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Brain metastases assessment by FDG-PET/CT: can it eliminate the necessity for dedicated brain imaging?

Mamdouh A. Zidan* , Radwa S. Hassan, Khaled I. El-Noueam and Yasser M. Zakaria

Abstract

Background: Brain metastases (BM) are the most common intracranial tumors in adults outnumbering all other intracranial neoplasms. Positron emission tomography combined with computed tomography (PET/CT) is a widely used imaging modality in oncology with a unique combination of cross-sectional anatomic information provided by CT and the metabolic information provided by PET using the $[^{18}F]$-2-fluoro-2-deoxy-D-glucose (FDG) as a tracer. The aim of the study is to assess the role and diagnostic performance of brain-included whole-body PET/CT in detection and evaluation of BM and when further imaging is considered necessary. The study was conducted over a period of 12 months on 420 patients suffering from extra-cranial malignancies utilizing brain-included whole-body PET/CT.

Results: Thirty patients with 71 brain lesions were detected, 18 patients (60%) had BM of unknown origin while 12 patients (40%) presented with known primary tumors. After brain-included whole-body FDG-PET/CT examination, the unknown primaries turned out to be bronchogenic carcinoma in 10 patients (33.3%), renal cell carcinoma in 2 patients (6.7%), and lymphoma in 2 patients (6.7%), yet the primary tumors remained unknown in 4 patients (13.3%). In 61 lesions (85.9%), the max SUV ranged from 0.2- < 10, while in 10 lesions (14.1%) the max SUV ranged from 10 to 20. Hypometabolic lesions were reported in 41 (57.7%) lesions, hypermetabolic in 3 lesions (4.2%), whereas 27 lesions (38.0%) showed similar FDG uptake to the corresponding contralateral brain matter. PET/CT overall sensitivity, specificity, positive and negative predictive, and accuracy values were 78.1, 92.6, 83.3, 90, and 88% respectively.

Conclusion: Brain-included whole-body FDG-PET/CT provides valuable complementary information in the evaluation of patients with suspected BM. However, the diagnostic performance of brain PET-CT carries the possibility of false-negative results with consequent false sense of security. The clinicians should learn about the possible pitfalls of PET/CT interpretation to direct patients with persistent neurological symptoms or high suspicion for BM for further dedicated CNS imaging.

Keywords: Brain, Computed tomography (CT), Fluoro-2-deoxy-D-glucose (FDG), Metastases, Positron emission tomography (PET)

* Correspondence: Mamdouh.zidan@alexmed.edu.eg;
Mamdouh_zidan@yahoo.com
Diagnostic Imaging Department, Faculty of Medicine, Alexandria University, Alexandria, Egypt

Background

Management protocols and treatment decisions in patients with brain tumors are based on a precise description of tumor extent. Brain metastases (BM) are the most common intracranial tumors in adults outnumbering all other intracranial tumors [1, 2]. The most common primary tumors causing brain metastases are lung, breast, melanoma, and colorectal cancers [3]. In around 10% of patients with BM, the primary tumor is unknown (cancer of unknown primary, CUP) [4, 5]. Currently, studies report that 72.2% of BM patients have solitary lesion [6], and nearly 37% have a minimum of three tumors [7]. The biological characteristics of the tumors are expected to affect the spatial distribution of their BM by a theory called "seed and soil." This theory suggested a non-random distribution of metastases by special tumor cell properties and variances in microenvironments of different organs [8, 9]. In addition, BM distribution is dependent on an adequate supply and volume of cerebral blood; hence, BM varies in distribution with nearly 80% in the cerebral hemispheres, 15% in the cerebellum, or 5% in the brainstem [8]. Studies have shown a wide discrepancy in their estimations of the incidence proportions percentage of BM ranging from 3 to 50% [10]. In BM, headache, seizures, cognitive deficit, papilledema, and various focal neurological impairments are the main clinical manifestations [11]. BM in systemic cancers portends poor prognosis with a median survival of less than 6 months [12].

Imaging of BM can be conducted using many techniques considering that improved imaging techniques aid in early diagnosis and effective systemic treatment regimens. Of these techniques, contrast-enhanced CT is widely used owing to its accessibility, speed, and low cost. MRI with contrast is currently the procedure of choice, as MRI is more sensitive and specific than other imaging techniques in determining the presence, location, and number of metastases. MRI special sequences like arterial spin labeling (ASL) perfusion and diffusion tensor imaging (DTI) may be used for differentiating BM from primary brain tumors, e.g., gliomas. As assessment of combined ASL- and DTI-derived metrics of the peritumoral tissue may be useful in differentiating both pathologies [13]. Positron emission tomography (PET) can define metabolic activity (at the molecular level) of different subsets of metastatic brain tumor [5, 14]. [^{18}F]-2-Fluoro-2-deoxy-D-glucose (FDG) is the most used PET tracer in nuclear medicine [15]. The combined PET/cross-sectional imaging can obtain functional and anatomic images on the same scanner without moving the patient [16]. PET/CT is more informative than PET alone in localizing increased FDG activity to specific normal or abnormal anatomic locations [17].

Currently, clinical demand for FDG-PET/CT is being increased in our clinical practice as a way to determine both body and brain metastatic disease overlooking the pitfalls of FDG-PET/CT in brain assessment. These pitfalls may challenge the modality capability to detect BM and make its use in this clinical context debatable. In this study, we aimed to assess the role and diagnostic performance of brain-included whole-body PET/CT modality in the detection and evaluation of BM and when further imaging is considered necessary. This was achieved by evaluating the scans and follow-up of patients diagnosed with extra-cranial malignancies who were referred to our institution for brain-included whole-body PET/CT for staging and re-staging. The results were compared to the published data in attempt to reach a conclusion and recommendation regarding the use of the assessed modality in clinical practice.
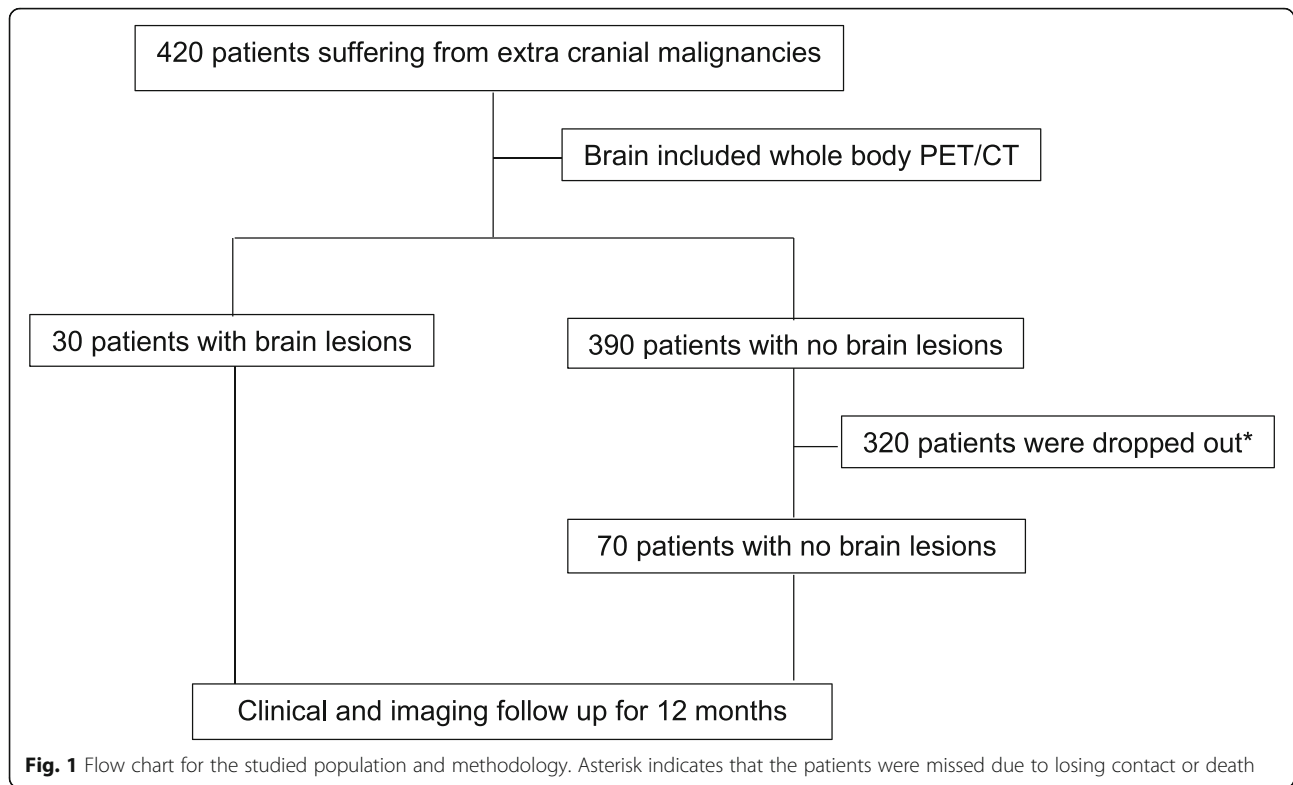
Methods

Study population

The studied group comprised 420 patients suffering from diagnosed or suspected extra-cranial malignancies referred to our hospital for brain-included whole-body PET/CT assessment and were followed up over a period of 12 months (Fig. 1). Informed consents were obtained from patients prior to conducting the current study, and the study was approved by our local research ethics committee. The clinical evaluation of all patients included full history taking, thorough clinical examination, laboratory evaluation, and other imaging modalities whenever available. Examinations were done and data were obtained using Siemens Bio-graph true point 64 PET/CT scanner. This dedicated system integrates a PET scanner with a multi-slice helical CT scanner permitting the acquisition of co-registered CT and PET images in one session. Inclusion criteria included patients diagnosed/suspected to have extra-cranial malignancy with no history of craniotomy, radiosurgery, or cerebral resection.

Imaging protocol

Patient preparation

All patients were asked to fast for 6 h prior to scan. The patients were instructed to stay in a warm quiet dark room devoid of distractions, and also asked to keep their movements, including talking, at an absolute minimum to avoid any kind of stimulation or activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG which can confound interpretation of the scan. Patients should be comfortable and relaxed. They were also asked to void immediately prior to scanning.

Serum glucose levels were routinely measured prior to FDG injection, and acceptable fasting levels were 70–

Fig. 1 Flow chart for the studied population and methodology. Asterisk indicates that the patients were missed due to losing contact or death

170 mg/dl. The strategies for decreasing brown fat up-take were providing a controlled-temperature (warm) environment for patients before FDG injection and high-fat, low-carbohydrate, protein-permitted diet before the examination.

Dosage administration of FDG

About 1 L of negative oral contrast agent (5% mannitol) is ingested approximately 1 h before the exam. A dose of 0.1 mCi/kg of FDG IV injection 45–90 min before exam-ination was administered. This period is referred to as the uptake phase and is the necessary amount of time for the FDG to be adequately bio-distributed and trans-ported into the patient's cells.

Scanning technique

CT scanning

Helical CT was performed following injection of about 125 ml (1-2 ml/kg) of iodinated contrast medium at a rate of 4 ml/s using a power injector. For a typical brain-included whole-body PET/CT study (head, neck, chest, abdomen, and pelvis), scanning began at the vertex of the skull and extended caudally to the level of the upper thighs.

PET scanning

PET was performed following the CT study without moving the patient. Approximately six to seven bed positions are planned in the three-dimensional acquisi-tion mode for scanning the entire patient with 3-5-min acquisition at each bed position.

PET/CT fusion

Hundreds of trans-axial PET and CT images were first reconstructed. These are then reformatted into coronal and sagittal images to facilitate image interpretation. For each of these sets of PET and CT images, corresponding fusion images, combining the two types of data, also were generated. The whole acquisition time for an inte-grated PET/CT scan was approximately 25-30 min. PET image data sets were reconstructed using CT data for attenuation correction, and co-registered images were displayed using special software.

Image interpretation

For every patient, 2 independent experienced radio-logists interpreted the images. Radiologists were aware of any patient's clinical data. Discrepant interpretations between readers were resolved by consensus after simultaneous review and discussion. Assessment of radiotracer uptake by normal and pathologic tissues was evaluated visually and semi-quantitatively using max-imum standardized uptake (SUV) values for each lesion and in comparison, to background activity. Abnormal-ities suggestive of metastatic disease were recorded which included number, location, size, and FDG uptake

compared to normal brain matter. The reference standard for the current study regarding the accuracy determination of BM was made after clinical and radiological follow-up whenever available.

Statistical analysis

The data collected were tabulated and analyzed by SPSS (Statistical Package for the Social Science Software) statistical package version 22 on IBM-compatible computer qualitative data were described using number and percent. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of FDG-PET/CT were determined compared to contrast-enhanced CT (CECT) using patients' data as reference.

Results

The study group comprised of 420 patients suffering from extra-cranial malignancies. Thirty patients had brain lesions with a median age of 58 years (range 45-77, mean ± SD 58.2 ± 9.4 years) and distributed as $n = 16$ males (53.3%) and $n = 14$ females (46.7%). Negative radiological findings for brain lesions were initially reported in 390 patients from whom follow-up data could be obtained for 70 patients (the rest of the patients were missed due to losing contact or death). All patients were followed-up over 12 months period for the development of any neurological complaints or positive brain imaging studies.

Table 1 shows the distribution of the studied cases according to the primary malignancy diagnosis and the clinical presentations. The suspected BM of unknown origin were $n = 18$ (60.0%), from which the unknown primaries identified following whole-body FDG-PET/CT examination were $n = 14$ (46.7%); while the unknown primaries that remained unidentified were $n = 4$ (13.3%). Twelve patients (40.0%) presented for reassessing and restaging of known primary tumors that caused BM. The number of patients suffered from bronchogenic carcinoma were ($n = 15$, 50%) and classified according to histopathological types into adenocarcinoma ($n = 7$, 23.3%), squamous cell carcinoma ($n = 5$, 16.7%), and small cell lung cancer ($n = 3$, 10.0%). Patients presented with systemic metastases along with BM were 16 patients (53.3%) and detected as bony, nodal, lung, suprarenal, hepatosplenic, and subcutaneous deposits while 14 patients (46.7%) presented with BM without systemic metastases. From those suffered from systemic metastases, 6 patients (37.5%) had bronchogenic carcinoma as the primary tumor. These results showed that bronchogenic carcinoma was the most common primary tumor both in the previously diagnosed patients and as more commonly presenting metastases of unknown origin.

Table 2 shows the 71 brain lesions identified in all 30 patients distributed according to anatomical features;

Table 1 Distribution of the studied cases ($n = 30$) according to primary malignancy and clinical manifestations

	Patients no. ($n = 30$)	%
Primary		
Unknown	18	60.0
Primary identified by PET-CT		
Bronchogenic	10	33.3
Renal cell carcinoma	2	6.7
Lymphoma	2	6.7
Unidentified	4	13.3
Known	12	40.0
Bronchogenic	5	16.7
Breast cancer	3	10.0
Melanoma	2	6.7
Renal cell carcinoma	1	3.3
Papillary thyroid carcinoma	1	3.3
Neurological symptoms		
Free	14	46.7
Headache	12	40.0
Hemi paresis	2	6.7
Disturbed level of consciousness	2	6.7
Systemic metastases		
Bony	12	40.0
Nodal	10	33.3
Lung	8	26.7
Suprarenal	4	13.3
Hepato-splenic	2	6.7
Subcutaneous	2	6.7
None	14	46.7

number, site, and laterality, while Table 3 shows morphological features of brain lesions including size, shape, special features; calcification and hemorrhage, pattern of enhancement, presence of edema, SUV max, and compared to the corresponding contralateral normal brain matter. The results showed that multiple brain lesions were more common than solitary lesions. Supratentorial metastases were more than the infratentorial being present in 100% of patients.

Regarding the pattern of enhancement, the studied lesions showed marginal enhancement ($n = 32$, 45.1%), ring enhancement ($n = 12$, 16.9%), intralesional enhancement ($n = 10$, 14.1%), and non-enhancement ($n = 17$, 23.9%) lesions. Some of the lesions showed patchy areas of no enhancement and no radiotracer uptake due to associated elements of necrosis, calcifications, or hemorrhage. None of the studied patients had leptomeningeal lesion or abnormal enhancement.

Table 2 Anatomical distribution of the studied brain lesions

Lesions	Patients no. (*n* = 30)	%	Lesions no. (*n* = 71)	%
Number				
1	5	16.7	5	7.0
2	11	36.7	22	31.0
More	14	46.7	44	62.0
Site				
Supratentorial	30	100.0	64	90.1
Parietal	24	80.0	36	50.7
Occipital	10	33.3	12	16.9
Frontal	10	33.3	8	11.3
Temporal	8	26.7	8	11.3
Infratentorial	8	26.7	7	9.9
Laterality				
Right	8	26.7	28	39.4
Left	5	16.7	8	11.3
Bilateral	17	56.7	35	49.3

Table 3 Classification of lesions according to morphological features

Lesions	Patients no. (*n* = 30)	%	Lesions no. (*n* = 71)	%
Size				
0.1-<2 cm	18	60.0	37	52.1
2-<4 cm	22	73.3	27	38.0
4-6 cm	8	26.7	7	9.9
Shape				
Ovoid	24	80.0	29	40.8
Rounded	18	60.0	42	59.2
Special features				
Calcification	2	6.7	8	11.3
Hemorrhage	2	6.7	2	2.8
Enhancement				
Marginal	14	46.7	32	45.1
Ring	6	20	12	16.9
Intralesional	10	33.3	10	14.1
None	8	26.7	17	23.9
Edema	12	40.0	13	18.3
SUV max*				
0.2- < 10	28	93.3	61	85.9
10 up to20	12	40.0	10	14.1
Compared to contralateral brain matter				
Less than	14	46.7	41	57.7
Equal	2	6.7	27	38.0
More than	14	46.7	3	4.2

*SUV standardized uptake value

SUV were measured and compared to the corresponding contralateral normal brain tissue. In 61 lesions (85.9%), the max SUV ranged from 0.2- < 10, while in 10 lesions (14.1%) the max SUV ranged from 10 to 20. When compared to the corresponding contralateral brain tissue, 41 lesions (57.7%) showed less FDG uptake than the corresponding contralateral brain matter, i.e., hypometabolic (Fig. 2), 3 lesions (4.2%) showed more FDG avidity than corresponding contralateral brain matter, i.e., hypermetabolic (Figs. 3 and 4), whereas 27 lesions (38.0%) showed similar FDG uptake to the corresponding contralateral brain matter (Fig. 5). A case presented with multiple variable-sized brain space-occupying lesions with small lesion that was not appreciated in the PET image (Fig. 6).

Table 4 shows the diagnostic performance of both PET/CT and contrast-enhanced CT techniques to detect BM. The true positive cases by PET/CT and contrast-enhanced CT were 25/30 and 26/30 patients, respectively, false positive: 5 and 4 patients, respectively, true negative: 63 and 64 patients respectively, and false negative: 7 and 6 patients, respectively. The sensitivity, specificity, PPV, NPV, and accuracy of FDG-PET/CT and contrast-enhanced CT in BM patient-based were as follows: the sensitivity of PET/CT examinations was 78.1%, specificity was 92.6%, PPV and NPV of PET/CT were 83.3%, and 90.0% respectively and 88% accuracy, while the sensitivity of CT alone was 81.2%, specificity was 94.1%, PPV and NPV were 86.7% and 91.4% respectively and 90% accuracy. Of the 5 false-positive patients diagnosed by FDG-PET/CT, 3 patients were proved to have old cerebral infarctions by MR, and 2 patients were interpreted as false positive due to uneven uptake of FDG tracer by the cortex cerebri on PET. Seven patients with initially negative scan complained from persistence of neurological symptoms, and MRI was done within 1-2 weeks from PET/CT scan that revealed positive MRI findings, e.g., small parenchymal lesions and leptomeningeal involvement. This MRI results reflected false-negative results of PET/CT scan.
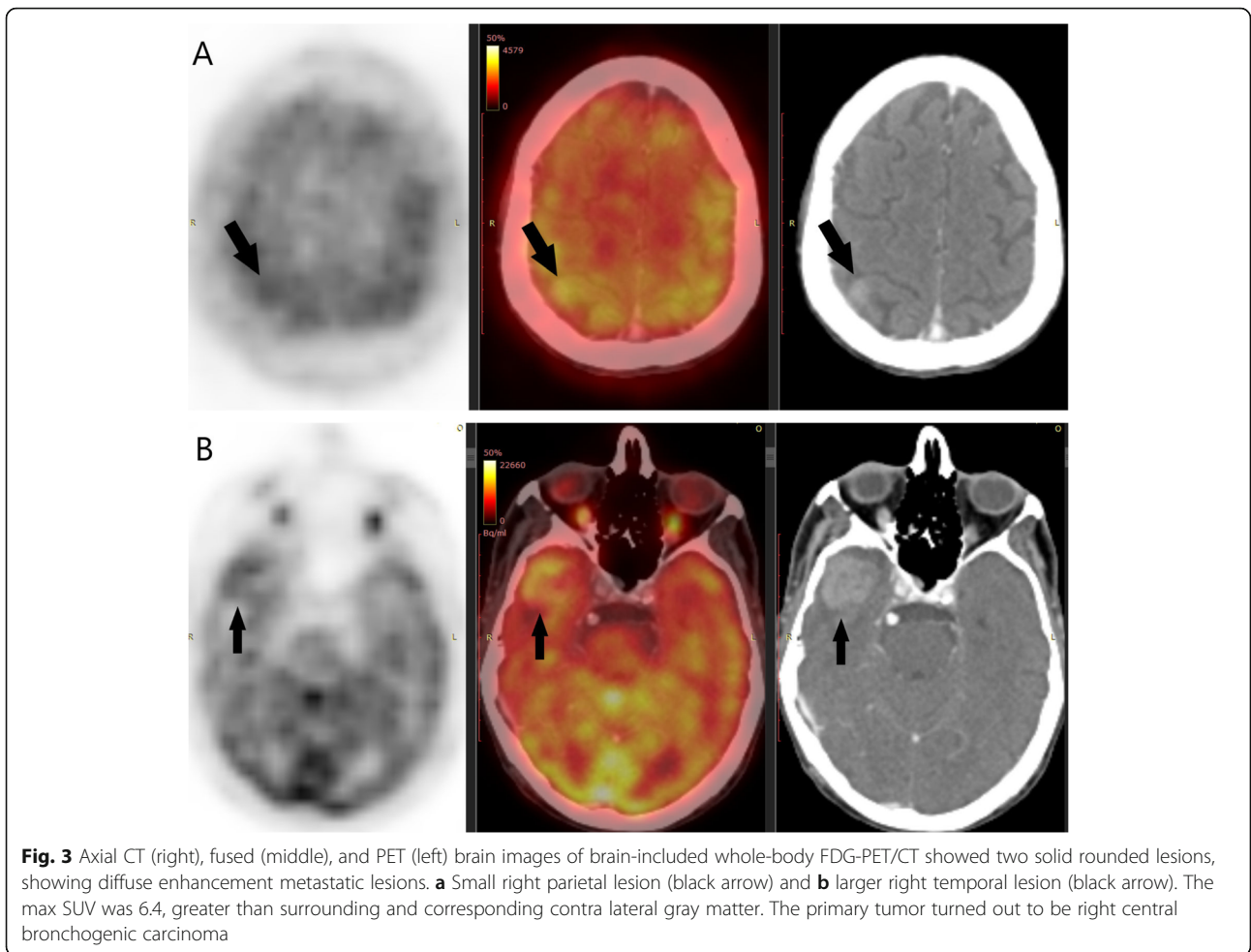
Discussion

PET/CT is a widely used imaging modality in oncology owing to its whole-body imaging coverage allowing detection of metastases in a large part of the body. Routinely, a whole-body PET/CT covers from the skull base to upper thigh region that can be described as lips- to-hips or eyes-to-thighs excluding the brain which makes the term whole body imprecise.

FDG-PET's role in detecting BM has been frequently questioned in literature and limited due to its low sensitivity [5, 18, 19]. However, this sensitivity increased with the introduction of IV contrast and the development of new fast CT scanners [20]. We addressed the role of including the brain in cancer patient's whole-body scans to increase the probability of BM being detected. Hence, the term "detection" as part of our aim was more toward the clinical application of the examination making more sense of the name "Whole body scan" and to be used as a single stop shop for patient's full assessment including the brain saving effort, time, and cost especially in low economy regions.

We examined 420 cases of extra-cranial malignancy from which 30 patients presented with 71 BM lesions with an incidence of 7.1%. Current literature reviewing incidence of BM showed high variability with an incidence proportions percentage ranging from 3 to 50% [10]. This could be explained in the context of methodological constraints related to inconsistency of studied data. The published data could be derived from population-, histology-, radiologic-, surgical-, or medical record-based data studies [4, 12, 21]. In addition, other epidemiological variables as age, sex, race, and regional
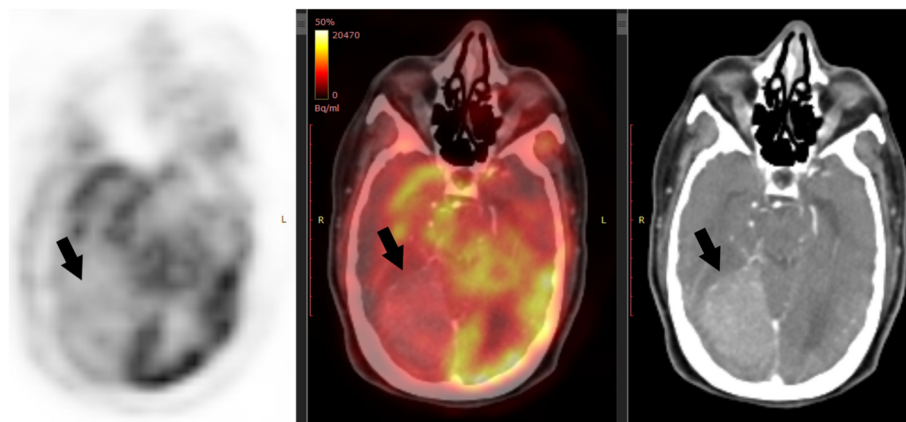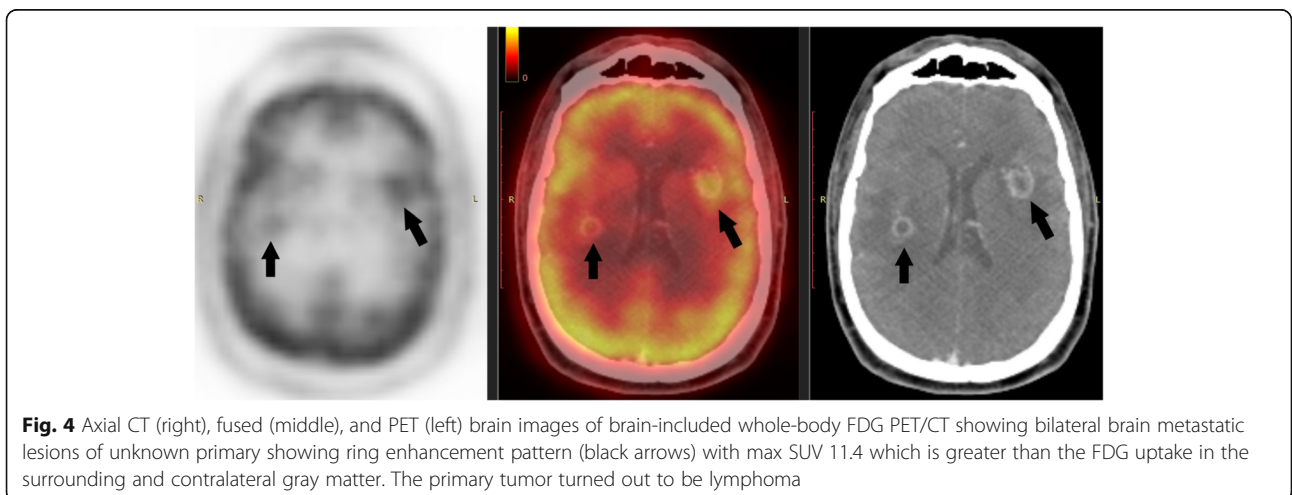

Fig. 2 Axial CT (right), fused (middle), and PET (left) brain images in brain-included whole-body FDG-PET/CT examination routine follow-up for a patient with thyroid carcinoma showed solitary, right sided, occipital, ovoid sizable lesion (black arrows) with diffuse intralesional enhancement and minimal vasogenic edema. Its max SUV was 4.2, less than surrounding and corresponding contralateral gray matter
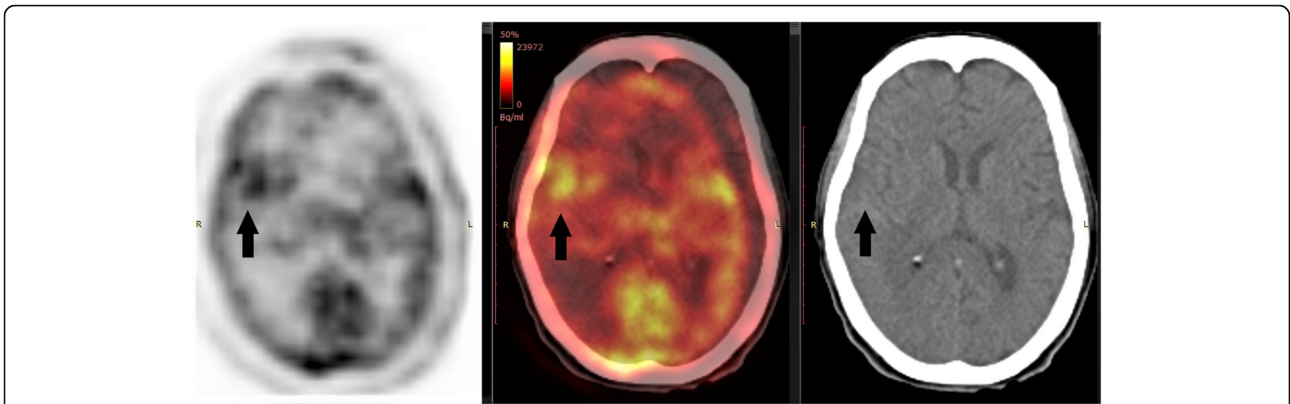
Fig. 3 Axial CT (right), fused (middle), and PET (left) brain images of brain-included whole-body FDG-PET/CT showed two solid rounded lesions, showing diffuse enhancement metastatic lesions. **a** Small right parietal lesion (black arrow) and **b** larger right temporal lesion (black arrow). The max SUV was 6.4, greater than surrounding and corresponding contra lateral gray matter. The primary tumor turned out to be right central bronchogenic carcinoma

area (North Africa in our case) can be responsible for the reported variations [10].

In the current study, bronchogenic carcinoma was the most common primary tumor both in the previously diagnosed patients and as more commonly presenting

metastases of unknown origin [22]. These results are in accordance with most of the published data where autopsy studies have suggested that lung cancer is the most common tumor to cause BM accounting for two-thirds of patients [12, 23]. In our study, the most common

Fig. 4 Axial CT (right), fused (middle), and PET (left) brain images of brain-included whole-body FDG PET/CT showing bilateral brain metastatic lesions of unknown primary showing ring enhancement pattern (black arrows) with max SUV 11.4 which is greater than the FDG uptake in the surrounding and contralateral gray matter. The primary tumor turned out to be lymphoma

Fig. 5 Axial CT (right), fused (middle), and PET (left) brain images of brain-included whole-body FDG PET/CT showing right temporal lesion (black arrow) that appears as a subtle hypodense area in CT with max SUV 4 which is nearly equal to the FDG uptake in the surrounding and contralateral gray matter. The primary tumor turned out to be right middle lobar bronchogenic carcinoma

histologic subtype associated with the development of BM was adenocarcinoma. This is in line with prior findings which may be related to the fact that adenocarcinoma is the most common histologic subtype of lung cancer overall [24]. In descending order, the common cancers to send BM in our study were breast carcinoma, renal cell carcinoma, melanoma, non-Hodgkin lymphoma, and thyroid carcinoma. Comparably, studies showed that breast cancer has the second most frequent incidence of BM, where autopsy studies reported an incidence rate of 18–30% [1, 25]. Melanoma is the third most common cause of BM and

accounts for nearly 6–11% of lesions, with a higher incidence of metastasis in males [26]. It was reported that 50% of advanced melanoma patients developed BM and 10% of metastatic lesions presented as an intraparenchymal hemorrhage [26]. With respect to renal cell carcinoma, it was estimated that BM occurred in 2–16% of patients and that when BM emerged late in illness, renal cell carcinoma was refractory to other therapies [27]. BM is an unusual event for patients with aggressive lymphoma [28, 29]. Thyroid cancer remote metastasis to the brain occurred in about 0.3-4.6% of cases and was associated
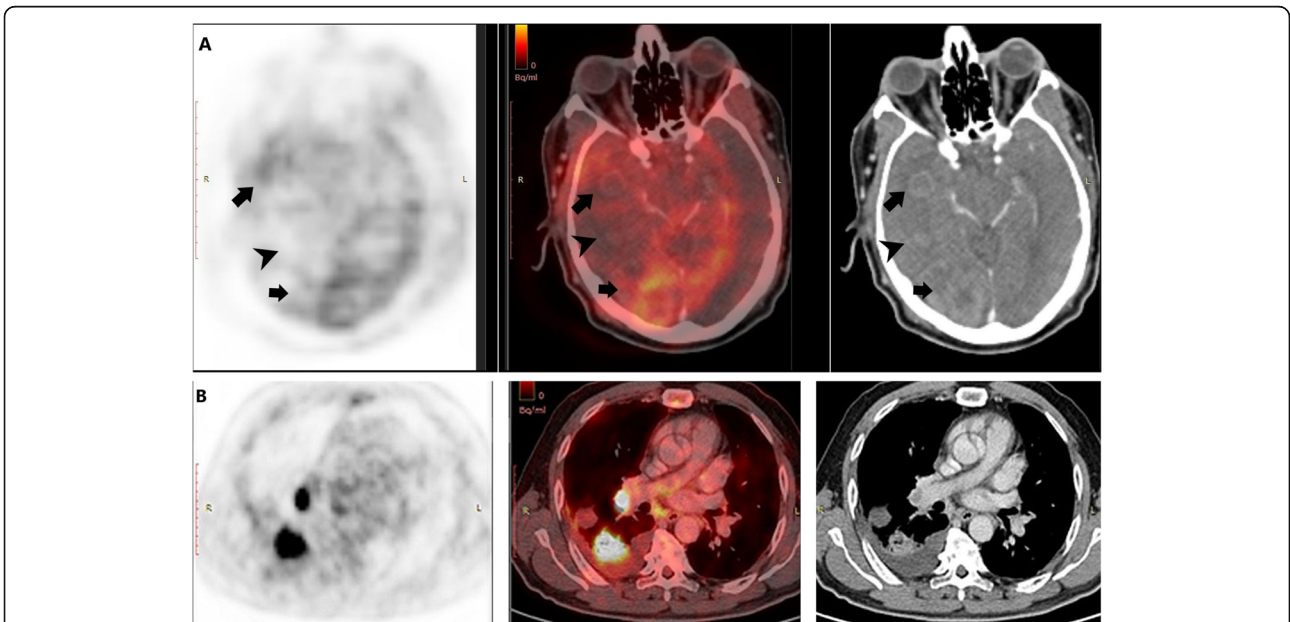
Fig. 6 A 65-year-old male patient presented with refractory headache. Brain-included whole-body FDG-PET/CT examination revealed **a** multiple variable-sized brain space-occupying lesions (black arrows). Small lesion (arrowhead) is seen in the CT image and not appreciated in the PET image. **b** Scans through the chest showed the primary tumor to be right lung cancer with concomitant pleural involvement

Table 4 Patient based diagnostic accuracies of FDG-PET/CT and CECT for detecting BM

BM	Sensitivity	Specificity	PPV	NPV	Accuracy
PET/CT	78.13	92.65	83.33	90.0	88%
CECT	81.25	94.12	86.67	91.43	90%

BM brain metastases, *PPV* positive predictive value, *NPV* negative predictive value

with aggressive behavior and worse prognosis [30–32]. Studies have shown that FDG-PET/CT detected location in nearly 25% of unknown primary disease patients [33, 34].

Neurological symptom presence may indicate BM. In this study, 16/30 patients (53.3%) with BM had neurological symptoms, whereas the remaining 14/30 patients (46.7%) had no neurological symptoms which represented nearly half of the studied patients. Patients with BM tended to be more appropriately diagnosed as positive by PET/CT in the symptomatic rather than in non-symptomatic patients. This is concordant with the published literature where Kitajima et al.'s study showed no statistical significance between these two patient groups [35]. A study proposed by Nia et al. showed that all studied patients with incidental BM were symptom free [36]. It is important to diagnose BM before patients become symptomatic to avoid dangerous complications as seizures.

Regarding the number of brain lesions, multiple lesions were more common than solitary lesions which agree with the published data [11, 25]. According to site, supratentorial metastases were present in 100% of patients with the parietal lesions representing 50.7%, while infratentorial lesions were detected in 26.7% of the studied patients. Similar results were reported by Delattre et al. [37] and Nussbaum et al. [38] where the supratentorial area was the preferential area for metastasis that can be explained in the context of the respective mass of these structures. This anatomical distribution of the BM being supratentorial in 100% of our studied patients justify the importance of including the brain in the scanned field; otherwise, they would not have been discovered with the routine base of the skull–to–thigh protocol.

In the current study, the enhancement patterns detected varied from none to marginal, ring- and intralesional enhancement. Some of the lesions showed patchy areas of no enhancement and no radiotracer uptake due to associated element of necrosis, calcifications, or hemorrhage. Schwartz et al. evaluated 221 ring-enhancing brain lesions and found that the most frequent pathologies associated with ring-enhancing lesions were gliomas (40%) followed by BM 30% [39].

The intensity of FDG uptake was variable in the current study, where the max SUV value was measured for every lesion separately, the least was 0.2 and the

most was 20. In attempt to appropriately assess the FDG uptake by the metastatic deposits in the presence of hypermetabolic background of normal brain tissue, we compared the FDG uptake to the corresponding contralateral gray matter uptake to set a reference range that is reliable for every patient during their specific status of examination. It was noticed that FDG avidity varied in the studied lesions when compared to the corresponding contralateral brain tissue showing iso-, hypo-, and hyper-avidity. It is worth mentioning that bronchogenic carcinoma metastatic deposits exhibited all three FDG uptake varieties.

Analysis of FDG-PET/CT diagnostic performance in the current study showed a moderately good sensitivity (78.1%) and specificity (92.6%) with an insignificant difference in performance as compared to CECT modality alone. In accordance with our data, Hjorthaug et al. studied lung cancer patients with suspected BM using FDG PET/CT as a triage for selecting patients who need further imaging. This study showed PET/CT sensitivity, specificity, and PPV were 72, 100, and 97%, respectively [40]. Several FDG-PET studies have demonstrated a broad range of sensitivities and specificity for identifying brain tumors, whether as known primary brain tumors or recurrence after treatment, ranging from 25–100% and 22-100%, respectively [41]. Sensitivity is limited by false-negative cases that resulted from absent or reduced FDG uptake by suspected brain tumors compared to surrounding normal brain tissue. Meanwhile, specificity is limited by false-positive cases as in cases of inflammation [42, 43].

FDG has been the tracer of choice for oncologic PET imaging, based on the principle of increased glucose metabolism by most tumors [44], long half-life, easy synthesis [15, 45]. Despite its recognized limitations in brain tumor imaging due to the high uptake in the background of normal gray matter, this imaging modality tracer remains the most used nowadays [15, 45]. FDG provides a comprehensive picture of the tumor, predicting aggressiveness, helping to differentiate recurrent tumors from treatment-related changes, and differentiating pharmaco-sensitive tumors [45]. Recent technical improvement in several PET/CT protocols including the implementation of intravenous contrast resulted in improvement of the overall yield of the hybrid study in detecting BM to exceed the reported low sensitivity of a PET alone. Adding that to the whole body coverage (including head) and the accessibility to faster scanners, the CT component of the PET/CT study can work as an independent CT scan of the brain with the possibility to preclude the requirement for a dedicated diagnostic brain CT.

Limitations of the FDG-PET/CT should be recognized. Previous studies suggested limitation of PET scanning as

possible false-negative results that could lead to inaccurate disease staging. In a prior study by Kruger et al., BM detected by PET-CT were evident only on the CECT portion of the examination, with FDG-PET only detecting altered metabolism in 1/8 patients [46]. In some patients, particularly those with neurological complaints, there is still a need for more imaging despite the improved diagnostic performance of PET/CT. False sense of security from negative PET/CT results should be regarded and the treating physicians must be informed about the study limits so as to avoid errors in treatment due to potentially misleading PET/CT results. Additionally, logistic issues like scanning time in an active PET service and the extra brain scanning time will reduce the overall number of patients scanned per day [19]. Radiation exposure could be considered a downside of the discussed modality; however, Osipov et al. showed that diagnostic exposure due to repeated PET-CT examinations in a group of oncological patients was not associated with changes in mortality [47]. Reduced kilovolts (kVs) with automatic exposure control were a suggested attempt to optimize the radiation exposure in head and neck scans [48].

We should recognize limitations in the current study as there was lack of a histological proof as a true reference standard for some of the detected lesions. With a reference standard based on imaging, false negatives may arise in small or slowly growing lesions in the absence of substantial morphological changes. Nevertheless, comparable with numerous studies of similar design, acquiring multiple biopsies for tissue confirmation would have been unfeasible and ethically unacceptable [20, 49]. Another recognized limitation could be the number of the studied cases which could have led to underestimating the incidence of BM. We believe that there are sources of bias as the defect in referral system, systemic brain study is not routinely performed or patients with end-stage diseases that may be considered untreatable may not have been included. Further studies aimed at improving brain PET/CT performance and a systemic diagnostic evaluation of FDG-PET/CT for the differentiation of the brain tumor are therefore essential.

Conclusion

No single modality can provide a full answer to a complex clinical question in oncology patients. Brain-included whole-body FDG-PET/CT provides valuable complementary information in the evaluation of patients with suspected BM that can be used for presumptive diagnosis to direct therapeutic decision-making and can be integrated in the routine workup protocols. However, considering the obtained results of the diagnostic performance of brain PET-CT, the possibility of false-negative results with consequent false sense of security should be considered especially in patients with suspicious neurological clinical manifestation. Those patients should have further dedicated CNS imaging for confirmation. Hence, the clinicians should learn about the possible pitfalls of PET/CT interpretation, and the prudent use of further standard brain imaging techniques needs to be promoted.

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