Original Article

1. Value of C-11 Methionine Whole Body PET Imaging in the Diagnosis of Skeletal Metastases

Abd-Elrazek Sh.[1], Yoshikawa K.[2], Hasebe M.[2], Ohashi S.[2], Ishikawa H.[2], Sagou K.[2], Tamura K.[2], Tanimoto K.[2], Kandatsu S.[2], Saga T.[2], Suzuki K.[2], Tsujii H.[2], and Wagih Sh[3].

Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University, Egypt [1]. The Clinical Diagnosis Section, Research Center Hospital for Charged Particle Therapy, National Institute of Radiological Sciences, Chiba, Japan [2]. Nuclear medicine unit, King Abdulla Medical city, oncology center, Jeddah, KSA[3].

ABSTRACT:

Introduction: There is an increasing clinical interest in imaging tumors' protein metabolism through PET studies using radiolabeled amino acids, and one of the most commonly used tracer in this regard is C-11 methionine. The latter was recently employed successfully for diagnosis and assessment of treatment response in some tumors. The aim of the current study is to assess the value of 11 C-Methionine (MET) in the diagnosis of skeletal metastases. **Patients and methods:** Over approximately 12 years in our institute (1994-2006), 8041 patients performed static MET PET scans for local assessment of tumor response to carbon ion radiotherapy (CIRT) in addition to whole body (WB) images without attenuation correction. Out of these patients, 254 cancer patients had reported areas of abnormal skeletal MET uptake on WB images. Sixty studies were only included because of available follow up with conventional imaging modalities (CIM), as the reference standard, for final diagnosis of the bony lesions whether metastatic or not. All suspected skeletal areas were counted and differentiated, according to the degree of uptake whether low, moderate or intense and reported as having low, equivocal or high metastatic possibility respectively. **Results:** 77 bony areas of abnormal MET accumulation were reported, out of them 14 were diagnosed to be metastatic in nature (18.2%), while the remaining 63 (81.8%) diagnosed as benign osseous lesions. Low, equivocal or high metastatic possibilities were encountered in 58, 7 and 12 osseous sites respectively. Diagnosis of metastases was confirmed in 1 out of 58 (1.7%), 2 out of 7 (28.6%) and 11 out of 12 (91.7%) sites with low, equivocal and intense tracer uptake respectively. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of MET- PET- WB study in diagnosis of

osseous deposits were 78.6%, 98.4%, 91.7%, 95.4 % and 94.8% respectively when equivocal lesions are included in the low possibility category. These figures were 68.4%, 98.3%, 92.9%, 90.5% and 90.9% respectively if equivocal lesions were included in the high possibility category of being metastatic.

Conclusion: MET PET WB imaging is an accurate tool in the diagnosis of skeletal metastatic lesions in various malignancies. Higher diagnostic accuracy is found when only lesions with high degree of tracer uptake are considered metastatic.

Key wards: WB MET PET in bone metastasis

Corresponding Author: Dr. Sherif Abd-Elrazek **Email;** sherif400m@yahoo.com

INTRODUCTION:

Bone metastases are the most common malignant bone tumor. Skeletal involvement occurs in 30%–70% of all cancer patients, with breast cancer being the leading cause for bone metastases in women and prostate cancer in men, followed by lung cancer [1, 2]. Patients can have osteolytic, osteoblastic, or mixed lesions containing both elements[3], and the diagnosis of bone metastases is essential for proper staging and optimal therapy[2,4].Bone scan (BS) is the most commonly used modality for detection of bone metastases because it is widely available and provides an entire skeletal visualization within a reasonable amount of time and cost[2,5]. It has been estimated that BS can detect malignant bone lesions 2–18 months earlier than x-ray[1]. However, bone scan is now used less often and is not considered routine in all cases of breast or prostate cancer, where its use is now restricted to higher-risk groups [6, 7].In the last two decades positron emission tomography (PET) and PET/CT had a lot of important and innovative clinical applications in oncology[8,9]. Using various PET tracers, functional changes occurring in the bone marrow and bone as a result of malignant infiltration may precede the structural changes required to identify the presence of malignant bone involvement by morphologic imaging modalities[8,10]. The most common PET tracers that are clinically used for assessment of malignant bone involvement are ^{18}F-fluoride and ^{18}F-FDG[2].^{18}F-fluoride PET seems to be more sensitive than conventional BS for the diagnosis of osteolytic bone metastasis[11]; yet,^{18}F-FDG PET assessment has the advantage of detecting both soft-tissue and skeletal disease[8,10]. Estimates of the sensitivity of ^{18}F-FDG PET for detecting bone metastases range between 62% and 100% and the specificity ranges between 96% and 100%[5].There is increasing clinical interest in protein metabolism imaging with PET through the use of radiolabeled amino acids[13], and the most frequently used

radiolabeled amino acid is Methionine (MET)[14]. MET uptake reflects increased amino acid transport and, in part, protein synthesis; and is related to cellular proliferative activity[15-17]. In cancer, methionine uptake also is correlated with the amount of viable tumor tissue [18, 19], and MET-PET imaging could allow for targeting the tumor tissue with the highest metabolic activity[20]. As regard to normal MET distribution, low-grade uptake of MET is seen in the brain, while somewhat higher uptake is seen in salivary glands, the lacrimal glands, bone marrow and occasionally in the myocardium. Abdominal uptake in the liver and the pancreas can frequently be seen.

Carbon ion radiotherapy (CIRT) enables giving safe effective dose of radiation to bulky primary cancer without causing damage to normal tissues[21]. MET PET is performed before and after therapy for evaluation of the local therapeutic effect on the primary tumor, however, some of these studies may show unusual MET uptake involving skeletal areas which might represent normal variants, tracer uptake in benign osseous lesions or metastatic bone deposits. The aim of the current study is to evaluate the role of WB MET PET imaging in the detection of skeletal metastatic lesions in different malignancies.

PATIENTS AND METHODS:

In this retrospective study, we searched among 8041 studies done with ^{11}C-Methionine for different oncologic patients examined in the period from 6/1994 to 12/2006 in the National Institute of Radiological Sciences (NIRS), Japan. Using computer search, 254 studies were found with reported areas of questionable skeletal Methionine uptake.

Sixty MET PET studies were included in the current study because of the following inclusion criteria:

1) All studies showed reported one or more areas of abnormal skeletal uptake of MET.

2)All patients had available conventional imaging modalities (CIM) for follow-up (as bone scan and/or CT scan), as the reference standard, for confirmation of the detected osseous lesions with extended follow up period up to more than 2 years post MET study, with all osseous lesions diagnosed finally by the treating oncologist whether metastatic or non-metastatic.

3) When only CT was available for confirmation of metastatic nature of the detected areas, the case was included only when the field of the CT scan covered all suspected bone areas detected in the MET study. In 9 cases, both bone and CT scans were available for follow-up and confirmation of the results. In 34 cases, only bone scans were available for follow-up, while in 17 cases only CT scans were available for confirmation. Follow-up CT scans were interpreted by experienced diagnostic radiologist. With follow-up bone scan, the presence of bone metastasis was established based on characteristic late bone scan findings or

subsequent lesion progression on follow-up scans. Mean follow up period was 21.8 months ±16.4 and 26.5 ±19.8 months for bone scan and CT scan respectively. Patients were 49 males and 11 females with age range of 45-86 years (mean; 71.6). Lung cancer was the commonest primary lesion in our group of patients, found in 42 patients representing 70 % of all patients (table1)

Table 1; Pathology of the primary tumor in 60 cases.

Primary tumor	Number of cases
Lung cancer	42
Malignant melanoma	4
Rectal cancer	4
Colon cancer	1
Vertebral sarcoma	1
Hypopharyngeal carcinoma	1
Gingival carcinoma	1
Nasal papillary adenocarcinoma	1
Prostate cancer	1
Renal carcinoma	1
Chordoma	1
Thyroid carcinoma	1
Tongue cancer	1
Nasal cavity cancer	1
Total	60

WB PET imaging protocol:

Whole-body scanners (ECAT EXACT HR+ and ECAT EXACT 47; Siemens CTI, Knoxville, Tenn.) were used providing an axial field of view of 15.5 and 16.2 cm, resulting in 63 and 47 transverse slices with a thickness of 2.5 and 3.4 mm, respectively. Emission data corrected for random events and dead time were reconstructed by filtered back projection using a ramp filter with a cutoff frequency of 0.4.

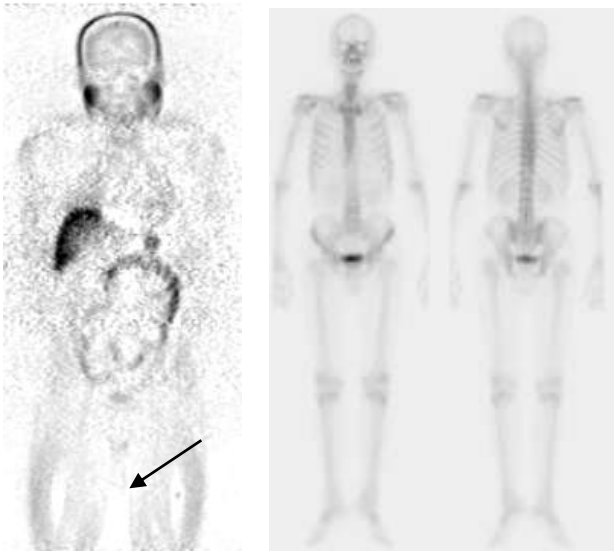
Mean dose of ^{11}C-Methionine was 714 ± 74 MBq (19.3 ± 2.0 mCi). All MET PET studies were performed with the primary intension of evaluation of the local therapeutic effect of carbon-ion radiotherapy (CIRT) on the primary tumor. Therefore the ideal imaging time in MET- PET study (about 20 minutes after injection) was reserved for local static imaging of the therapy field. WB-PET scanning was also been performed to get the advantage of WB survey for possible metastatic lesions. Whole body images were performed before static imaging (about 5 minutes after injection) and continued for about 10-11 minutes (9-10 bed positions with 68 seconds/bed position).

Image interpretation and findings evaluation:

The available WB ^{11}C-methionine PET images without AC with report stating presence of active bony lesions of variable intensity were selected and re-analyzed. The numbers of bony lesions were counted and each lesion was evaluated depending on degree and pattern of MET uptake. Uptake degree was judged by inspection in comparison to the contralateral normal bone and background tissue uptake by three experienced nuclear medicine physicians. For vertebral lesions, the comparison was made with the nearest normal vertebra. Based on the inherent assumption of higher degree of MET uptake in areas with more viable tumor tissue, the detected lesions were divided according to 3-point scale as those with low, moderate, and intense tracer uptake pattern, and were interpreted as low possibility (considered benign uptake lesion, figure1), equivocal (either benign or malignant, figure2), and high possibility (metastatic, figure 3) lesions respectively, table 2.

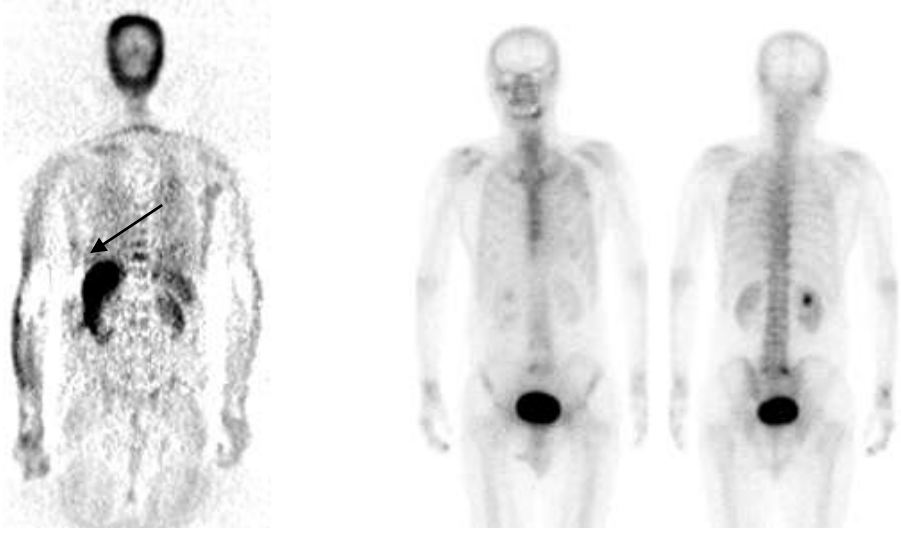
Table 2: Qualitative criteria for scan interpretation and metastatic possibility.

Metastatic Possibility	Criteria in comparison to contralateral normal bone and background tissue uptake
Low possibility	Skeletal lesion showing faint tracer uptake pattern
Equivocal	Skeletal lesion showing moderate tracer uptake pattern.
High possibility	Skeletal lesion showing intense tracer uptake pattern



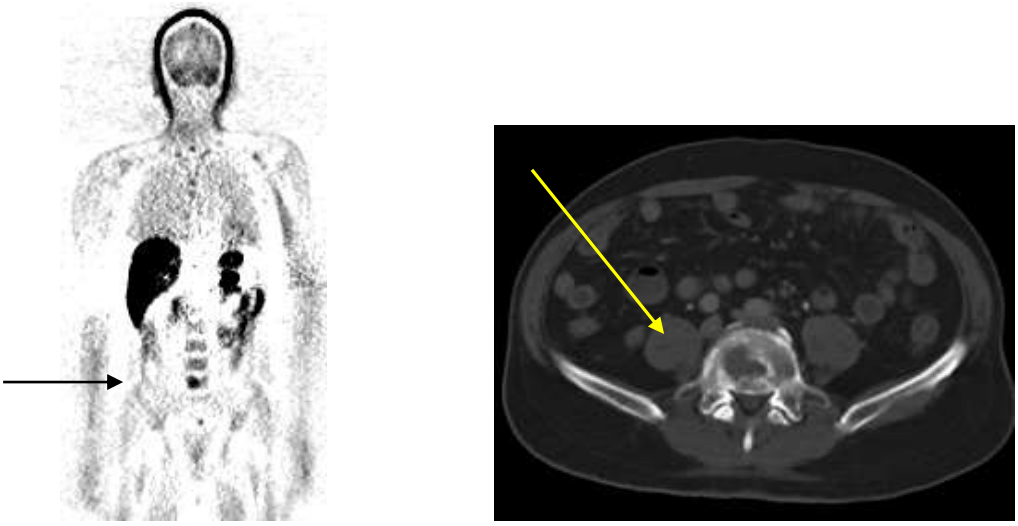
A **B**

Figure 1: Male patient 55 years old with choroidal melanoma. A) WB MET PET images showed low possibility lesion at upper part of left femur. B) Anterior and posterior WB images of follow up bone scan (3.2 months apart) was negative.



A **B**

Figure 2: Male patient 76 years old with lung cancer; **A)** WB PET images show an equivocal lesion at lower dorsal spine. **B)** Follow up Bone Scan (ant. and post. WB images) up to 35.6 months was negative.



A **B**

Figure 3: A case of thyroid carcinoma; **A)** WB MET PET images showed high possibility lesion at 5th lumbar vertebra. **B)** Follow up CT showed predominately osteolytic metastatic bone lesion.

Statistical analysis:

Statistical analysis was performed on a lesion basis. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were determined for the value of MET PET WB in the diagnosis of metastatic skeletal metastases. These values were measured once with equivocal osseous lesions considered as metastatic and in the second time, these values were calculated with equivocal lesions considered metastatic. Statistical analysis was done using SPSS version[13].

RESULTS:

The total number of skeletal sites enumerated with variable degree of enhanced MET uptake on WB MET PET images of the 60 cases was 77 bone areas, the majority of which were located in the axial skeleton. Out of these 77 bone sites, 14 were diagnosed as metastatic by CIM and clinical follow up representing 18.2% of all lesions, while the remaining 63 areas were diagnosed as benign (81.8%).

Low, equivocal and high possibility lesions reported in 58, 7 and 12 osseous lesions respectively, out of them one (1.7%), 2 (28.6%) and 11 (91.7%) lesions were diagnosed and treated as being metastatic respectively (table 3). It was clearly evident that the higher the degree of MET uptake the higher the possibility for the suspected lesion to be metastatic in nature. WB MET PET images clearly identified two bone lesions with predominantly osteolytic nature (one case is presented in figure3).

Table 3; final diagnosis of the high, equivocal and low metastatic possibility lesion

Metastatic possibility	Number	Number of lesions diagnosed as metastatic	Percent
High possibility	12	11	91.7%*
Equivocal possibility	7	2	28.6%*
Low possibility	58	1	1.7%*

(* = p<0.05)

Table 4 shows all the reported anatomical sites with questionable MET uptake in correlation to their metastatic possibility together with the data of the final diagnosis done by the treating physician according to CIM follow up results.

Table (4): Different possibilities and final diagnosis of detected osseous lesions in relation to anatomical sites.

Skeletal site	Metastatic possibility			Total	Metastatic	Non metastatic
	Low possibility	Equivocal	High possibility			
Shoulder joint	5	2	1 (1)	8	1	7
Clavicle	2	1	0	3	--	3
Sterno-clavicular joint	2	0	0	2	--	2
Sternum	0	1 (1)	0	1	1	--
Humerus	0	0	1	1	--	1
Rib	16	0	0	16	--	16
Costovertebral junction	0	0	1 (1)	1	1	--
Cervical vertebrae	3	0	2 (2)	5	2	3
Thoracic vertebrae	8 (1)	1	1 (1)	10	2	8
Lumbar vertebrae	1	0	1 (1)	2	1	1
Sacrum	0	1	1 (1)	2	1	1
Sacroiliac joint	1	0	0	1	--	1
Ileum	7	0	3 (3)	10	3	7
Hip	1	1 (1)	1 (1)	3	2	1
Pubis	1	0	0	1	--	1
Upper Femur	11	0	0	11	--	11
Total	58 (1)	7 (2)	12 (11)	77	14	63

(Number between parentheses represents diagnosed metastatic lesions).

By considering the 7 osseous lesions with equivocal MET uptake pattern as low possibility category of being metastatic in nature, the overall low metastatic possibility was found in 65 lesions, with only 3 out of them (4.6%) were diagnosed as metastatic versus 12 lesions of high possibility of being metastatic with 11 out of them (91.7%) were diagnosed as being metastatic. On the other hand, when considering these 7 equivocal lesions as being in the metastatic category, the overall lesions with low metastatic possibility will be 58 with only one of them (1.7%) was diagnosed as metastatic versus 19 lesions of high metastatic possibility, out of them 13 were diagnosed as metastatic (68.4%). Table 5 summarizes the sensitivity, specificity, positive and negative predictive values and accuracy of WB MET images in the detection of bone metastasis in 77 bone sites of the 60 cases. Higher accuracy (94.8%) was obtained when equivocal category were interpreted as negative for malignancy in comparison to (90.9%) when equivocal lesions were considered malignant.

Table (5): The sensitivity, specificity, PPV, NPV and accuracy of WB MET PET in the detection of skeletal metastatic lesions in 77 bone sites of 60 MET PET studies.

	Equivocal lesions added to low metastatic possibility group	**Equivocal lesions added to high metastatic possibility group**
Sensitivity	78.6%	68.4%
Specificity	98.4%	98.3%
Positive predictive value (PPV)	91.7%	92.9%
Negative predictive value (NPV)	95.3%	90.5%
Accuracy	94.8%	90.9%

DISCUSSION:

^{99m}Tc-phosphonate–based planar skeletal scintigraphy is the standard conventional method for the initial staging of patients with malignancy, and it has been employed for many decades in variable malignancies for assessment of metastatic osseous deposits. However, sensitivity, specificity and delineation of anatomical details of conventional bone scanning are limited. It also has the disadvantage of depicting bone metastases at a relatively advanced stage of tumor infiltration when osteoblastic host reaction to tumor deposits has already occurred [(23)].

In adults, the sensitivity of skeletal scintigraphy in detection of bone metastases was reported to be about 62–89%[(24,25)]. Gayed et al, 2003[(26)] reported sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 81%, 78%, 34% and 93% respectively. Lavely et al in 2006[(27)] reported planar bone scan sensitivity, specificity and accuracy of 66.7%, 91.4% and 79.1 % for conventional bone scanning in diagnosis of metastatic osseous lesions.

Alternative screening modalities, such as conventional radiography and CT, for the detection of early bone metastases have been also employed, yet, they appeared to be less sensitive than skeletal scintigraphy[(28, 29).]

C-11 methionine has been used to monitor amino acid metabolism in malignant lesions, and was employed successfully in tumor diagnosis and in assessment of response to therapy in various malignancies. Lindholm et al in 2009 [(30)] reported that MET PET may be useful in assessing the early response to therapy in advanced breast cancer. Also, Tamura et al in 2009 [(31)] stated that MET PET is an alternative tool for evaluating the response to radiotherapy in patients with choroidal melanoma. Nunez et al, 2002 [(22)] in his study on 12 patients with cancer prostate had concluded that whole-body ^{11}C-methionine PET is a feasible imaging

technique that detects significantly more bone and soft tissue lesions than ^{18}F-FDG PET. These encouraging data about the value of C-11 Methionine in malignant disorders raise the idea of the current study for retrospective data analysis to assess the value of C-11 Methionine in the detection and evaluation of bone metastases.

The previously reported positive results of MET PET with its significant value in assessment of malignant lesions goes in agreement with the results of the current study with sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 78.6%, 98.4%, 91.7%, 95.3% and 94.8% respectively in the detection of skeletal metastatic deposits. So, MET PET has higher PPV, NPV and accuracy compared to those previously reported for planar bone scanning suggesting a potential effective role of MET in the detection and evaluation of skeletal metastasis in various oncological patients.

In a trail to assess possible role of amino acid tracers in diagnosis of osseous metastases, Fuccio et al 2010 [(24)] studied 25 patients with cancer prostate with single equivocal osseous lesion in conventional bone scanning. They reported that PET/CT using C-11 Choline could provide more information especially in the detection of additional metastases. In 11 patients (44%), PET/CT detected more lesions with 9 cases out of them had more osseous metastatic lesions with or without soft tissue involvement. Six patients were negative on PET/CT, 3 of them (50%) had osteoblastic metastatic lesion on conventional imaging while the remaining 3 patients proved to have degenerative benign osseous lesions. The overall sensitivity and specificity were 86% and 100% respectively with an overall accuracy of 88%. These figures are higher than sensitivity and specificity in the current study, yet, the overall accuracy is lower than the 94.8% figure found in our study. Their use of less number of patients together with minimizing false positive results by CT component, which was not employed in our study, may be responsible for these differences.

As the use of ^{11}C-Methionine in the detection of skeletal metastatic lesions is still under investigation, so it is important to differentiate between metastatic pattern of its uptake from normal variants and other causes of false-positive interpretations. Iohashi K, et al 2013[(25)] reported high MET uptake in liver and pancreas with moderate degree of uptake in bone marrow. Also, it is reported that bone marrow uptake of MET can be quite focal at the medial tips of the clavicles [(26)]. Taking into consideration the fact that over 90% of bone metastasis are found in the distribution of the red active marrow [(2)], this normal bone marrow uptake of MET should be of particular concern when evaluating suspected osseous areas so as to differentiate normal variants or physiological uptake from malignant osseous uptake. These facts suggest that relatively higher degree of methionine uptake is needed to suspect skeletal metastatic lesions. In our study analysis we tried to minimize false positive results related to this physiological distribution, by interpreting bone areas

with faint uptake of MET (whether focal or diffuse) as low possibility (non-metastatic).A well-known relative limitation of bone scintigraphy is the possibility of false negative results in predominantly osteolytic bone metastases. Lavely et al in 2006[23] reported, as per lesion analysis, sensitivity for lytic and mixed lesions using PET/CT of 100% and 99% respectively. These figures for bone scan were significantly lower, found to be 14.9%, and 20.8% respectively, keeping with the limited value of conventional bone scanning in diagnosis of lytic lesions. In the current study, two patients had a predominantly osteolytic metastatic bone lesion and showed avid MET uptake. The osteolytic nature was evident on the follow up CT scan. This indicates that osteolytic bone lesions can be clearly visible with MET WB PET imaging which can be expected because MET uptake is related to tumor cellular proliferation activity, while in bone scan, the uptake is related to the degree of osteoblastic activity around the tumor tissue. The ability to detect pure lytic lesions by MET PET gives an additional advantage to this imaging tool. Further studies on more lytic osseous metastases are advisable to assess its actual sensitivity, specificity and accuracy in detection of these lesions.

Isohashi et al, 2013[25] favored the initiation of scanning 20 minutes post administration of MET, to ensure that MET uptake reaches plateau in various important organs. Unfortunately, in the current study, the ideal imaging time (about 20 minutes after injection) was reserved for static imaging dedicated for local evaluation of the effect of CIRT on the primary tumor. Taking the additional advantage of WB imaging for detection of other lesions was therefore performed at a non-ideal imaging time (about 5 minutes after injection) with subsequently higher background activity leading to relatively diminished image quality. This may affect the uptake pattern in the lesions with subsequent impact on scan interpretation and results in our study. Otherwise, it is recommended to start WB MET imaging at the optimum time (20 min post administration of MET), which may result in better figures for detection of skeletal metastases. In addition, most modern PET/CT scanners are now capable of performing high quality WB imaging within reasonable time.

CONCLUSIONS:

In addition to its main purpose for imaging in assessment of the primary tumors and soft tissue metastases, our study findings suggested that WB PET imaging with MET can also be a potentially valuable tool for diagnosis of skeletal metastases with high PPV, NPV and accuracy.

REFERENCES:

1. **Padhani A, Husband J. Bone metastases.** In: Husband JES, Reznek RH, eds. Imaging in Oncology. Oxford, U.K.: Isis Medical Media Ltd.;:765–787. 1998.
2. **Even-Sapir E.** Imaging of Malignant Bone Involvement by Morphologic, Scintigraphic, and Hybrid Modalities. J Nucl Med; 46:1356–1367, 2005.
3. **Werner Langsteger, Martin Heinisch, and Ignac Fogelman:** The Role of Fluorodeoxyglucose, 18F-Dihydroxyphenylalanine, 18F-Choline, and 18F-Fluoride in Bone Imaging with Emphasis on Prostate and Breast. Semin Nucl Med. 36:73-92, 2006.
4. **Rybak LD, Rosenthal DI.** Radiological imaging for the diagnosis of bone metastases.Q J Nucl Med.; 45: 53– 64, 2001.
5. **Hamaoka T, Madewell JE, Podoloff DA, Hortobagyi GN, Ueno NT.** Bone imaging in metastatic breast cancer. J Clin Oncol.; 22: 2942–2953; 2004.
6. **Fogelman I, Cook G, Isrel O, Van der Wall H.** Positron emission tomography and bone metastases. Semin Nucl Med; 35: 135-142; 2005.
7. **Fujimoto R, Higashi T, Nakamoto Y, Hara T, Lyshchik A, et al.** Diagnostic accuracy of bone metastasis detection in cancer patients: Comparison between bone scintigraphy and whole-body FDG-PET. Annals of Nuclear Medicine Vol. 20, No. 6, 399-408, 2006.
8. **Cook GJR, Fogelman I:** The role of positron emission tomography in the management of bone metastases. Cancer Suppl 88:2927-2933, 2000.
9. **Langsteger W, Heinisch M and Fogelman I:** The Role of Fluorodeoxyglucose, 18F-Dihydroxyphenylalanine, 18F-Choline, and 18F-Fluoride in Bone Imaging with Emphasis on Prostate and Breast. Semin Nucl Med. Jan; 36 (1): 73-92; 2006.
10. **Rohren EM, Turkington TG, Coleman RE.** Clinical applications of PET in oncology. Radiology.; 231: 305–332; 2004.
11. **Schirrmeister H, Guhlmann A, Elsner K, et al:** Sensitivity in detecting osseous lesions depends on anatomic localization: Planar bone scintigraphy versus 18F PET. J Nucl Med 40:1623-1629.
12. **Even-Sapir E, Metser U, Flusser G, et al:** Assessment of malignant skeletal disease: Initial experience with 18 F–fluoride PET/CT and Comparison between 18F–fluoride PET and 18F–fluoride PET/CT. J Nucl Med 45:272-278, 2004.
13. **Jager PL, Vaalburg W, Pruim J, et al:** Radiolabeled Amino Acids: Basic Aspects and Clinical Applications in Oncology. J Nucl Med; 42:432–445; 2001.
14. **Langstrom B, Antoni G, Gullberg P, et al.** Synthesis of L- and C-[methyl 11C]methionine. J Nucl Med.; 28: 1037–1040;1987.
15. **Schober O, Duben C, Meyer G, et al:** Nonselective transport of [11Cmethyl]- L- and D-methionine

into a malignant glioma. Eur J Nucl Med 13:103-105, 1987.

16. **Heiko Schöder, MD, and Steven M. Larson, MD.** Positron Emission Tomography for Prostate, Bladder, and Renal Cancer. Semin Nucl Med 34: 274-292; 2004.
17. **Zhang H, Yoshikawa K, Tamura K, et al.** Carbon-11-methionine positron emission tomography imaging of chordoma. Skeletal Radiol33:524-530; 2004.
18. **Heiko Schöder, MD, and Steven M. Larson, MD.** Positron Emission Tomography for Prostate, Bladder, and Renal Cancer. Semin Nucl Med 34:274-292; 2004
19. **Kubota R, Kubota K, Yamada S, et al:** Methionine uptake by tumor tissue: A microautoradiographic comparison with FDG. J Nucl Med 36:484-492, 1995.
20. **Geets X, Daisne JF, Gregoire V, Hamoir M, Lonneux M.** Role of 11-C-methionine positron emission tomography for the delineation of the tumor volume in pharyngo-laryngeal squamous cell carcinoma: comparison with FDG-PET and CT. Radiotherapy and Oncology 71, 267 –273; 2004.
21. **Zhang H, Yoshikawa K, Tamura K, et al:** 11C-Methionine Positron Emission Tomography and Survival in Patients with Bone and Soft Tissue Sarcomas Treated by Carbon Ion Radiotherapy. Clinical Cancer Research, Mar 1; 10 (5): 1764-72; 2004.
22. **Nunez R, Macapinlac HA, Yeung HW, et al:** Combined 18F-FDG and 11C-methionine PET scans in patients with newly progressive metastatic prostate cancer. J Nucl Med 43:46-55, 2002.
23. **Lavely W, Jacene H, Leal J, Zhang Z, and Wahi R.** Comparative performance of FDG PET/CT and Tc-99m bone scintigraphy for detecting and localizing bone metastases in patients with breast cancer. J Nucl Med.; 47 (Supplement1): 35P, 2006.
24. **Fuccio C, Castellucci P, Schiavina R, et al.** Role of ^{11}C-choline PET/CT in the restaging of prostate cancer patients showing a single lesion on bone scintigraphy. Ann Nucl Med; 24 (6): 485-492; 2010.
25. **Iohashi K, Shimosegawa E, Kato H, Kanai Y, Naka S, Fujino K, Watabe H, Hatazawa J.** Optimization of [11C] methionine PET study: appropriate scan timing and effect of plasma amino acid concenterations on the SUV. EJNMMI Res. Apr 15;3 (1):27. Doi: 10.1186/ 2191 -219X -3-27; 2013.
26. **Gary J.R. Cook1, 2, Michael N, et al:** Normal variants, artefacts and interpretative pitfalls in PET imaging with 18-fluoro-2-deoxyglucose and carbon-11 methionine. Eur J Nucl Med 26: 1363 –1378; 1999.