EVALUATION OF ROLE OF COMBINED PET/CT SCANNING IN IDENTIFICATION OF OSSEOUS AND MARROW METASTATIC DEPOSITS

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ABSTRACT:

Background: *To improve a patient's long-term survival and reduce potential hematological, neurological, and orthopedic challenges, early cancer identification is critical. Osseous and marrow deposits are frequently seen as significant cancer consequences that can cause excruciating pain and have a bad prognosis.*

Objectives: *The study's objective was to show how combined 18F-FDG PET/CT is superior to standalone CT in detecting osseous and marrow deposits in cancer patients.*

Patients and Methods: *There were 75 participants in the trial, and 18F-PET/CT scans were carried out. Retrograde lesion-based analysis was carried out. The negative predictive value (NPV), positive predictive value (PPV), sensitivity, and specificity of each of these modalities were assessed as part of the statistical study. Whenever feasible, a biopsy of the underlying neoplastic lesion, pattern of dissemination, and follow-up were used to confirm a final diagnosis of metastasis.*

Results: *The detection of osseous and bone marrow metastatic deposits which are not visible on traditional CT studies is made possible by combined PET-CT examination, an extraordinarily sensitive imaging technique.*

Conclusion: *The identification of osseous and bone marrow metastases was reported to be substantially more sensitive and specific with combined 18-F FDG PET/CT than with standalone CT. In order to start a treatment regimen and improve the overall prognosis and result of the illness process, it adds a major value that can detect lesions.*

Keywords*: PET/CT, osseous, marrow metastatic lesions, cancer*

INTRODUCTION:

To improve a patient's long-term survival and reduce potential hematological, orthopedic, and neurological problems, early cancer identification is crucial. Important cancer consequences, including osseous and marrow deposits, are regularly seen and can cause excruciating pain. Skeletal-related events (SREs) and death risk were always elevated in the presence of bone metastases. According to[(1)], SREs were linked to lower life quality, higher treatment costs, and increased morbidity.

The diagnostic method of positron emission tomography (PET) using the tracer 2-(18F) fluoro-2-deoxy-D-glucose (FDG PET) is functionally based on the concept that rapidly developing cancer cells have improved glucose metabolism, facilitating the detection of areas with cancer cells. Integrated FDG-PET/computed tomography (CT) had been developed to address the

drawbacks of FDG-PET scanning (poor anatomical information), and it was widely used for staging, planning radiation fields in cancer management, or determining the extent of surgical resection [(2)].

PET imaging has the capability to recognize osseous metastases at an early stage of development and even before the host fights with the tumor cells. Furthermore, because of the early enhanced glucose consumption by the neoplastic cells, early malignant bone marrow infiltration might be visualized by 18F-FDG PET [(3)].

Anatomical and functional information can be obtained in co-registered pictures using the combined PET/CT method, which scans the entire body in a single session as opposed to CT, which usually requires numerous sessions to scan the entire body and is therefore time demanding. Due to superior anatomical localization in CT and the activity of lesions by the PET scan, it thus combines the benefits of both technologies [(4)].

The predictive potential of deoxy-2-[18F] fluoro-D-glucose ([18F] FDG) positron emission tomography/computed tomography (PET/CT) for predicting clinical outcomes and treatment response in cancer patients was also very high [(5)].

AIMS OF THE WORK:

The aim of this work was to determine the value of PET/CT scanning in the detection of osseous and bone marrow metastatic deposits compared to the sole use of CT scanning.

PATIENTS AND METHODS:

This study was retrospective; it was conducted at the Radiology Department at Ain Shams University for 6 months. Oncology patients were referred for metastatic workup as they were suspected to have osseous, and marrow metastatic deposits had been included. Patients with primary neoplastic bone tumors were excluded.

Inclusion Criteria:

- There is no age limitation.
- Patients presenting with clinical symptoms of bone marrow metastases, including back pain, pathological fractures, anemia, bleeding tendency, and recurrent infections, and those known to have primary malignancy elsewhere.

Exclusion Criteria:

- Patient with primary bone tumors since our target were metastatic deposits only so as to avoid the overlap between the primary and the metastatic disease.
- Patients known to have metabolic osseous diseases.

Sample Size:

Using the Epi Info 7 program for sample size calculation, it was estimated that a sample size of 75 patients will be needed to detect the expected accuracy of PET/CT scanning for the detection of metastatic lesions of 95% ± 5% with a confidence level of 95%.

Study procedure:

Pre-procedural preparation in the form of taking verbal consent from the patients after a brief explanation of the study aim and procedure, measuring the height and weight of the patients, and fasting for 8 hours, diabetic patients were instructed to control their blood sugar level for the previous 3 days to be less than 200 mg/L and to stop taking insulin 6 hours before the study.

A PET/CTPET/CT using a hybrid PET/CT system was performed. A 16-slice multi-slice scanner was the integrated CT system. Firstly, a CT without contrast images was taken. Followed by IV contrast administration with 1 mL/kg of iodinated contrast agent, and an additional set of CT images were taken, except in cases of renal impairment. A 5-ring GE Discovery system was used for the integrated PET scan. Images were conducted after 45–60 min of administering 1 mCi/10 kg (maximum dose =

10 mCi) of 18F-FDG". The study was done with patients in the supine position and on the whole body, from the skull base down to the mid-thighs. A PET scan with the patient in the supine bed position was performed after the attenuation correction. A CT with an approximately 15-cm axial field of view covering the same field of view as the CT with approximately 9 to 11 bed positions was planned in the 3D acquisition mode for scanning the patient in one and a half minutes for image acquisition at each bed position. A GE Discovery workstation was used to view all CT, PET, and PET/CT images, which were reconstructed in multi-planar reformation and viewed in different planes for all, as well as "3D maximum intensity projection images (MIP)" PET images in video mode.

Ethical considerations:

The study was approved by the Research Ethical Committee with Assurance No. FWA 000017585, Faculty of Medicine, Ain-Shams University.

Statistical analysis:

The collected data were coded, tabulated, and statistically analyzed using the SPSS program (Statistical Package for Social Sciences).

RESULTS

75 individuals were enrolled in the trial, with a mean age of 57.03 years + 16.12 (34 females and 41 men). The pathology results for 61 patients were obtained; these patients were classed as known 1ry, whereas the 14 patients whose pathology data were unavailable were labeled as unknown primary.

The location of the primary neoplastic lesion was also recorded. Breast was the most common primary tumor in our study, followed by lung, renal, thyroid, and prostate.

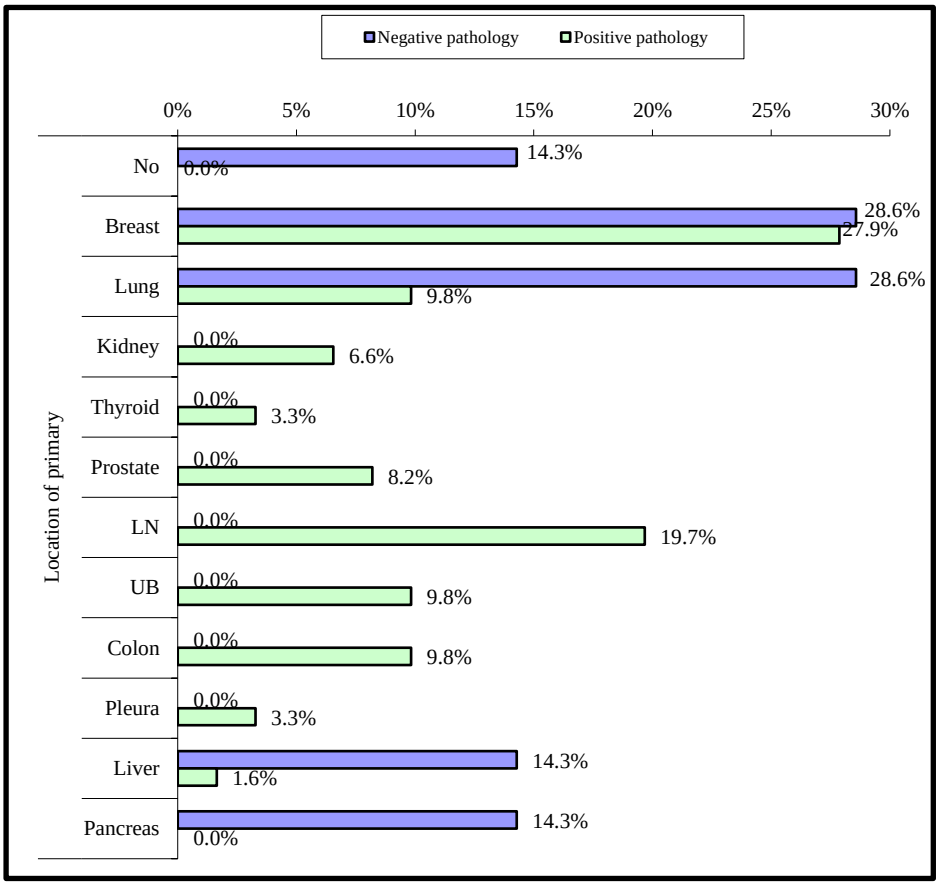

Figure 1: Descriptive data regarding the location of primary tumor.

There is no statistically significant correlation between the pathology findings (known as 1ry) and the type of osseous lesions, the lesions' FDG uptake in the initial and follow-up studies, the lesions' change in CT appearance, or the lesions' distribution. However, the main tumor's metastatic deposits will also be active if it is FDG-avid, and vice versa (the metabolic signature). The relation between FDG uptake in the initial study and types of osseous lesions is demonstrated in the following table, which shows a significant statistical relation between the FDG uptake and the marrow lesions (CT occult), with a range of uptake between 4.5 and 40, a median uptake of 8.5, and a P-value of 0.000 (table 1):

Table 1: Showing the relation between the FDG uptake and the type of osseous lesions.

	FDG uptake in initial study		Test value	P-value	Sig.
	Median (IQR)	Range			
Osteolytic	5 (4.5 – 7.1)	3 – 17	-0.812‡	0.417	NS
Osteosclerotic	4.5 (2 – 13.1)	2 – 15	-0.500‡	0.617	NS
Mixed	6 (3.5 – 9.5)	1.2 – 12.2	-0.079‡	0.937	NS
Marrow lesions	8.5 (7.05 – 13.75)	4.5 – 40	-4.064‡	0.000	HS
Degenerative/Inflammatory	3.35 (2.8 – 3.6)	2.4 – 3.7	-2.510‡	0.012	S

P-value >0.05: Nonsignificant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS)
‡: Mann Whitney test; ‡‡: Kruskal Wallis test.

The following table shows really positive (42) and false positive (12) lesions for CT-evident lytic, sclerotic, or mixed lytic/sclerotic lesions with positive (known 1ry) or negative (unknown 1ry) pathology. The lesions that had benign criteria and were positive (known 1ry) or negative (unknown 1ry) in pathology, on the other hand, were categorized as false negative (14) / true negative (7) lesions, respectively, and the marrow lesions (no underlying CT abnormalities). (Table 2).

Table 2: Showing the TP, TN, FP and FN results of the CT lesions in relation to the pathology results.

		Pathology	
		Unknown 1ry	Known 1ry
CT	Deg., marrow lesions	7	14
	Lytic, sclerotic, mixed	12	42

The following table shows genuine positive (54) and false positive (10) lesions that had significant FDG uptake and were positive (known 1ry) or negative (unknown 1ry) in pathology, respectively.

On the other hand, lesions with poor or no FDG uptake that exhibited positive or negative pathology were referred to as false negative (7) or true negative (4) lesions, respectively. (Table 3).

Table 3: Showing the TP, TN, FP and FN results of the combined PET-CT appearance of the lesions in relation to the pathology results.

		Pathology	
		Unknown 1ry	Known 1ry
PET CT	Lesion + low/no uptake	4	7
	Lesion+ high uptake	10	54

The study showed that the sensitivity of the combined PET CT examination was higher than that of the CT alone in detecting the positive lesions (88.5% in comparison to 75% for CT), and the specificity to exclude the negative lesions was lower than that of the CT (28.6% in comparison to 36% for CT), and the accuracy was on the PET CT side

(77.3% in comparison to 65% for CT), and PPV and NPV were higher for PET CT (84.4% and 36%) in comparison to 78% and 33% for CT, respectively (Table 4).

Table 4: Showing the accuracy, sensitivity, specificity, PPV and NPV results of the CT alone and the combined PET-CT examinations.

Parameter	TP	TN	FP	FN	Accuracy	Sensitivity	Specificity	PPV	NPV
PET CT	54	4	10	7	77.3 %	88.5 %	28.6 %	84.4 %	36 %
CT	42	7	12	14	65 %	75 %	36 %	78 %	33 %

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
FDG uptake	0.836	>6.5	87.5	81.48	58.3	95.7

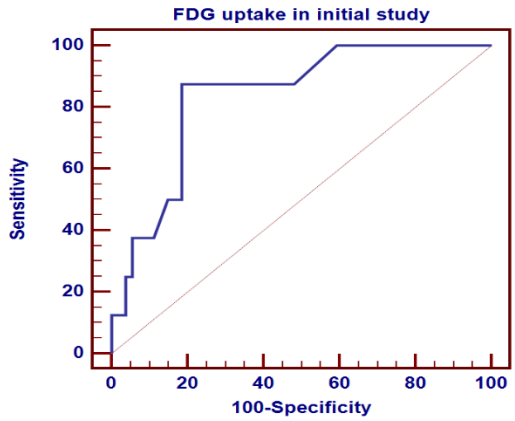

Figure 2: ROC curve of FDG uptake in initial study as a predictor of marrow lesion.

The previous ROC curve shows that the best cut-off points for FDG uptake to detect marrow lesions was > 6.5, with a sensitivity of 87.5%, a specificity of 81.48%, and an area under curve (AUC) of 83.6%. In other words, 87.5% of cases that have no underlying CT abnormality proved to be early metastatic lesions (marrow lesions) with FDG uptake above SUV max. 6.5.

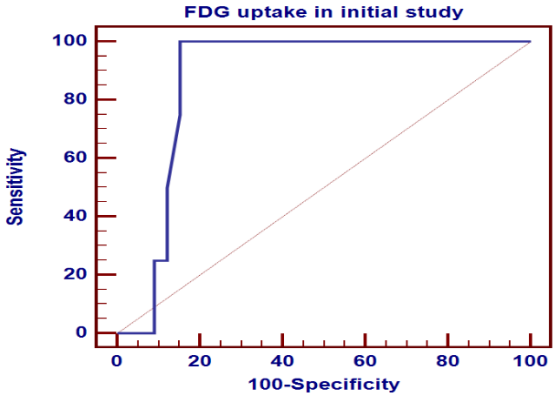

Figure 3: ROC curve of FDG uptake in initial study as a predictor of degenerative/ Inflammatory.

Parameter	AUC	Cut of Point	Sensitivity	Specificity	PPV	NPV
FDG uptake	0.875	≤ 3.7	100.0	84.85	28.6	100.0

The previous ROC curve shows that the best cut-off points for FDG uptake to detect degenerative or inflammatory lesions was found to be ≤ 3.7, with a sensitivity of 100%, a specificity of 84.85%, and an area under curve (AUC) of 87.5%. In other words, 100% of cases that have CT criteria for degenerative lesions have FDG uptake equal to or below 3.7.

Cases

Case 1

History and clinical data:

A 65-year-old patient who suffered from a rectosigmoid mural lesion and was later found to have colonic invasive cancer underwent a PET CT scan for the purpose of evaluating metastatic spread.

CT findings:

A CT scan showed sigmoid colon, rectal, and anal canal mural thickening with luminal encroachment. There were no underlying bony abnormalities and no lytic or sclerotic lesions.

PET CT findings:

A whole-body PET CT scan revealed metabolically active foci with SUV max. 9.5 at multiple levels of the vertebral and appendicular skeletons, which were not visible on the CT scan.

Diagnosis:

Sigmoid colon-invasive adenocarcinoma with early marrow metastatic deposits

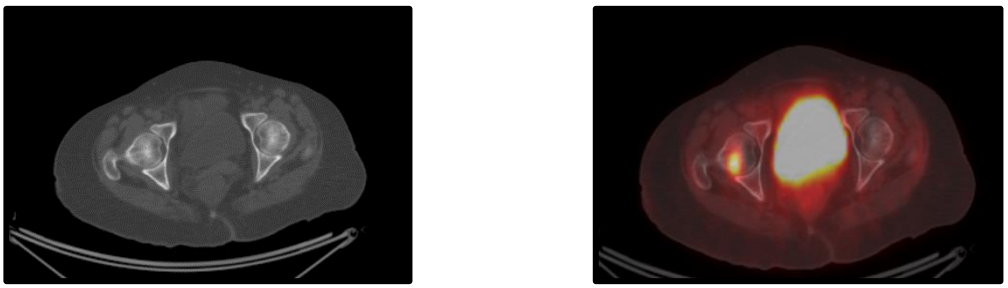

Figure 4: Showing right femoral head active focus with no underlying CT abnormality.

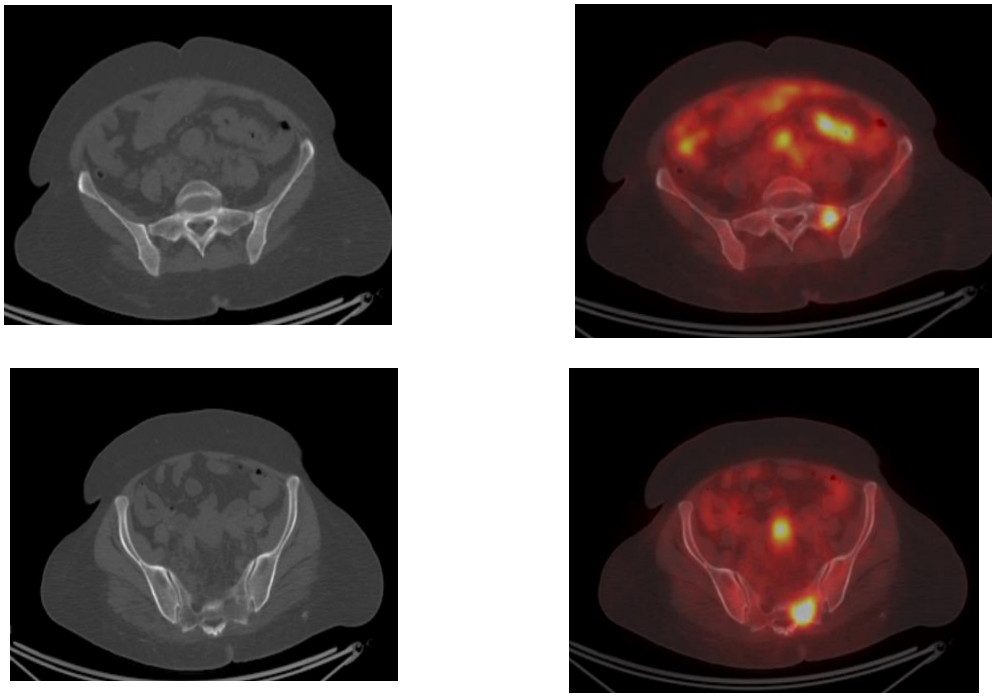

Figure 5: Showing left sacral metabolically active foci with no underlying CT abnormalities.

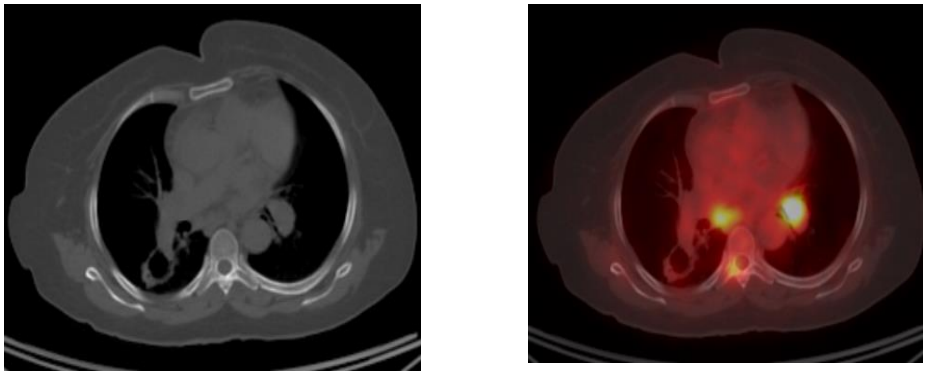

Figure 6: Showing right vertebral pedicle active focus with no underlying CT abnormalities.

Case 2

History and clinical data:

A 39-year-old female patient with a known case of bilateral breast cancer is on chemotherapy. Metastatic work was done.

CT findings:

It showed bilateral breast ill-defined soft tissue mass lesions with irregular skin thickening. The surveyed skeleton showed neither lytic nor sclerotic osseous lesions.

PET CT findings:

Bilateral breast lesions with strong FDG uptake, attaining SUV maximums of 7 on the right side and 6.1 on the left, were visible on whole-body PET CT imaging. FDG uptake of SUV max. 21.1, which was not visible in CT scans, was implemented to detect the active focus of the left femoral head.

Diagnosis:

Bilateral breast carcinoma with a newly developed left femoral head bone marrow metastatic deposit

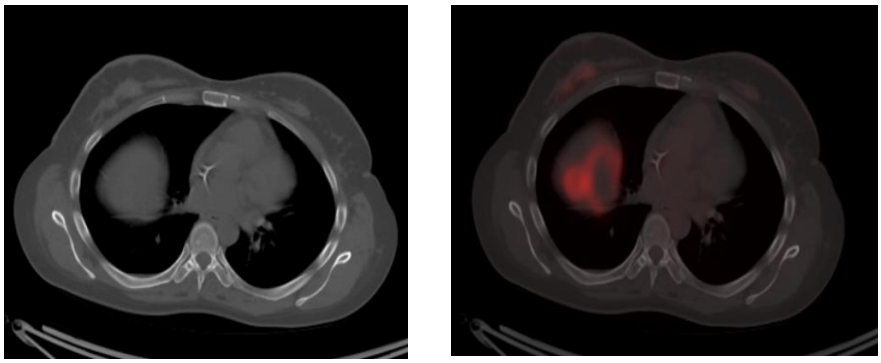

Figure 7: Show bilateral breast lesions with increased metabolic activity.

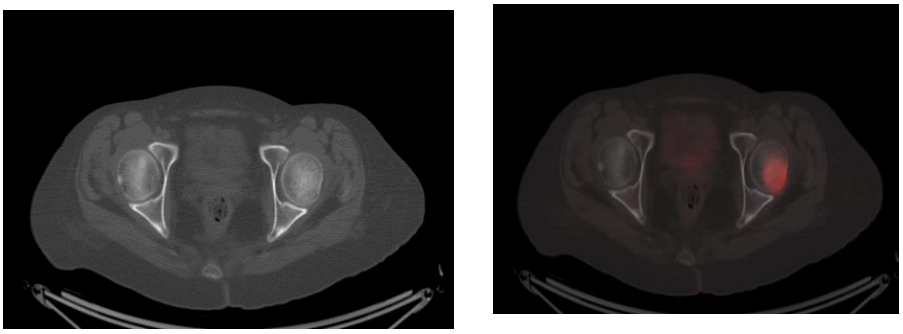

Figure 8: Shows left femoral head small focus of increased metabolic activity with no underlying CT abnormality.

Case 3:

History and clinical data:

A 61-year-old male patient with a history of Hodgkin's lymphoma is coming for a routine follow-up PET CT scan.

CT findings:

Multilevel vertebral bodies have sclerotic lesions involving mainly the vertebral endplates as well as right iliac bone chondromatous lesions.

PET CT findings:

The multiple vertebral endplate sclerotic foci as well as the right iliac bone chondromatous lesion show no evident FDG uptake.

Diagnosis:

A known case of Hodgkin's lymphoma has right iliac lesions that were thought to be degenerative or non-metastatic in nature and vertebral endplates that were inadvertently determined to be inactive in metabolism. There are no metastatic foci with metabolic activity.

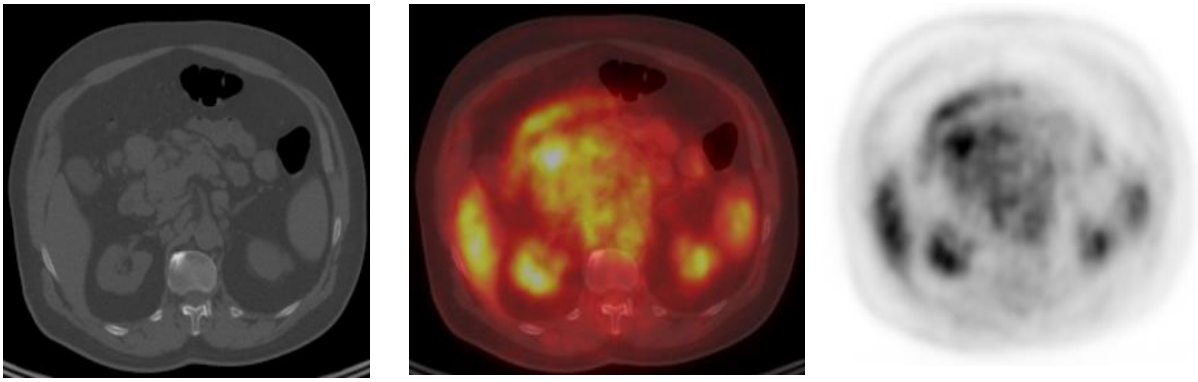

Figure 9: Showing vertebral endplate sclerotic focus with no metabolic activity.

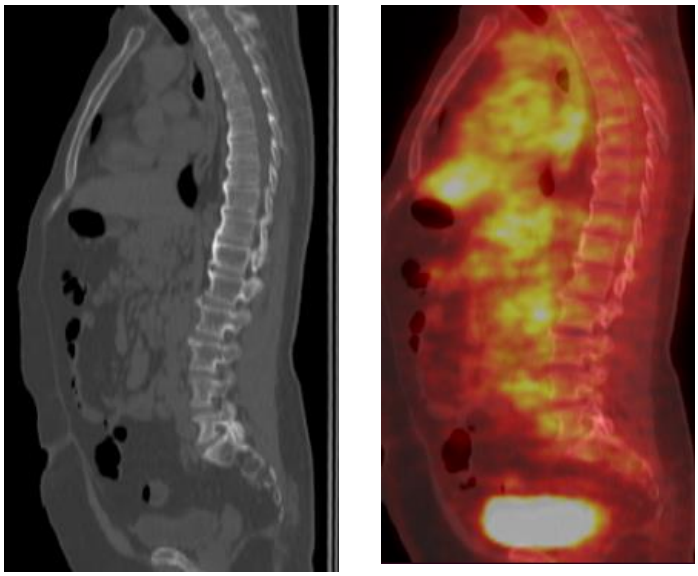

Figure 10: Showing multilevel vertebral end plates sclerotic foci with no metabolic activity.

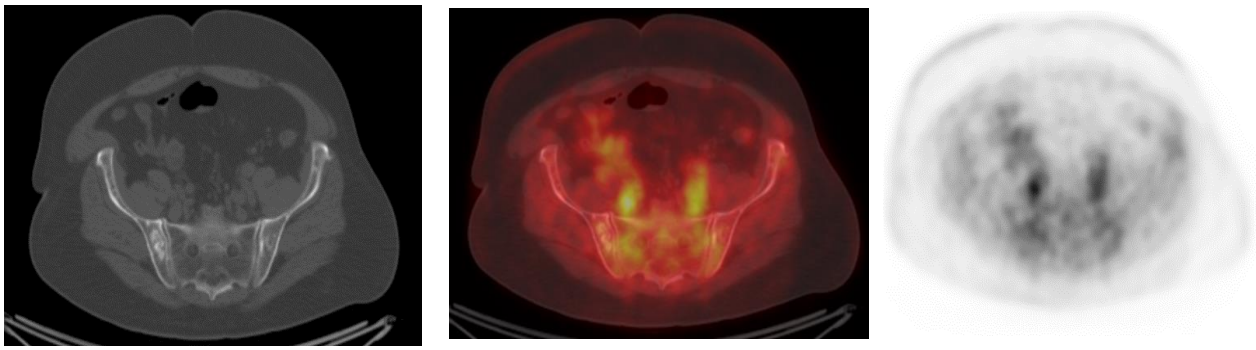

Figure 11: Showing right iliac bone chondromatous lesions.

Case 4:

History and clinical data:

An 83-year-old male patient with a history of pathologically proven medullary thyroid carcinoma with high calcitonin levels came for routine follow-up.

CT findings:

Wide-spread axial and appendicular skeleton sclerotic foci

PET CT findings:

Corresponding PET CT images show low metabolic activity with SUV max. <2.

Diagnosis:

High calcitonin levels in a case of medullary thyroid cancer with recently acquired diffusely scattered sclerotic foci of low metabolic activity, which are thought to be low metabolically active metastatic deposits

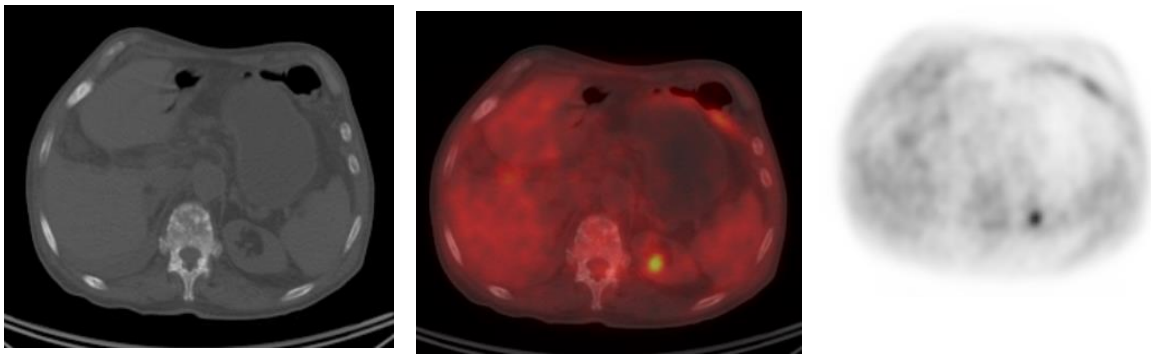

Figure 12: Show vertebral bodies sclerotic foci of low metabolic activity.

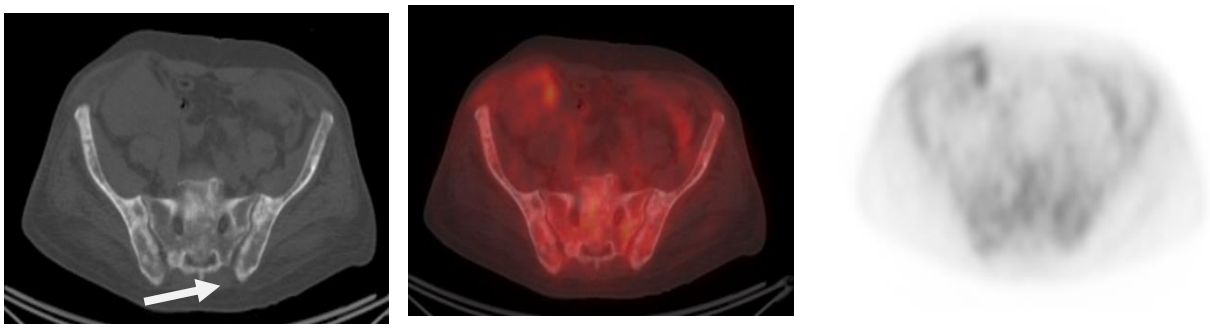

Figure 13: Show bilateral iliac bones and sacral multiple sclerotic foci of low metabolic activity.

DISCUSSION:

For additional characterization of malignancies in the brain, paracortical, and periosteal sites, CT has been beneficial. To characterize the posterior components of the spine, rib bone lesions, and other flat bones with a higher cortex/medullary bone ratio, CT is frequently required [(6)].

Even when using the ideal CT window level and width, early BM metastases (CT occult lesions) are incredibly difficult to detect with CT [(7)].

In contrast, F18-FDG-PET/CT has a good sensitivity for detecting osteolytic bone metastases and bone marrow metastases [(8)].

In other words, CT is not the best method for detecting BM metastases, an early stage of bone metastasis [(7)].

Our study population included 75 patients with osseous metastatic lesions; their ages ranged from 10 to 92 years, with a mean age of 57.03 years, and a male predilection with 41 male patients and 34 female patients.

Our study candidates were divided into 30 patients (40%) with osteolytic lesions, 9 (12%) with osteosclerotic lesions, 15 (20%) with mixed lesions, 16 (21.3%) with marrow lesions (CT occult), and 5 cases (6.7%) with degenerative lesions.

Our study revealed that the sensitivity of the combined PET CT examination was higher than the CT alone in detecting the positive lesions (88.5% vs. 75% for CT), but the specificity to exclude the negative lesions was lower (28.6% vs. 36% for CT). Additionally, the accuracy, PPV, and NPV were higher for PET CT (77.3%, 84.4% vs. 33%) than for CT (65.7%, 78% vs. 33%).

In a 2017 study titled "Bone Marrow Metastasis Is an Early Stage of Bone Metastasis in Breast Cancer Detected Clinically by F18-FDG-PET/CT Imaging,"[(7)], it was stated that "Bone marrow metastases were noted clinically on F18-FDG-PET/CT in about half of our patients who presented with new bone metastases. Our findings demonstrated that, as shown clinically in pre- and post-treatment F18-FDG-PET/CT, bone marrow metastases played a substantial role in the development of metastatic bone disease. This study shows that BM metastases may be detected by molecular imaging (FDG-PET scanning) but not CT scanning. This study demonstrated that bone marrow metastases were present before osteolytic and osteoblastic metastatic bone lesions.

Furthermore's,[(9)] study from 2020, "The added value of hybrid 18F-FDG PET/CT over CT in the detection of breast cancer metastatic deposits," was in agreement with ours in that it "revealed similar sensitivities where they were for CT at 89% and for PET at 100%. Even when there are no morphologic abnormalities shown on CT, PET/CT was able to identify metastases at an early stage; this may be because PET detected activity in the bone marrow when there was insufficient bone damage.

Our study revealed similar sensitivities: for CT, it was 89%, and for PET, it was 100%. Hybrid PET/CT was found to give optimum sensitivity and specificity in our study. PET/CT was able to detect metastases at an early stage, even when there is no morphologic abnormality detected on CT; this may be due to the fact that PET detected activity within the bone marrow in the absence of sufficient bone destruction. A study conducted by [(10)], revealed similar results as our study, where the sensitivities of CT and PET were 77.9% and 94%, respectively.

Also, similar results were agreed upon by [(11)], who found a sensitivity of 93.4% and a specificity of 99.4% for hybrid PET/CT.

This study is limited by being retrospective, as bone marrow metastasis is a temporary state of bone metastasis. It is worth saying that the detection of BM metastasis is

affected by when to do a molecular scan. Within the limitations of this retrospective study, it is not yet confirmed whether early detection of bone marrow metastases by molecular imaging will have a significant impact on patients' management and prognosis or not.

Conclusion:

Early in the illness phase, bone marrow metastasis is easy to be overlooked in cases of delayed presentation. In other words, the timing of the molecular scan affects the identification of BM metastases.

Combining PET and CT imaging can be used to detect early bone marrow metastatic lesions that are not yet visible on conventional CT scans. This adds significant value because it allows for the early detection of lesions and the subsequent initiation of treatment, which helps to improve the course of the disease.

Our study has limitations due to its retrospective nature, and additional follow-up after therapy is required to determine how early marrow diagnosis affects treatment results and prognosis.

Conflict of interest:

This study has no conflict of interest between the authors.

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قيمة الماسح البوزيتروني المقترن بالأشعة المقطعية في الكشف عن الثانويات العظمية وثانويات نخاع العظام في مرضى السرطان

شيرين محمد إبراهيم شرارة ومصطفى عبد الوهاب حسين عبد الفضيل وهبة يسرى النجار

فسم الأشعة التشخيصية والتداخلية ـ كلية الطب ـ جامعة عين شمس

يظل الإنتشار السرطاني للعظام أكثر آفات العظام شيوعًا التي تصيب الإنسان ، مع ظهور أعراضه في جميع أنواع السرطانات تقريبًا. تحدث النقائل العظمية في نصف المرضى المصابين بالسرطان ، والنمط الأكثر شيوعًا للنقائل العظمية هو في منطقة العمود الفقري ، مع وجود سرطان أولي غير معروف في 10٪ من المرضى.

تعتبر الثانويات العظمية للأورام الخبيثة أمرًا شائعًا كما انها تعتبر أكثر انتشارًا من الأورام الخبيثة الأولية في العظام. يعد العظم ثالث أكثر الأماكن شيوعًا للورم الخبيث ، ولا يتجاوزه سوى الرئتين والكبد.

تعتبر الفقرات والحوض والأضلاع ونهايات العظام الطويلة هي المواقع المفضلة لعملية النقائل بسبب محتواها العالي من النخاع الأحمر. داخل العمود الفقري ، يكون الموقع الأكثر شيوعًا للانبثاث في منطقة أسفل الظهر ، وأقل في العمود الفقري الصدري ، ونادرًا في العمود الفقري العنقي (52٪ ، 36٪ و 12٪ على التوالي).

تُصنف الآفات العظمية الثانوية إلى ورم خبيث ليتي (لوسنت) أو متصلب (كثيف) ، على الرغم من أن السمات غالبًا ما تتطابق. يعتمد هذا على التوازن بين نشاط ترقق العظام (الذي يسبب ارتشاف العظم) ، ونشاط ورم العظم (الذي يسبب ترسب العظام) ، بالإضافة إلى التغيرات العظمية التفاعلية (النخر ، والتليف ، أو الاستجابة للعلاجات).

التصوير المقطعي المحوسب بانبعاث البوزيترون الفلورو ديوكسي الجلوكوز هو طريقة تصوير جزيئي حساسة قادرة على تشخيص نقائل نخاع العظام عن طريق زيادة امتصاص الفلورو-ديوكسي-الجلوكوز في الخلايا السرطانية المتنامية.

لا ترتبط الإصابة المبكرة لنخاع العظام دائمًا بمشاكل في التصوير الشعاعي. و لذلك يعتبر التصوير المقطعي بالماسح البوزيتروني حساس للغاية في الكشف عن هذه النقائل المبكرة لنخاع العظام. من ناحية أخرى ، فإن التصوير المقطعي غير قادر على اكتشاف النقائل المبكرة لنخاع العظام (آفات التصوير المقطعي الخفي) حتى عند استخدام عرض ومستوى نافذة التصوير المقطعي المحوسب الأمثل.

أظهرت نتائجنا أن التصوير المقطعي المحوسب بانبعاث البوزيترون كان أعلى في الحساسية والدقة والقيمة التنبؤية الإيجابية والقيمة التنبؤية السلبية من دراسة التصوير المقطعي المحوسب التقليدية مع وجود قيمة احتمالية مقدرة (0.000) والتي كانت ذات دلالة عالية.