

# Malignant pleural mesothelioma: utility of $^{18}\text{F}$ -FDG PET



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## Malignant pleural mesothelioma: utility of $^{18}\text{F}$ -FDG-PET

*Malignant Pleural Mesothelioma is a rare tumour that arise from the mesothelial cells of the pleura and in recent time the incidence of this disease is rising.*

*Because of the implications for management and therapy, it is important to assess the accurate staging.*

*$^{18}\text{F}$ -fluorodeoxyglucose Positron Emission Tomography ( $^{18}\text{F}$ -FDG PET) is become a useful tool in the diagnosis of many neoplasms, such as Malignant Pleural Mesothelioma.*

*In particular it has been shown to be useful in the evaluation of the extent of pleural disease, in the establishment of lymph node involvement, in the evaluation of tumour invasion into the lung and thoracic wall, in the diagnosis of extrathoracic metastases, in the assessment of the response to treatment, and in planning radiotherapy.*

*Developments in system technology, like improvements in hybrid system (integrated Positron Emission Tomography/Computed Tomography) and the discovery of new radiopharmaceuticals, promise to make PET much more useful and versatile in the future.*

KEY WORDS:  $^{18}\text{F}$ -FDG, Malignant pleural mesothelioma, PET.

## Introduction

Malignant Pleural Mesothelioma is a rare tumour generally related to asbestos exposure<sup>1</sup> and it is characterized of pleural thickening on chest CT<sup>18</sup>.

In recent time we found that the incidence of this disease is rising and because of the implications for management it is important to determine the accurate staging for select patients for potentially curative resection<sup>2</sup>. The failure of "single-modality" therapy has resulted in the use of "multi-modality" therapy with the association of chemio-radio-immunotherapy and surgery, but with the tendency to reserve surgery in the case of limited disease (no metastatic lesions)<sup>3</sup>.

Extrapleural-Pneumonectomy is often considered the surgical procedure of choice in TNM stage I or II (according to Mesothelioma Interest Group Staging System)<sup>4</sup>. Computed Tomography (CT) and Magnetic Resonance (MR) often failure to detect tumour invasion of the chest

wall and diaphragm, as well as the presence of mediastinal nodal metastases<sup>5</sup>.

For all these reasons sometimes it's difficult for CT and MR to identify patients that are potentially candidates for radical surgical resection<sup>6</sup>.

Recently  $^{18}\text{F}$ -fluorodeoxyglucose Positron Emission Tomography ( $^{18}\text{F}$ -FDG PET) is become a useful tool in the diagnosis of many neoplasms, such as Malignant Pleural Mesothelioma<sup>7</sup>.

## Material and method

$^{18}\text{F}$ -FDG is a glucose analogue and actually is the most common radiopharmaceutical used in PET imaging. The  $^{18}\text{F}$ -FDG uptake is proportionally related to the degree of tissutal glucose metabolism which is increased in many neoplasms and in Malignant Pleural Mesothelioma<sup>8</sup>. Such as endogenous glucose,  $^{18}\text{F}$ -FDG is transported into cells by specific membrane proteins (that are called "glucose transporters-GLUT") and then it is phosphorylated by the enzyme hexokinase to yield FDG-6-phosphate. FDG-6-phosphate isn't a substrate for the glycolytic pathway because of the presence of the radioactive  $^{18}\text{F}$  in C2 position in the FDG molecule. Finally  $^{18}\text{F}$ -FDG is biochemically trapped into cells<sup>9</sup>. Neoplastic tissue has an increased number of glucose transporters and an

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increased activity of enzyme hexokinase. This results in a high rate of  $^{18}\text{F}$ -FDG uptake and retention into tumoral cells when compared with normal tissue<sup>10</sup>.

#### QUALITATIVE AND SEMI-QUANTITATIVE ANALYSIS

PET scans are analyzed visually and semi-quantitatively.  $^{18}\text{F}$ -FDG uptake is considered abnormal on visual analysis when it is substantially greater than the mediastinal blood pool activity on the attenuation-corrected images<sup>3</sup>. Besides the visual analysis of the tissutal  $^{18}\text{F}$ -FDG uptake, it is possible to evaluate the degree of  $^{18}\text{F}$ -FDG uptake with a semi-quantitative analysis. The Standardized Uptake Value (SUV) is the most common approach to obtain this information and it is based on the uptake of  $^{18}\text{F}$ -FDG in grams per millilitre corrected for the injected dose of  $^{18}\text{F}$ -FDG (adjusted for the patient's weight or for surface body)<sup>3</sup>.

Generally a SUV > 2.5 is considered to be predictor of the presence of malignant tissue<sup>11</sup>.

Flores et al. reported that when SUV and histology are taken together, may be observed a significative differences in survival: high SUV (> 4) and non-epithelioid histology reflecting the worst survival when low SUV and epithelioid histology are associated with the best survival (more than 80% of survival in three years follow up)<sup>12</sup>.

#### ACQUISITION

Whole body PET is performed 50-60 min after intravenous injection of 260 MBq of  $^{18}\text{F}$ -FDG, with an integrated PET-CT scanner. Patients had to fast for 6 h before PET scanning.

CT data are also used to correct the PET emission images for photonic self-attenuation by the human body (Attenuation Correction).

Addition of CT to PET seems to improve specificity, but also sensitivity, in tumour imaging<sup>13</sup>.

### Results

#### EVALUATION OF PLEURAL THICKENING

Discrimination between malignant and benign pleural thickening (observed on CT or MR) is an important step for early diagnosis and treatment of pleural disease. Malignant Pleural Mesothelioma has to be distinguished from other causes of pleural thickening (such as benign solitary fibrous tumour of the pleura).

Kramer et al. evaluated the utility of  $^{18}\text{F}$ -FDG PET in the differential diagnosis of pleural thickening (benign *vs* malignant), and the histology was considered as gold standard. Their results confirmed that  $^{18}\text{F}$ -FDG PET really discriminates malignant from benign process with an high accuracy and high negative predictive value (94% and 92% respectively)<sup>18</sup>.  $^{18}\text{F}$ -FDG PET shows an absence of increased FDG uptake in benign lesions.

False positive results are pleural effusion, empyema, infection or inflammation (active asbestosis or tuberculosis)<sup>24</sup>.

#### STAGING

Use of "multi-modality" treatment (radio-chemio-immunotherapy) results in to reserve radical surgery in a few number of cases of patients that present limited disease (stage I or II). Moreover it is important for the clinicians to identify the patients who have potentially resectable disease<sup>19</sup>.

The most widely accepted staging system is the TNM-system of the International Mesothelioma Interest Group<sup>1-20</sup>.

However, CT and MR often fails in predict resectability<sup>15</sup>.

In several studies CT and MR have shown an overall staging accuracy of 50%-70%<sup>14-15</sup> while some literature reports that the accuracy of  $^{18}\text{F}$ -FDG PET in staging malignant pleural disease is 88%-92%<sup>16-17</sup>.

$^{18}\text{F}$ -FDG PET/CT has been shown to be useful in the evaluation of the extent of pleural disease, establish lymph node involvement, evaluate tumour invasion into the lung and thoracic wall, diagnose extrathoracic metastases<sup>13</sup>.

#### PLANNING AND RESPONSE TO TREATMENT

$^{18}\text{F}$ -FDG PET-CT can be used for radiation therapy planning. It has a considerable effect on the decision-making process prior to radiation therapy. Particularly it can be useful for prevention of inappropriate radiation therapy, radiation dose or the planning target volume<sup>13</sup>. In patients undergoing therapy, imaging can play a crucial role and may aid in predicting the outcome of treatment regimens.  $^{18}\text{F}$ -FDG PET is advantageous in the monitoring of response to treatment because anatomic imaging alone has a limited utility after radiotherapy, as tumour sites may be confused by fibrosis or inflammatory infiltration related to radiation pneumonitis<sup>25</sup>.

#### FUTURE PROSPECTIVE: NEW PET RADIO-PHARMACEUTICAL

FDG is the most widely used radio-tracer in PET imaging that allows to establish an *in vivo* assessment of tissue glucose utilization. Such as many tumour tissue, malignant pleural mesothelioma shows a strong uptake of FDG<sup>21</sup>.

Because tumoral cells exhibit derangement of a number of physiologic cell process, different PET tracers have been developed to assay these process *in vivo*.  $^{11}\text{C}$ -methionine and choline, which are incorporated into cell membrane as phosphatidylcholine, have been recently developed and studied in lung cancer. 3'-deoxy-3'-[ $^{18}\text{F}$ ]-fluorothymidine (FLT) is a thymidine analog used to assess cell proliferation and DNA synthesis. Copper-labeled diacetyl-bis(N(4)-methylthiosemicarbazone) ( $^{64}\text{Cu}$ -ATSM) is another tracer that is taken up and trapped into ipoxic cells but washes out of normoxic

cells.  $^{64}\text{Cu}$ -ATSM has the potential role in predicting response to treatment because the oxygen tension within solid tumours influences the ability of tissue to respond to radiation therapy and chemotherapy<sup>22</sup>.

All these tracers have the potential to be more specific in identifying malignant cells than FDG.

Only  $^{11}\text{C}$ -choline has been studied in malignant pleural mesothelioma *in vivo*. This tracer has shown the ability to identify more brain metastases than  $^{18}\text{F}$ -FDG<sup>23</sup>.

## Conclusions

Malignant Pleural Mesothelioma is a rare tumour that arises from the mesothelial cells of the pleura. In recent times we found that the incidence of this disease is rising and the use of "multi-modality" therapy is increasing with the tendency to reserve surgery in the case of limited disease (no metastatic lesions, stage I-II). Because of the implications for management it is important to assess the accurate staging for select patients for potentially curative resection.

$^{18}\text{F}$ -FDG PET is a useful tool in diagnosis, follow up and evaluation of response to treatment in patients with malignant pleural mesothelioma, especially in identifying extrathoracic metastases and lymph node.

PET imaging with  $^{18}\text{F}$ -FDG allows the assessment of tumour glucose metabolism *in vivo*; however other PET tracers are being used in oncologic research to assess changes in other cellular processes associated with malignant disease.

Developments in system technology (like improvements in systems performance-PET/CT) and new radiopharmaceuticals promise to make PET much more useful and versatile in the future.

## Riassunto

Il mesotelioma pleurico maligno è una neoplasia derivante dalle cellule mesoteliali pleuriche che negli ultimi tempi ha visto un incremento della sua incidenza nella popolazione.

Allo stesso tempo ha acquistato sempre più importanza una diagnosi precoce e l'impostazione di un corretto iter terapeutico.

Recentemente la tomografia ad emissione di positroni con Fluoro 18-Fluorodesossiglucosio ( $^{18}\text{F}$ -FDG PET) si è dimostrata utile per la corretta diagnosi e per la stadiazione di numerose neoplasie, incluso il mesotelioma pleurico maligno. In particolare essa può fornire un valido supporto nella diagnostica differenziale benigno vs maligno, nel documentare l'estensione della patologia pleurica, nel valutare il coinvolgimento dei linfonodi mediastinici, l'invasione nel parenchima polmonare e l'infiltrazione della parete toracica, nell'individuazione di metastasi extratoraciche, nella valutazione della risposta

alla terapia, nel pianificare il trattamento radioterapico. Lo sviluppo di nuove tecnologie (come l'imaging ibrido PET/TAC) e la messa a punto di nuovi radiofarmaci rappresenterà in futuro un ulteriore strumento per il corretto inquadramento diagnostico-terapeutico dei pazienti affetti da tale patologia.

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