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Added Value of SPECT/CT in Characterization of Extra-Skeletal Uptake of Tc-99m MDP on Planar Bone Scintigraphy in Known Cancer Patients.

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ABSTRACT:

Introduction: Extra-skeletal Tc-99m MDP uptake is not uncommon. It could be a problematic when it mimics a metastatic osseous lesion. Due to lack of proper anatomical localization, Planar bone scintigraphy (PBS) alone can't resolve this problem. Adding single photon emission tomography / computed tomography (SPECT/CT) images increases the diagnostic accuracy of planar bone scintigraphy. SPECT/CT has great impact on patients' management by preventing misinterpretation through precise localization and proper characterization of these uncertain lesions. In this study, we compared the diagnostic accuracy of SPECT/CT versus PBS in characterization of extra-skeletal lesions detected on conventional PBS in known cancer patients. **Materials and Methods:** This is a retrospective study including 50 patients with known cancer referred for conventional (PBS) for metastatic work up. PBS was acquired followed by SPECT/CT images for the concerned area. Diagnostic performance indices from both modalities (PBS& SPECT/CT) were compared against the reference standard (clinical/imaging follow-up). **Results:** A total of 50 known cancer patients were included in this study (37 females, 13 males) with median age 64 years (range: 15-79). The sensitivity, specificity, and accuracy for SPECT/CT in identification of extra-osseous lesions all were 100% compared to 28%, 72% and 44% respectively for PBS. Uncertain lesions decreased from 38% to 0% by adding SPECT/CT.

Only 10% of lesions showed calcium deposition, while the rest had other causes for extra-skeletal uptake. **Conclusion:** SPECT/CT enhances the diagnostic accuracy of planar bone scan for characterizations of extra-skeletal lesions that mimic osseous metastasis thus significantly impact patient's management.

Key Words: SPECT/CT, bone scan, extra-skeletal, uncertain, extra-osseous lesions.

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INTRODUCTION

Extra-skeletal uptake in known cancer patients could be a problematic if it mimics metastatic osseous lesions. Extra-skeletal uptake on bone scintigraphy can occur due to different causes including traumatic, inflammatory, neoplastic, infarction, excretory, and iatrogenic [(1-5)]. Understanding the mechanism of extra-skeletal uptake is of great value in identification and recognizing these uncertain lesions thus resulting in accurate interpretation and diagnosis. Diagnosis of extra-osseous lesions is really a challenge when planar bone scintigraphy used alone.

The diagnostic accuracy of planar bone scintigraphy (PBS) increases by adding SPECT/CT imaging for these lesions [(6)]. SPECT/CT is useful in characterization and anatomical localization of these uncertain lesions that might be misinterpreted as skeletal metastasis in planar bone scintigraphy leading to misdiagnosis with inaccurate management of patients and unnecessary treatment [(7, 8)].

The aim of this study was to assess the value and diagnostic performance of SPECT/CT over planar bone scintigraphy (PBS) for characterization and localization of extra-skeletal lesions, increasing the awareness to that problem thus avoiding incorrect diagnosis.

PATIENTS AND METHODS:

Patients: known cancer patients referred to our nuclear medicine unit in South Egypt Cancer Institute for metastatic work up by conventional planar bone scintigraphy from January 2014 to December 2015 were retrospectively reviewed for extra-skeletal or uncertain lesions at conventional PBS with additional SPECT/CT images acquired for the concerned area. Patients without known primary cancer were excluded from the study. Any PBS with uncertain lesion not followed by SPECT/CT images was also excluded. Because of the retrospective nature of the study, no need for written informed consent.

Imaging Protocol: 2-3 hours after IV injection of about 15-25 mCi of Tc-99m MDP, planar whole-body scintigraphy was acquired in the anterior and posterior projections. A dual-head γ-camera (Symbia T_2, Siemens Medical Solutions, Erlangen, Germany) with parallel-hole high resolution low-energy collimators using a 15% energy window set at 140 kev was used. The table speed was 12 cm/min, matrix size 256 x 1024. Immediately after PBS was acquired, planar images were reviewed if there was a probability of uncertain lesion, additional SPECT/CT for the suspected area was performed in the same day. SPECT procedure was performed using a step and shoot protocol, 25 seconds⁄ view for a total of 32 views using a noncircular orbit over 360 degrees of rotation (180ºper head) and a matrix size of 128 x128.Immediately after completing SPECT acquisition, low-dose CT study was acquired with a tube current of 70 mAs, a tube voltage of 130 kV, employing a dose-reduction algorithm (CARE Dose 4D, Siemens Medical Solutions, Erlangen, Germany).The CT dose index per volume (CTDI vol) was on average 7.6 mGy. Low dose CT (2 mm slices) used for the purpose of anatomical localization and attenuation correction. After completion of acquisition, the images were reconstructed with attenuation and scatter correction using 3D iterative algorithm (OSEM 3D Flash, Siemens Medical Solutions, Erlangen, Germany). The reconstructed attenuation-corrected SPECT /CT images were transferred to the viewing system (OsiriX MD, Pixmeo, Switzerland) for revision in axial, coronal, and sagittal planes.

Imaging analysis: all images were examined for any abnormal radiotracer uptake that could be extra-skeletal in Planar Bone Scintigraphy (PBS) and followed by SPECT/CT images. The lesions were classified into extra-osseous, uncertain (lesions with indefinite location) and intra-osseous. The criteria for classifying the lesion as extra-osseous were that the lesion is located outside the skeletal region and not considered as a physiological uptake. The criterion for considering the lesion as intra-osseous is that the lesion located over the usual site of a skeletal area. And in between extra and intra-osseous lesions there were uncertain lesions that couldn't be categorized into extra or intra-osseous. A finding was considered as **negative** if the lesion was intra-osseous (skeletal lesion) and **positive** if it was extra-osseous. During analysis lesions with uncertain location were categorized to the negative side. A lesion was considered true-positive if the lesion is diagnosed as extra-osseous by PBS or SPECT/CT and proved to be extra-skeletal in final diagnosis.

A finding was considered true-negative if the lesion was intra-osseous or uncertain in PBS or SPECT/CT and proved to be skeletal lesion. SPECT/CT images were evaluated for presence or absence of **calcification** in each lesion.

Statistical analysis: collected data was entered in excel data sheet and was analyzed by SPSS software. Continuous data was described as means ±standard deviations (SD). Categorial data was described as frequencies (%) and proportion. Value <0.05 was considered as statistically significant. The diagnostic performances of SPECT/CT for locating Tc-99m MDP uptake in extra-osseous site were calculated and compared to PBS.

RESULTS:

A total of 50 patients (13 male & 37 females) with median age 64 years (range: 15-79) were included in this study. Patients' characteristics were summarized in ***Table (1)***.

Table (1): Patients' characteristics.

Characteristic	Results
Age "years"	
Mean ± SD	53.8±13.38
Median (range)	64 (15-79)
Gender:	
Female	37
Male	13
primary cancer:	
Breast cancer	31(62%)
UB cancer	8 (16%)
Lung	3 (6%)
GIT	2 (4%)
Prostate	1(2%)
Others	5 (10%)
Total	50 (100%)

Extra-skeletal activity was confirmed in **32** patients (64%) and intra-osseous lesions in **18** patients (36%). Lesions were classified by **planar bone scintigraphy (PBS)** into 34% (17/50) ***intra-osseous*** lesions, 38% (19/50) lesions with ***uncertain*** location and 28% (14/50) ***extra-osseous*** lesions [4 lesions in breast, 3 in chest, 2 in stomach, 2 in thyroid, 1 kidney, 1 in pelvis and 1 in the head]. Although PBS detected 14 extra-osseous lesions, only 9 of them were true and 5 lesions were incorrectly diagnosed (false positive). **SPECT/CT** reclassified lesions into 64% (32/50) ***extra-osseous*** lesions and 36% (18/50) ***intra-osseous*** lesions. Lesions with ***uncertain*** location detected in PBS decreased to 0% in SPECT/CT as described in ***Table (2)***.

Table (2): PBS and SPECT/CT classification of lesions.

		Planar	SPECT/CT	Final diagnosis
Site	Intra-Osseous	17	18	18
	Uncertain	19	–	–
	Extra-osseous	14	32	32
	Total	50	50	50

SPECT/CT correctly detected **all 32 extra-osseous lesions** compared to 9 lesions only for PBS. The anatomical distributions of these extra-osseous lesions in planar bone scintigraphy and SPECT/CT with their final diagnosis were described in ***Table (3)***. Only 10% (5/50) of lesions showed calcification in SPECT/CT.

True and false results for PBS and SPECT/CT were calculated to find the diagnostic indices for each modality using final diagnosis as a reference. Agreement between PBS and SPECT/CT in detection of lesions was described by the cross tabulation of true and false results between them. They agreed in 9 TP lesions and 13 TN, while disagreed in 23 and 5 lesions considered by PBS as FN and FP respectively as shown in ***Table (4)***. Sensitivity, specificity and accuracy for SPECT/CT were all 100% compared to 28%, 72% and 44% respectively for PBS.

Normally nonspecific bilateral symmetrical uptake occurs in both breasts. Unilateral focal breast uptake is suspicious and most probably due to primary breast cancer as shown in ***Figure (1)***.

Accumulation of Tc-99m MDP also occurs in benign tumors with internal calcifications, such as a calcified meningioma which could be misinterpreted as a skull lesion as shown in ***Figure (2)***.

Sometimes metastatic enlarged lymph nodes show necrosis with secondary calcium deposition. This lesion mimics a metastatic osseous lesion in PBS. SPECT/CT can help in localization and characterization of these lesions excluding bone metastasis in such cases as in ***Figure (3)***.

Also ectopic kidney may be confused with pelvic skeletal metastasis as shown in ***Figure (4)***.

Table (3): PBS and SPECT/CT anatomical locations of all detected extra-skeletal lesions.

No	Clinical diagnosis	planar	SPECT/CT		Final diagnosis
	Cancer type	site	site	*calcification*	
1	GIT	uncertain	Peritoneum	*yes*	*metastatic peritoneal nodules*
2	Rt. Breast	Rt, shoulder	tendon	_	*tendinitis in shoulder*
3	Lt Breast	RT. femur	contamination	_	*contamination*
4	Urinary Bladder	sacrum	kidney	_	*pelvic kidney*
5	Prostate Cancer	skull	subcutaneous lesion	–	*subcutaneous lesion*
6	RT. Breast	sacrum	adnexa	_	*adnexa*
7	LT. Breast	Lt. breast	Lt. breast	_	*Breast cancer*
8	Medullary ca.	sinusitis	Maxillary sinus	_	*sinusitis*
9	Urinary Bladder	uncertain	colon	_	*colon*
10	Stomach	uncertain	bladder	_	*bladder*
11	RT. Breast	uncertain	Frontal sinus	_	*Sinusitis*
12	LT. Breast	uncertain	kidney	_	kidney
13	Suprarenal	uncertain	Para-aortic LN	–	*Para aortic LN metastasis*
14	Urinary Bladder	uncertain	colon	_	Colonic activity
15	Lung cancer	uncertain	lung	_	*Lung cancer*
16	RT. Breast	skull	brain	*yes*	*Calcified meningioma*
17	RT. Breast	uncertain	Bone marrow	*yes*	*Bone marrow infarction*
18	RT. Breast	stomach	stomach	_	gastritis

19	Urinary Bladder	uncertain	contamination	_	contamination
20	RT. Breast	uncertain	contamination	_	*contamination*
21	RT. Breast	uncertain	adnexa	_	*adnexa*
22	LT. Breast	uncertain	Subcutaneous	_	*intramuscular iron injection*
23	Urinary Bladder	uncertain	rounded calcified nodule mostly LN	*yes*	Lymph node
24	Lung Cancer	uncertain	Para hilar calcified soft tissue lesion	*yes*	*Para hilar lymph node*
25	Lung Cancer	skull	brain	_	*brain metastasis*
26	LT. Breast	stomach	stomach	_	*Free technetium*
27	Bilateral breast cancer	breast	breast	_	*breast cancer*
28	LT. Breast	breast	breast	_	*breast cancer*
29	LT. Breast	breast	breast	_	*edema*
30	Urinary Bladder	lung	lung	_	Lung cancer infiltrating ribs
31	RT. Breast	kidney	kidney	_	left renal mass
32	Endometrial carcinoma	uncertain	uterus	_	*Endometrial carcinoma*
33	LT. Breast	[1]Thyroid uptake	Mid cervical vertebral lesion	_	*Intraosseous*
34	Bilateral Breast	pelvi-calyceal uptake	Rib lesion	_	*Intraosseous*
35	RT. Breast	Uptake in Port-A-Cath	Rib lesion		*Intraosseous*
36	RT. Breast	Thyroid uptake	Mid cervical vertebral lesion	_	*Intraosseous*
37	RT. Breast	Pelvic mass	lytic lesion in lumber vertebrae	_	*Intraosseous*

Table 4: Cross tabulation of true and false results from planar and SPECT/CT.

Modality	**SPECT/CT**			
Planar	**Result**	**TP**	**TN**	**Total**
	TP	9	0	9
	TN	0	13	13
	FP	0	5	5
	FN	23	0	23
	total	32	18	50

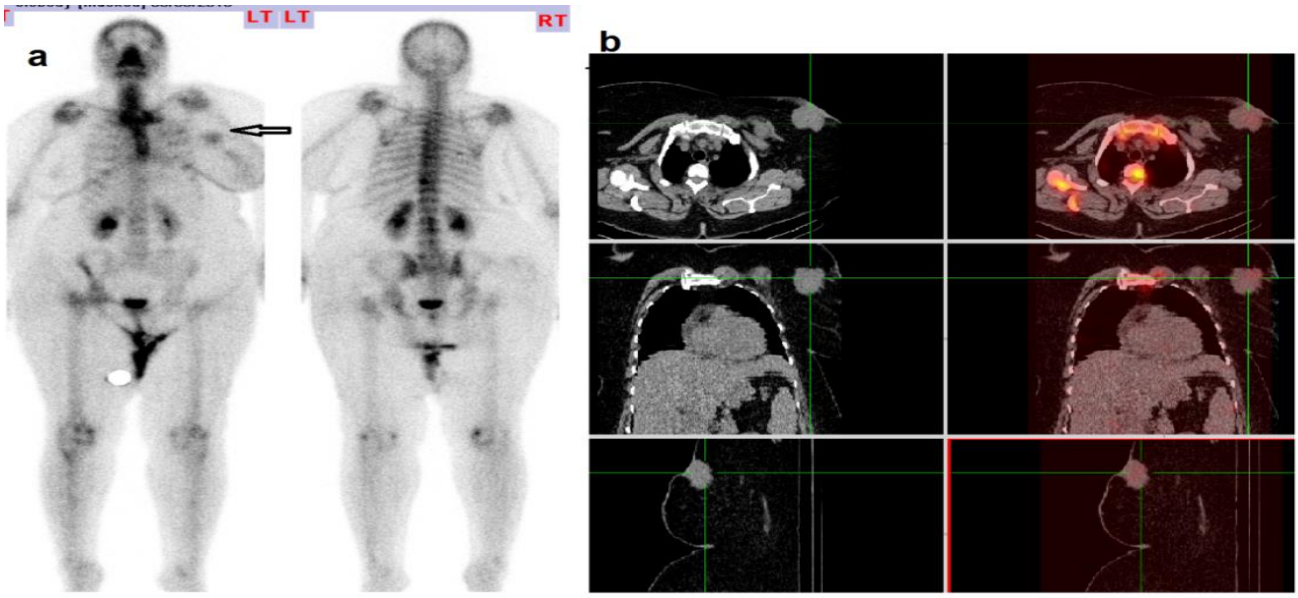

Figure (1): A 55-year-old female with left breast cancer referred for metastatic work up a) PBS showed focal radiotracer uptake in the left breast, b) SPECT/CT images showed left breast avid irregular soft tissue density matched with primary breast cancer.

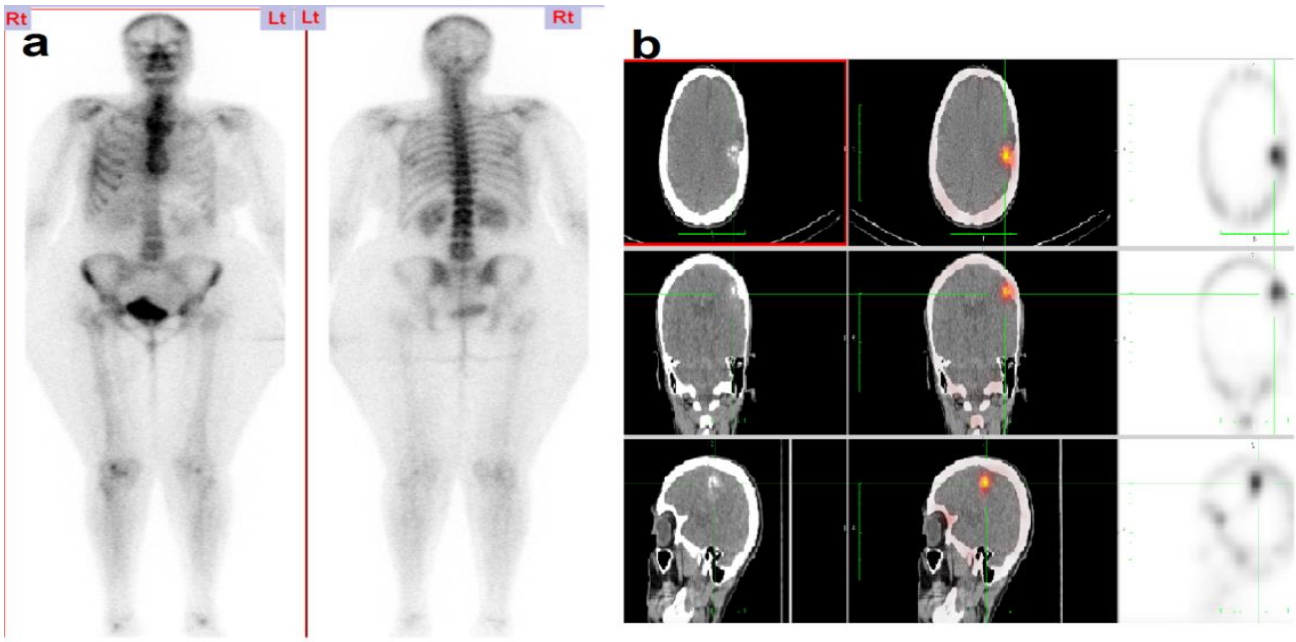

Figure (2): A 57-year-old female with right breast underwent MRM, a) PBS showed focal increased tracer uptake in left parietal region of skull b) SPECT/CT images showed brain soft tissue lesion with calcification proved to be calcified meningioma.

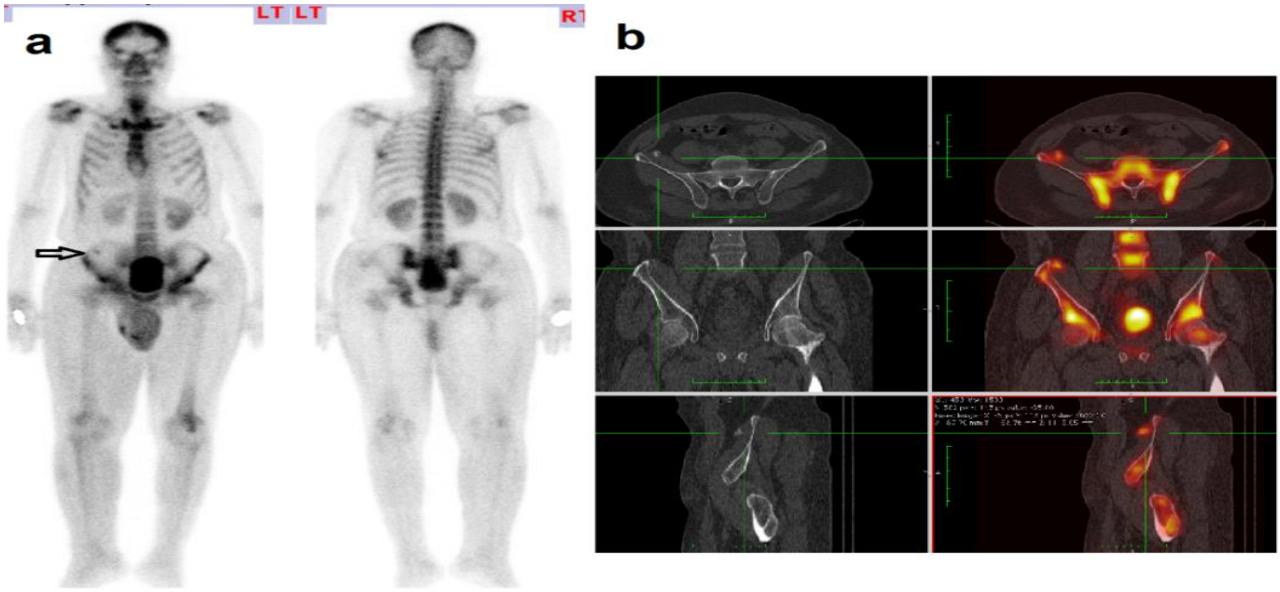

Figure (3): A 41-year-old male with UB cancer a) PBS showed small focal tracer uptake at right iliac bone that seems to be bone metastasis, b) SPECT/CT images showed rounded calcified nodule mostly metastatic LN.

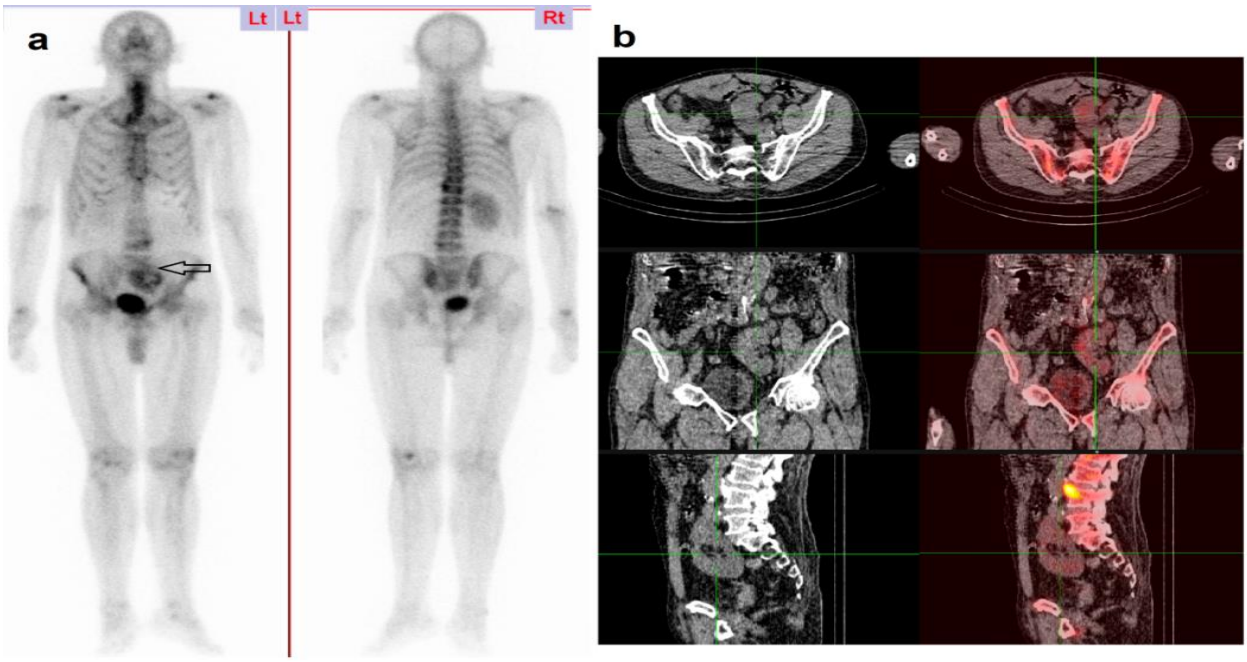

Figure (4): A 73-year-old male with UB cancer a) PBS showed heterogeneous radiotracer uptake in the pelvis that mimics metastatic osseous lesion, b) SPECT/CT images showed ectopic pelvic kidney.

DISCUSSION:

Confirmation or exclusion of bone metastasis in known cancer patients is of great value in patient's management [9]. Diagnosis of extra-osseous lesions is really a challenge when planar bone scintigraphy used alone due to inappropriate localization of the lesion leading to misinterpretation and inaccurate diagnosis [10]. Adding SPECT/CT images to the site of concern decreases the false results by its precise localization and proper characterization of these lesions [7]. Also understanding the pathophysiology and the mechanism of extra-osseous uptake can contribute to accurate diagnosis of such cases preventing unnecessary treatment to patients. To the best of our knowledge few studies compared the diagnostic performances between planar and SPECT/CT in discrimination of extra-skeletal activity. In our study sensitivity, specificity and accuracy of SPECT/CT in detection of extra-skeletal activity were all 100% compared to 28%, 72% and 44% for PBS which agreed with Zhang et al, in which SPECT/CT accuracy was 100% compared to 35% for PBS. Uncertain lesions decreased from 38% (19/50) lesions to 0% (0/50) lesion by adding SPECT/CT. Therefore, SPECT/CT decreased the uncertainty of lesions to great extent by precise localization and excellent characterization of these lesions, this result comes in agreement with other studies [1,7,11,12].

In the present study only 10% (5/50) of the lesions had calcium deposition which means that not only calcification was the cause of extra-skeletal uptake but also there were other causes for extra-skeletal activity such as inflammation with increased vascularity, hairy like calcification in primary tumors which is not visible in CT images, mucinous type of tumors with glycoproteins contents that bind to calcium salts thus accumulating Tc-99m MDP, urine contamination and ectopic kidney[11, 13].

Normally nonspecific bilateral symmetrical uptake occurs in both breasts. Unilateral focal breast uptake is suspicious and most probably due to primary breast cancer. The exact mechanism is still unknown, but many factors are supposed to be the cause. Calcium deposition and increased tumor vascularity, both are two important causes in tracer accumulation in primary breast cancer. In addition to, adenocarcinomas of the lung, breast, gastrointestinal tract which have a mucinous component possess a glycoprotein which is similar to ossifying cartilage. Glycoprotein in turn binds to calcium salts and accumulates Tc-99m MDP [6].

Benign tumors accumulate Tc-99m MDP due to internal calcifications, such as (calcified meningioma, fibroma, etc.) which could be misinterpreted as metastatic osseous lesions [5, 6].

Sometimes metastatic enlarged lymph nodes show necrosis with secondary calcium deposition. This lesion mimics a metastatic osseous lesion in PBS. SPECT/CT can help in localization and characterization of these lesions excluding bone metastasis in such cases. Also ectopic kidney may be confused with pelvic skeletal metastasis. Good clinical history with non-visualized kidney in its normal position can help in diagnosis. Adding SPECT/CT can easily resolve this problem. Inflammation with increased blood flow and intramuscular injection of iron are also other causes for extra-skeletal activity [1,6].

This study has few limitations. First, the sample size of patients was small. Second, excluding many planar scans with suspected extra-osseous lesions that not followed by SPECT/CT images may results in underestimation of the actual rate of extra-osseous lesions. Finally, although retrospective nature may allow much more time for patients follow up, therefore confirmation of lesions nature, the exact mechanism of extra-skeletal uptake in some cases may remain unknown.

Further prospective studies assessing this issue to detect exact rate of extra-skeletal abnormalities are recommended.

CONCLUSIONS:

Extra-skeletal Tc-99m MDP uptake is not uncommon and can be misinterpreted as a skeletal lesion in patients with known cancer when PBS used alone. Adding SPECT/CT images increases the diagnostic accuracy of PBS by its precise anatomical localization and good characterization of this extra-skeletal uptake. SPECT/CT can alter patient's management by preventing misdiagnosis and avoiding unnecessary treatment.

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