

Original Article, Oncology**Role of ^{18}F -FDG PET/CT in Malignant Pleural Mesothelioma, Initial Study****Abou-Gabal M^{*}, Taalab Kh^{**}, Abbas, T^{**} and Moustafa H^{*}****Nuclear Medicine Unit (NEMROCK), Faculty of Medicine, Cairo university,****International Medical Centre, Cairo.***ABSTRACT**

Introduction: Malignant pleural mesothelioma (MPM) is an uncommon aggressive tumor arising from mesothelial cell lining the pleura. Local regional progression remains the major cause of death. **Aim of the study:** To review the clinical role of ^{18}F -FDG PET/CT in diagnosis and staging of malignant pleural mesothelioma in comparison to CT. **Patients and methods:** A retrospective study included 21 patients who were subjected to diagnostic CT imaging and ^{18}F -FDG PET/CT with qualitative and semi quantitative assessment using standardized uptake value (SUVmax). **Results:** Twenty one patients were reviewed, 14 males (66%) and 7 females (34%). Their age ranged between 30 and 78 years with a mean of 58.2 ± 12.6 years. PET/CT and CT

alone showed the primary lesions in 19/21 patients. Two patients showed negative FDG uptake denoting successful response to chemotherapy. PET/CT detected mediastinal lymph node lesions in 6 patients versus 3 patients detected by CT alone. PET/CT identified 9 metastatic lesions compared to only 1 metastatic lesion identified by CT alone. SUVmax was above 3.5 (range=3.6-16) in the entire primary lesions (mean= 6.7 ± 4.3) and metastatic lesions. PET/CT accurately upstaged 8 cases and down staged 3 cases.

Conclusion: F-18 FDG PET/CT can be used for staging, restaging and assessment of response to therapy and follow up of patients with malignant pleural mesothelioma for detection of metastatic lesions.

Key words: Malignant pleural mesothelioma (MPM), F-18 PET/CT, CT, SUVmax.

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INTRODUCTION:

Malignant pleural mesothelioma (MPM) is an uncommon tumor. The clinical presentation of mesothelioma, especially if in early phase, is insidious and not specific. Dyspnea is the predominant symptom, chest pain related to tumor infiltration of chest wall and intercostal nerves also appears [1].

Staging, assessment of the anatomical extent of MPM, determines treatment and prognosis is mandatory for selecting the relatively few patients who are candidates for intended curative surgery by extrapleural pneumonectomy (EPP). Various imaging techniques have been utilized to stage MPM, which is difficult to evaluate radiologically because of its tendency to grow locally along tissue planes. Computed tomography (CT) and magnetic resonance imaging (MRI) are helpful in identifying the location and extent of the involved area [2].

However, these imaging techniques often fail to detect non-resectable tumor invasion in the chest wall, mediastinal structures or the diaphragm [3].

Approximately 20—30% of MPM patients have exploratory thoracotomy or pleurectomy/decortications only because the staging procedures underestimate the extent of tumor spread. Improved methods for determining resectability are thus needed in addition to standard radiological methods [4].

Combined PET/CT devices provide both the metabolic information from ^{18}F -FDG

PET and the anatomic information from CT in a single examination. As shown in some clinical scenarios, the information obtained by PET/CT appears to be more accurate in evaluating patients with known or suspected malignancies than does the information obtained from either PET or CT alone or the results obtained from combined PET and CT together [5,6].

^{18}F -FDG PET is a sensitive method for detecting, staging, and monitoring the effects of therapy of many malignancies [7].

PET appears to be a useful imaging modality for the evaluation of malignant pleural mesothelioma. It is particularly valuable for distinguishing between benign and malignant pleural processes. In MPM, preliminary data indicate that ^{18}F -FDG/PET provides important functional data for a correct staging and restaging, integrating morphological results of CT. This is important to the therapeutic approach, in order to improve prognosis [8].

The aim of this study was to review the clinical role of ^{18}F -FDG PET/CT in diagnosis and staging of malignant pleural mesothelioma and its diagnostic accuracy compared to diagnostic CT.

PATIENTS AND METHODS:

A retrospective analysis of all cases with malignant pleural mesothelioma who were referred to International Medical Center during the period from March 2009 to December 2011 to receive chemotherapy and/or radiotherapy.

This study included 21 patients (14 males and 7 females) with histopathologically proven malignant pleural mesothelioma. 19 out of 21 patients received treatment in the form of chemotherapy and/or radiotherapy. Patients were analyzed for full history taking with special emphasis on their job, place of residence and environmental condition including previous exposure to radiation or asbestoses fibers. Detailed clinical status was also recorded involving main complaint, presence of chest pain, dyspnea or features of metastatic lesions and accompanied other diseases. Clinical examination data was reviewed including assessment of the chest and general body appearance. All patients performed initial CT chest and ^{18}F -FDG PET/CT for staging or restaging.

^{18}F -FDG PET/CT imaging

PET/CT was performed on an integrated scanner (Philips; 64 slice CT) that combines both CT and PET capabilities in two sequential gantries leading to accurate co-registration of the CT and PET data.

Patients were fasting for at least 6 hours before the PET/CT study. PET images were acquired during normal breathing in the three-dimensional mode for 4 minutes per bed position 60 minutes after intravenous administration of 0.1 mCi ^{18}F -FDG /Kg. PET images are reconstructed by using standard reconstruction algorithm Ordered Subsets – Expectations Maximization (OSEM). Attenuation correction of PET images is performed by using attenuation data from the low dose CT

component of the examination; emission data are corrected for scatter, random events and dead-time losses by using the manufacturer's software. Interpretation of PET/CT scans were done independently by 2 experienced physicians blinded to the clinical situation and any disagreement was resolved by consensus. PET and fused PET/CT images were analyzed both qualitatively and semi quantitatively.

Qualitative evaluation: A visually abnormal focus of FDG uptake was defined as a focal uptake relatively higher than that of surrounding tissue with no similar activity seen in the contra lateral side of the body.

Quantitative evaluation: The intensity of FDG uptake within specific lesion is calculated by using a volume of interest over the lesion, according to the following formula: $\text{SUV}_{\text{max}} = \text{maximum measured activity in the volume of interest divided by the injected dose of } ^{18}\text{F}\text{-FDG per gram of body weight where SUV = standardized uptake value. A cutoff SUV}_{\text{max}} \text{ value } \geq 3 \text{ was considered malignant}^{[9]}$.

The CT component of the study comprises a multi-detector CT examination from the base of the skull to the upper thighs (120 mA, 140 kVp, table speed = 13.5 mm per rotation). CT images were also used for attenuation correction of the PET images.

Statistical analysis

In view of the small number of patients, descriptive statistical methods using Microsoft excel version 2010 was used.

Comparison of results of PET/CT with CT alone was done on both patients and lesions basis.

RESULTS:

Twenty one patients with histologically proven malignant pleural mesothelioma (MPM) were reviewed (18 patients were proved to have epithelioid subtype and 3 patients had sarcomatoid subtype). Their age ranged between 30 and 78 years with a mean of 58.2 ± 12.6 years. Fourteen patients had right sided mesothelioma and 7 patients had left sided lesion.

Table 1 demonstrates the characteristics and ^{18}F -FDG PET/CT results of the 21 patients with MPM included in the study.

Patients number 8 and 12 in the current study had negative ^{18}F -FDG uptake at time of performing ^{18}F -FDG PET/CT 6 weeks after last cycle of chemotherapy treatment denoting no residual malignancy and favorable response to given therapy (**Table 1, Figure 1**).

All SUVmax values in the 19 patients with positive FDG uptake were above 3.5 with a mean of 6.7 ± 4.3 (range=3.6-16). It was noted that primary lesions with higher pathologic stages showed higher values of SUVmax (Table 1).

According to ^{18}F -FDG PET/CT results, 19/21 patients showed positive FDG uptake and accurately localized primary tumor sites in 7 patients, loco-regional lesions in 4 patients and metastatic lesions in 8 patients (Table2).

Lesions with higher SUVmax were associated with other loco-regional and metastatic lesions; however, a non-significant statistical correlation was detected. **Table 2** displays the distribution of patients with different lesion sites among different ranges of SUVmax values. **Figure (2)** represents a case with positive FDG PET/CT at initial diagnosis of MPM with bone metastases.

Both CT chest and ^{18}F -FDG PET/CT were concordant in detecting all the primary lesions in the positive 19 patients. In addition, ^{18}F -FDG PET/CT detected six mediastinal LN lesions and nine metastatic lesions compared to only three LN lesions and only one metastatic lesion detected by the CT alone.

Accordingly, restaging of 11/19 patients after ^{18}F -FDG PET/CT showed upstaging in 8/19 patients (42%) and down-staging in the other 3/19 patients (16%).

Table (1) Patients' characteristics and ¹⁸F-FDG PET/CT results in 21 patients with malignant pleural mesothelioma.

Patient no.	Gender	Age	Histo-pathological subtype	Stage	Treatment	¹⁸ F-FDG PET/CT result	SUVmax
1	F	65	Epithelial	II	Non	+	8
2	F	46	Sarcomatoid	IV	Chemotherapy	+	7
3	F	62	Epithelial	II	Chemotherapy	+	5
4	F	61	Epithelial	I	Chemotherapy	+	9.9
5	F	32	Epithelial	I	Chemotherapy	+	5.5
6	F	66	Epithelial	I	Non	+	8
7	F	71	Epithelial	IV	Chemotherapy	+	16
8	M	66	Epithelial	I	Chemotherapy	-	-
9	M	42	Epithelial	I	Radio-Chemotherapy	+	4
10	M	69	Epithelial	I	Chemotherapy	+	4
11	M	62	Sarcomatoid	II	Chemotherapy	+	3.7
12	M	51	Epithelial	I	Chemotherapy	-	-
13	M	78	Epithelial	II	Chemotherapy	+	3.6
14	M	67	Epithelial	IV	Radiotherapy	+	7.3
15	M	58	Epithelial	IV	Chemotherapy	+	9
16	M	54	Epithelial	IV	Chemotherapy	+	7.9
17	M	48	Epithelial	I	Chemotherapy	+	3.6
18	M	63	Epithelial	IV	Chemotherapy	+	16
19	M	62	Sarcomatoid	III	Chemotherapy	+	6
20	M	70	Epithelial	IV	Chemotherapy	+	12.5
21	M	30	Epithelial	I	Chemotherapy	+	4.5

Table (2) Distribution of MPM patients with different lesion sites according to the different ranges of SUVmax.

SUVmax (Mean=6.7±4.3)	No. of patients	No of patients with Local lesions	No of patients with Loco-regional lesions	No of patients with Loco-regional & Metastatic lesions*
3.5-6	9	3	4	2
6.1-9	6	2	0	4
□ 9	4	2	0	2
Total (%)	19	7	4	8

* Metastatic lesions were seen in: liver (1 patient), bone (4 patients), abdominal and peritoneal lymph nodes (3 patients).

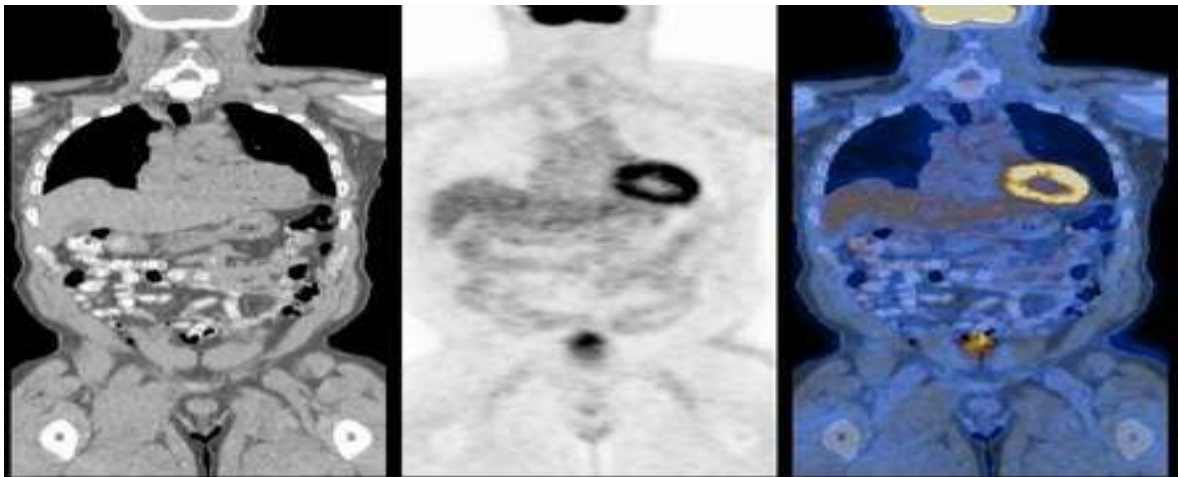


Fig. 1: 66-year-old male patient diagnosed as left epithelial mesothelioma. He received 6 courses of chemotherapy with clinical favorable response. Initial CT revealed left pleural parietal polypoidal thickening (not shown). Follow up FDG PET/CT showed homogenous tracer distribution all over the surveyed body with no evidence of any focal tracer lesions in pleura suggesting recurrence or metastatic lesion.

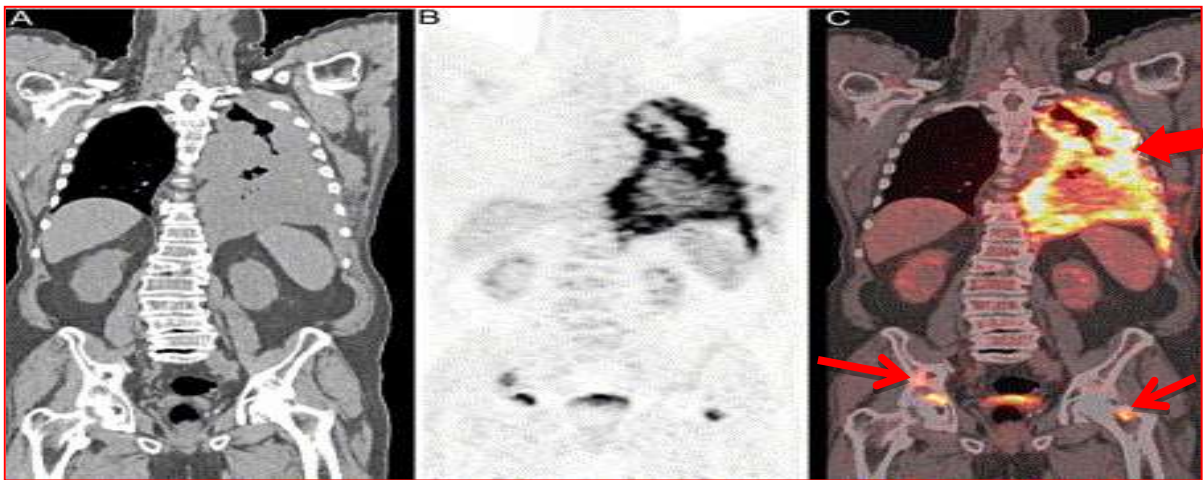


Fig. 2: 68-year-old male presented with histologically proven malignant pleural mesothelioma. Coronal sections: (A) Initial CT revealed diffuse left pleural thickening. Baseline FDG image (B) and fused PET/CT image (C) exhibited heterogeneous intense diffuse uptake of FDG in primary left pleural tumor with $SUV_{max}=7.9$ (broad arrow) and focal areas of increased uptake in the pelvis localized to right iliac bone and left femoral neck representing bone metastasis (arrows) with $SUV_{max}=5.7$.

DISCUSSION:

Computed tomography (CT) continues to be the primary and initial imaging modality. Magnetic resonance imaging (MRI) complements CT scan and is superior in determining chest wall and diaphragmatic invasion. ^{18}F -FDG PET/CT provides anatomic and metabolic information and is superior to both CT and MRI in overall staging and monitoring response to therapy^[10].

Increasingly, PET/CT imaging is playing a crucial role in the assessment of patients with known or suspected malignant pleural mesothelioma (MPM). This combined modality is likely to become the instrument of choice for examining patients of MPM. ^{18}F -FDG PET/CT can determine the most appropriate biopsy site for obtaining positive results^[11].

From the available data, the major role of PET-CT at present appears to be in the preoperative disease staging, response to treatment assessment, and post-treatment disease surveillance of MPM. In all these three areas, PET-CT convincingly shows better results than conventional anatomical imaging alone and thereby can aid in exploring novel therapeutic approaches. Disease prognosis and radiotherapy planning are evolving areas where this modality has demonstrated significant promise, but this needs further investigation^[12].

MPM has a poor prognosis, and conventional imaging modalities do not reflect the prognosis of MPM. The clinical significance of ^{18}F -FDG PET/CT was evaluated for the differential diagnosis, staging and

prognosis in MPM patients. **Abe et al.** evaluated ninety patients with ^{18}F -FDG PET/CT scanning with a clinical diagnosis or suspicion of MPM prior to therapy. Of 90 patients, 31 were pathologically diagnosed as MPM. PET/CT showed metastasis in the lymph node in 7 patients (23%) and in the systemic lesions in 8 patients (26%) with MPM. They concluded that ^{18}F -FDG PET/CT were very useful for the diagnosis of pleural diseases. High uptake of ^{18}F -FDG PET/CT may be a predictive factor of prognosis in MPM patients^[13].

In the current study we have explored the promising role of integrated ^{18}F -FDG-PET/CT in the overall management of MPM. Despite the small number of patients, our reviewed PET/CT results of 21 patients with pathologically proved MPM were almost similar to that of **Abe et al.**, 19/21 patients showed positive FDG uptake at the primary sites in the pleura with accurate localization of the lesion site.

FDG PET/CT is an accurate modality to diagnose and to estimate the extent MPM recurrence, and it carries independent prognostic value **Gerbaudo et al.**, studied 50 patients with suspected MPM to investigate the value of ^{18}F -FDG PET/CT. Their results revealed evidence of single site of recurrence in the ipsilateral hemithorax in 18 patients (44%), contralateral hemithorax in 2 patients (5%) and in the abdomen in 1 patient (2%). Bilateral thoracic relapse was detected in three patients (7%). Simultaneous recurrence in the

ipsilateral hemithorax was observed in ten patients (24%) and in seven patients (17%) in abdomen. Unsuspected distant metastases were detected in 11 patients (26%) [14].

In the current study, high detectability of locoregional lesions in 4 patients (21%) and distant lesions in 8 patients (42%) was also noted.

Zahid et al. evaluated 14 study groups with malignant pleural mesothelioma and showed that FDG-PET is superior to MRI and CT but inferior to PET/CT, in terms of diagnostic specificity, sensitivity and staging of MPM. Lymph node metastases were detected with higher accuracy (80% vs. 66.7%) than that with CT. CT-guided needle biopsy definitively diagnosed MPM in (100% vs. 92.9%) than PET/CT. Overall, the high specificity and sensitivity rates seen with open pleural biopsy make it a superior diagnostic modality to CT, MRI or PET for diagnosing patients with MPM [15].

Based on the number of lesions detected by PET/CT and CT in the present study, we demonstrated that PET/CT had

higher sensitivity than CT in detecting MPM lesions especially intrathoracic (mediastinal) lymph nodes and extrathoracic metastasis. So, PET/CT helped in restaging of 11/19 patients as it upstaged 8/19 patients (42%) and downstaged 3/19 patients (16%).

In the present, we noted that primary MPM lesions with higher pathologic stages were associated with additional loco-regional and metastatic lesions. This could explain the relatively higher values of SUVmax among these lesions likely due to the presence of higher metabolic activity.

In such pilot study, we concluded that ¹⁸F-FDG PET/CT should be considered as an excellent noninvasive diagnostic test for malignant pleural mesothelioma (MPM). It showed higher diagnostic accuracy in detection of primary lesion, mediastinal lymph nodes and extrathoracic metastasis. It can be also used for staging, restaging, monitoring response to therapy and follow up of patients with malignant pleural mesothelioma.

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