasting blood sugar levels < 180 mg/dL. At 60 to 90 minutes, acquisitions were made by an integrated PET/CT scanner (Biograph™ scanners, Siemens Healthineers). Patients underwent a CECT from the skull base to mid-thigh with a 70 to 140 kVp and tube current of 80 mA, followed by PET acquisition for 2 minutes per bed position. We took a separate PET-CECT brain image 5 minutes per bed in all patients. PET data were reconstructed using a three-dimensional (3D)-ordered subset expectation-maximization algorithm (two iterations, 21 subsets, Gaussian filter 2.0 mm, matrix size 400 × 400, and slice thickness 2.0 mm).

Image Interpretation

Two experienced nuclear medicine physicians interpreted the FDG PET/CECT images (SG and MO, 15 and 11 year experience, respectively). Discrepant interpretations between readers were resolved by consensus after simultaneous review and discussion. FDG uptake by normal and pathologic tissues was evaluated visually and semiquantitatively using the maximum standardized uptake (SUVmax) values for each lesion. All lesions with SUVmax ≥ 3.0 were considered significant. We evaluated corresponding CECT images to confirm the lesion and rule out physiological uptake. The overall PET/CECT interpretation defined the brain lesions as BP or BM.

Diagnosis of BP was based on no extracranial disease. All the patients with the substantial extracranial disease burden were categorized as BM. We evaluated the extracranial primary mass, loco-regional lymph nodes, and metastases in BM patients. SUVmax of brain lesions, perilesional edema,

and contralateral normal-appearing brain parenchyma were measured.

Data Analysis and Reference Standard

The patients underwent additional diagnostic tests based on the PET/CT (ultrasonography, tumor markers, or biopsy, etc.) to confirm the primary malignancy. Biopsy of the accessible extracranial lesion in the BM group or brain lesion in the BP group was done.

The reference standard was based on:

- HPE of the extracranial or brain lesion.
- The overall appearance of the PET/CECT (e.g., a patient with a lung mass, mediastinal lymph nodes, and multiple skeletal lesions was considered as having lung carcinoma. This patient was referred to as BM group)

Statistical Analysis

The normality of the continuous data was tested using the Shapiro–Wilk test. Continuous variables are presented as mean ± standard deviation (SD). Categorical variables are expressed as frequency and percentages (%). Confidence intervals (CI) are ± 95%. Independent samples *t*-test was used to compare the means between the two groups. The chi-square test was used to compare the proportions between the groups. The expected frequency count was at least 5; otherwise, Fisher's exact test was used. SUVmax of brain lesions, perilesional edema, contralateral brain parenchyma, and their ratios were compared in the BM and BP groups. A *p* < 0.05 considered statistically significant. Data were analyzed using a statistical package for social sciences, version 23 (SPSS-23, IBM, Chicago, USA).

Results

Demography

The study included 50 patients (M:F, 24:26; mean age, 58 ± 12.2 years). Twenty (40%) patients had solitary brain lesions. Demographic and clinical profiles are shown in ►Table 1.

FDG PET-CECT Findings

Metabolic activity (SUVmax > 3) was noted in 44 (88%) of the brain lesions. The SUVmax values of the brain lesions and peripheral edematous regions were 11.20 ± 17.26 (Q1–4, Q3–14.62) and 3.61 ± 1.81 (Q1–2.07, Q3–5.0), respectively. In 26 patients (54%), no significant extracranial lesions were noted on FDG PET-CECT. Based on the imaging, a possible diagnosis of BP was considered (►Fig. 1).

Twenty-four (48%) patients had significant FDG avid extracranial disease burden and were categorized as BM (►Figs. 2 and 3). The most common extracranial finding was lung lesions, as noted in 22 patients (44%). Out of these, 20 (40%) had mass lesions, while the other 2 had discrete lung nodules. Other common sites of involvement were bones (11, 22%), adrenal (10, 20%), and liver (7, 14%) (►Table 1). Based on the overall imaging appearance, lung masses were considered as BM with primary lung carcinoma. In four patients, the primary extracranial malignancy was

Table 1 Distribution of demographic and clinical variables between tumor location

Variables	Brain primary (n = 26)	Brain metastasis (n = 24)	Total (N = 50)	p-Value	
Sex (male) ^b	12 (46.2)	12 (50)	24 (48)	0.786	
Lymph nodes	Cervical ^b	1 (3.8)	8 (33.3)	9 (18)	0.009
	Mediastinal ^b	2 (7.7)	20 (83.3)	22 (44)	<0.001
	#Abdominal	1 (3.8)	6 (25)	7 (14)	0.045
	#Pelvic ^a	0 (0)	2 (8.3)	2 (4)	0.225
Number of brain lesions (single/multiple) ^b	14 (53.8)/12 (46.2)	6 (25)/18 (75)	20 (40)/30 (60)	0.038	
Lung lesions ^b	0 (0)	22 (91.6)	22 (44)	<0.001	
Liver lesions ^a	0 (0)	7 (29.2)	7 (14)	0.003	
Skeletal Lesions ^b	0 (0)	11 (45.8)	11 (22)	<0.001	
Pleural effusion ^a	0 (0)	2 (8.3)	2 (4)	0.225	
Adrenal lesion ^b	0 (0)	10 (41.6)	10 (41.6)	<0.001	

^aFisher exact test used.

^bPearson chi-square test.

Notes: Bold values indicate $p < 0.05$ is significant.

The table shows the mean distribution of the clinical values between brain primary and brain metastasis. All parentheses are percentages.

suggested in the kidneys, prostate, esophagus, and tongue. The involvement of lymph nodes, lungs, hepatic, skeletal, and adrenal lesions was statistically significant in the BM group (► **Table 1**). Out of the 20 patients with a solitary brain lesion, 6 (30%) had lung masses and were diagnosed with BM. In the rest of the 30 patients with multiple brain lesions, 12 (36%) had no extracranial lesions and were considered BP (► **Fig. 4**).

Histopathology

Twenty-nine (58%) patients underwent a biopsy for further evaluation. Out of 26 patients in the BP group, 13 (26%) underwent surgical excision and biopsy of the brain lesion. In the BM group, the extracranial site's biopsy was available in 16 (32%) patients. One patient in the BM group had a prostatic lesion on the PET/CECT and raised serum PSA level (>100 ng/mL); a provisional diagnosis of the carcinoma prostate was suggested. The rest of the patients denied further management or were lost to follow-up.

Final HPE was available for 29 patients (► **Table 2**). The most common HPE was squamous cell carcinoma (10),

followed by adenocarcinoma (6), and glioma (7). One patient who had brain lesions and peripheral lymphadenopathy underwent axillary lymph node biopsy. HPE was suggestive of tuberculosis. Few patients (4, 8%) in the BM group had metabolically active peripheral lymphadenopathy. It was considered inflammatory based on the scan's overall appearance (size, fatty hilum, enhancement, etc.)

Role of SUVmax

We could not differentiate between BP and BM based on the SUVmax of the brain lesion (10.52 ± 8.08 and 11.95 ± 6.36) or perilesional edema (3.47 ± 1.67 and 3.78 ± 1.98). There was no significant difference between SUVmax ($p = 0.492$) and their ratios in BM and BP groups (► **Table 3**). Multiple brain lesions were commoner in the BM group.

Discussion

We evaluated FDG PET-CT's role in 50 patients with suspected CUPS-BM. In 24 (48%) patients, significant FDG

Table 2 Histopathology of suspected brain primary patients who underwent excision of the mass or biopsy

Group	Histopathology	No. of patients (%)
Brain primary (n = 26)	Glioblastoma multiforme	5 (10)
	Glioma grade III	2 (4)
	Atypical meningiomas	3 (6)
	Liponeurocytoma	1(2)
	Non-Hodgkin's lymphoma	2 (4)
Brain metastases (n = 24)	Squamous cell carcinoma	10 (20)
	Adenocarcinoma	6 (12)

Table 3 Descriptive statistics of the demographic and clinical variables

	Final Diagnosis	Mean	Standard deviation	p-Value
SUVmax brain lesion	Brain primary	10.52	8.08	0.492
	Brain metastasis	11.95	6.36	
SUVmax brain opposite lobe	Brain primary	5.77	2.81	0.263
	Brain metastasis	6.63	2.59	
SUVmax perilesional	Brain primary	3.47	1.67	0.557
	Brain metastasis	3.78	1.98	
SUVmax ratio (lesion/perilesional)	Brain primary	3.44	3.36	0.557
	Brain metastasis	2.99	1.30	
SUVmax ratio (lesion/opposite lobe)	Brain primary	2.04	1.66	0.640
	Brain metastasis	1.86	0.87	

Showing the distribution of standard uptake values (SUVmax) between brain primary neoplasm and brain metastasis.

Note: Independent samples *t*-test used, $p < 0.05$ significant.

avid extracranial disease was noted, and the brain lesion was categorized as BM. The most common findings were lung masses (20, 40%) followed by bones (11, 22%), adrenal (10, 20%), and liver (7, 14%) involvement. In the remaining 26 patients, no significant extracranial disease was found, and the patients were categorized as BP. Half of them underwent biopsy, and all were brain primaries.

BM often occurs in advanced malignancies but may also present as CUPS. Indeed, they are the most common intracranial

tumors and occur up to 3–to 10 times more frequently than BP.²⁰ The most common primary sites in CUP-BM are lungs (40–50% of all BM), followed by breasts (15–20%), melanoma (5–20%), and renal (5–10%) and gastrointestinal tract (5%).²¹ A combined chest-CT and MRI-brain could identify a biopsy site in most patients (97%).²² However, it will require further evaluation to stage the disease burden.

Only a few studies are available exploring the role of PET-CT in CUPS-BM and have shown good diagnostic

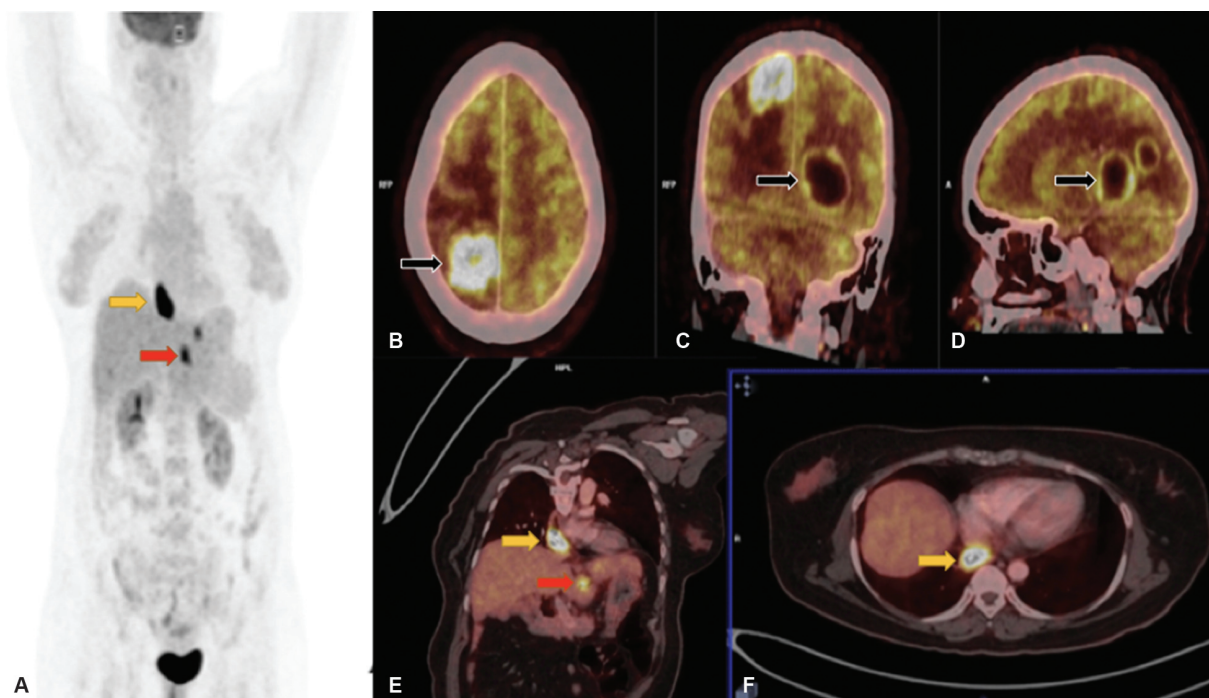


Fig. 2 A 50-year female patient presented with a headache and left hemiparesis for 15 days. MRI brain (not shown) was suggestive of multiple brain lesions with perilesional edema. (A) Whole-body FDG PET/CT MIP reveals intensely FDG avid (SUVmax 32) wall thickening involving the lower esophagus (yellow arrow). Few focal areas of uptake are noted lower to it (red arrow), likely lymph nodes (B–D) axial, coronal, and sagittal images of the brain show multiple lesions. (E) Coronal and (F) axial images show esophageal lesions along with gastrohepatic lymph nodes. Biopsy from the lower esophagus was suggestive of adenocarcinoma.

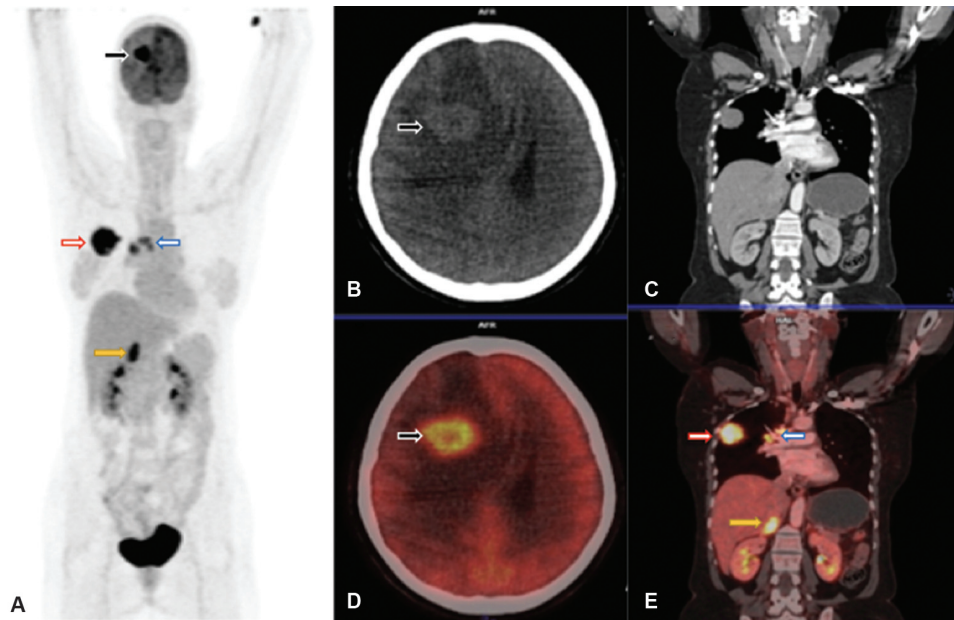


Fig. 3 A 48-year-old lady presented with a headache for 1 month. MRI (not shown) suggested a solitary mass lesion in the right frontal lobe with significant perilesional edema and mass effect. (A) MIP FDG PET/CT shows lesions in the right frontal lobe (black arrow), a lesion in the upper lobe of the right lung (red arrow) with multiple enlarged mediastinal lymph nodes (blue arrow), and right adrenal (yellow arrow). (B and D): CT and fused PET/CT images show well-defined solitary mass lesions in the right frontal lobe. (C and E) Coronal CT and fused PET/CT show a mass in the lungs, multiple mediastinal lymph nodes, and a right adrenal lesion.

performance in this specific group.^{15–18} It could differentiate BM from a BP, and it also helps in the localization of the primary in BM.^{15,16} In a study including 77 patients with BM, primary lesions were detected in 61 patients by PET-CT. The

sensitivity, specificity, positive and negative predictive values, and accuracy for the primary detection were 79.2%, 94.0%, 95.3%, 74.6%, and 85.0%, respectively.¹⁶ A recent study has shown a higher detection rate (~77%).¹⁷ In our study, we

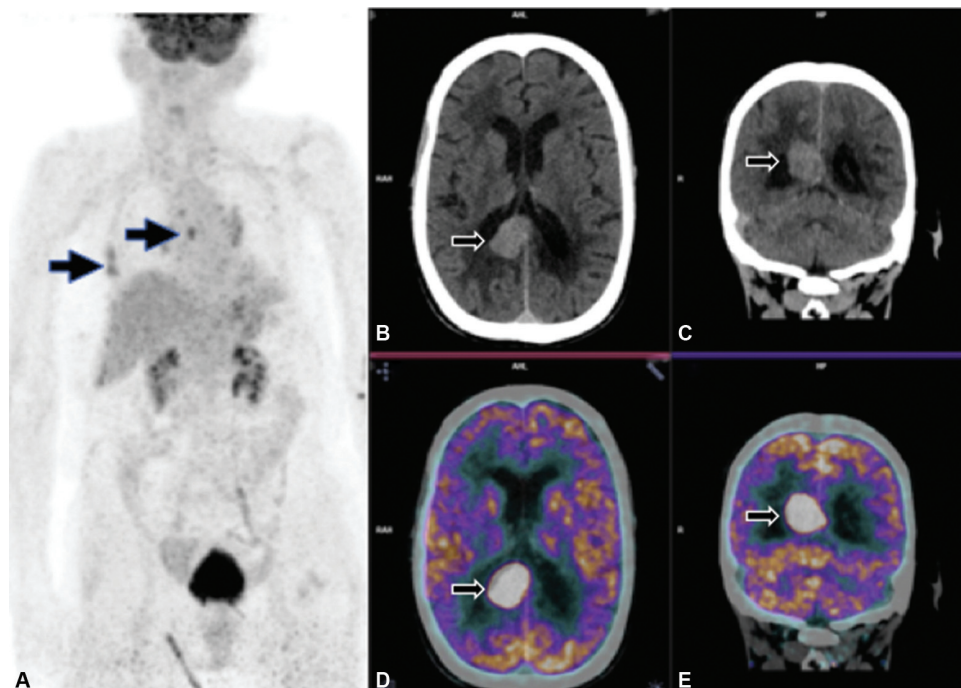


Fig. 4 (A) 58-year-old man presented with a headache for 2 months. MRI (not shown) was suggestive of enhancing lesion in the corpus callosum with mild perilesional edema. FDG PET/CT MIP shows a focal area of mild uptake in the mediastinum and right chest wall. Faintly FDG avid (SUVmax 2.8) mediastinal lymph nodes are noted with foci of calcification, likely inflammatory. Focal uptake areas are noted in the multiple ribs anteriorly with callus formation (not shown), suggestive of recent trauma. (B–D) CT and fused PET CT brain in axial and coronal planes show FDG avid (SUVmax 14) lesion in the corpus callosum's splenium and adjacent right occipital lobe. Biopsy from the brain lesion was suggestive of GBM.

also found similar detection rates. We did all PET/CT studies with intravenous contrast. It could be another reason for higher detection rates.

Koç ZP et al compared the FDG-PET/CT with chest/abdomen CT in CUPS-BM. The authors found that PET/CT disclose more metastases in 14 of 64 patients (22%) and upstaging disease.¹⁷ Another recent study demonstrated that PET/CT identified additional extracranial metastases and shifted the graded prognostic assessment score from 3 with CT alone to 2.5 for PET/CT.¹⁸ Another remarkable finding from our study is that all patients diagnosed with BP and who underwent brain biopsy were found to have HPE of BP only. The absence of significant extracranial disease in PET/CT reduces the possibility of futile biopsy for BM. Our study could not differentiate BM and BP based on metabolic findings. It has been shown that there is no significant difference in SUVmax between these.²³

There are a few limitations of the study. It was a retrospective, single-center study, and biopsy was not available in all patients. Many of the patients were lost to follow-up. However, on scanning, the diagnosis of BP and BM was quite convincing. The remote possibility of other inflammatory pathologies could not be ruled out. PET is expensive than CT, and additional costs may emerge because of a workup for new lesions detected by PET. A further prospective study is necessitated to evaluate PET/CT's impact on patient management change, the cost of treatment, adding comfort to the patient, and decreasing the time to the final diagnosis.

Conclusion

FDG PET/CT could identify the extracranial primary and metastatic disease burden in nearly half of the patients suspected of brain metastases. The absence of extracranial disease in the patient presented with suspected brain metastases favors BP. PET/CT recognizes extracranial potential biopsy sites, evades unnecessary brain biopsy, and provides comprehensive information about staging and prognosis. Brain biopsy yield could be more beneficial in the "brain primary" group of patients with less futile metastatic disease results.

Availability of Data and Material (Data Transparency)

Data are partially available after a request from the corresponding author. It contains patient no. identification.

Ethical Approval Statement

It was a retrospective study on anonymized data, and all investigations and procedures were done as part of the standard of care. The ethical committee's permission was not required.

Authors' Contribution

M.O. and S.G. contributed to the concept and design of the study. A.H.N., P.M., and A.M. did data collection, data, and statistical analysis. M.O., N.S. wrote the first draft. A.H.N.,

N.S., A.M., did manuscript preparation and figure preparation. M.O., N.S. and S.G. finalized manuscript.

Conflict of Interest

None declared.

Acknowledgment

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