ARTIGO DE REVISÃO REVIEW ARTICLE

WHY AND WHEN TO REQUEST FOR A PET/CT SCAN IN A LUNG CANCER PATIENT?

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Abstract

This review will focus on whole-body functional imaging applied to lung cancer disease and patient management.

Lung cancer needs to be avoided… (but if not well succeeded), suspected, screened, histologically confirmed, anatomically inventoried, prognostically staged, molecularly characterized, genetically studied and finally, therapeutically managed.

Functional imaging using 18F-fluoro-deoxy-glucose (FDG) is a non-invasive method that is widely used in oncologic disease, mainly for clinical staging and re-staging, with impact on therapy planning.

For lung cancer, the functional imaging with FDG-PET/CT is used for clinical staging and also to provide information on a pre-diagnostic phase, to categorize lung nodules according to the metabolic risk of malignancy.

Clinicians need to be aware of the different possibilities of the functional imaging information, to provide the better use of it.

This review will focus on data from the different medical fields that are considered important to informed decision making when asking for functional imaging in the daily clinical routine of a lung cancer patient.

INTRODUCTION

The purpose of this work is to review the indications for positron emission tomography with computed tomography (PET/CT), in the management of lung carcinoma, in the era of the 8th Edition of the AJCC cancer TNM staging.

The TNM staging classification applies to carcinomas of the lung including non-small cell carcinomas, small cell carcinomas and bronchopulmonary carcinoid tumours.[1] It codes the anatomic extent of the disease and creates prognostic stage groups.

The staging procedure may include a variety of non-invasive and invasive methods, and constitutes the basis for planning therapy and multicentric therapeutic clinical trials.

Whole-body PET/CT is a non-invasive anatomic and metabolic imaging modality that integrates detailed anatomic information with metabolic information.

HIGHLIGHTS OF SOME TECHNICAL ASPECT OF A PET/CT SCAN.[2]

Image acquisition:

PET/CT is a hybrid imaging technology introduced by Townsend, Nutt, and Beyer in 1998, and became commercially available in the beginning of 2001.

This imaging technique comprises the acquisition of a low radiation dose whole body computerized tomography (CT) immediately followed by the acquisition of a whole body positron emission tomography (PET).

Attenuation-corrected PET images will be reconstructed and a hybrid whole body PET/CT image will be accessible for medical interpretation.

The PET imaging component comprises a whole body in vivo distribution of a positron emission radiopharmaceutical.

Positron emission (^{18}F and ^{68}Ga) Radiopharmaceuticals:

In this work two different radiopharmaceuticals will be reviewed, presently available to perform a PET/CT scan in the clinical work-up of lung carcinomas;

^{18}F-Fluoro-deoxy-glucose (FDG) is a Fluor-18(18F) analogue of glucose largely used in oncology, mainly because of its high sensitivity to detect viable neoplastic lesions.

- At a cellular level the FDG molecule competes with glucose transporters (GLUTs) into tumour cells and also competes for phosphorylation by hexoquinase. But the FDG phosphorylated form will not progress in the glycolytic metabolic pathway, will be trapped within the cell, accumulate there and, because of

that, the radioactive signal progressively increases to be detect on PET imaging.

- The FDG uptake of a neoplastic lesion reflects a mix of biologic variables: the amount of vascularisation of that lesion, cell density, cellular rate of exogenous glucose consumption, cellular expression of GLUTs and hexokinases. On the contrary, necrosis or the amount of non-FDG uptake material like mucin, will reduce the FDG uptake/signal.
- Because of this metabolic nature, FDG is not specific for neoplastic cells and normal cell FDG uptake will also occur, according to each cell glycolytic activity rate.
- The reason for the wide use of FDG in oncology is because a large group of neoplastic cells have a very high glycolic rate that will produce high contrast uptake of neoplastic cells in between normal tissue.

FDG not only enhances most malignant tumours but can also enhance areas of active inflammation. When interpreting images, it is important to be aware that inflammatory activated cells might also show high FDG uptake and false positives could occur with granulation tissue, healing wounds, talc deposits in the pleura after pleurodesis, placement of central lines, chest tubes and gastrostomy tubes or recent percutaneous needle biopsy.

The clinical information and the anatomic data coming from CT imaging contributes to clarify the causes of these FDG uptakes, preventing imaging misinterpretation.

^{68}Ga-DOTA-somatostatin analogpeptides is a Galium-68(68Ga) positron emission-radiopharmaceutical with in vivo affinity to somatostatin (SST) cell membrane receptors (Rs).

- Somatostatin cell receptors (SSTRs) belong to the group of seven transmembrane helix proteins, able to transmit an extracellular signal into the cell.
- Five distinct subtypes of somatostatin receptors (SSTR1, SSTR2, SSTR3, SSTR4, SSTR5) have been identified, with SSTR2 showing the highest affinity for natural SST and synthetic SST analogs.
- Most neuroendocrine tumors (NETs) have high expression of SSTRs, and that opens the possibility for tumor imaging and therapy with radiolabeled SST analogs.

PET Imaging quantification

The ability to quantify physiological variables has an important role in clinical practice and is a crucial tool in multicentric oncology trials.

Particularly in PET imaging, quantifying means that the tissue or lesion's radioactive signal that is acquired will be transformed into the absolute concentration of the radiopharmaceutical in that tissue, at a specific point in time. That will be expressed by the *standard uptake value* (SUV).

In SUV calculation the most used patient variable is body weight, and not body surface area (BSA) nor lean body mass (LBM), and the most used imaging methodology is the highest activity of pixel image in the tumour region (SUV_{max}).

Another quantitative variable also used is clinical practice is SUV_{peak}. Its calculation is based on the highest activity of a spherical volume of interest (VOI) with a 1mL volume, located in tumour region position that provides the maximal activity VOI average.

A deep understanding of this imaging quantification methodology might be gained by reading two interesting references that nicely express this theme nuances over time.[3,4]

FDG-PET imaging patient preparation

Patients need to fast (except for water) for at least 6 hours.

Blood glucose level is always verified and needs to be lower than 200 mg/dL, ideally lower than 140 mg/dL.

Radiopharmaceutical administration will be intravenous, and the patient will then rest for a 60 minutes period (corresponding to the biologic FDG uptake time).

Next step will be a whole-body imaging (PET-CT) acquisition, approximately in-between 20 to 30 min.

Attenuation-corrected PET images are reconstructed and integrated PET and CT images are obtained automatically.

Diabetic patients also need to achieve a proper fast blood glucose level (« 200mg/dL, preferentially «140mg/dL), ideally just with diet control but, if necessary also with oral anti-diabetic drugs or with long-acting insulin.

Rapid-insulin should not be used before FDG intravenous administration, because it will affect FDG in-vivo distribution, increasing mass muscle uptake and reducing lesions uptake.

Dual time lung acquisition applied to solitary lung nodules

This means two image acquisitions;

- Initial whole body PET/CT scan after 60min post-FDG injection uptake time
- Second delayed segmental lung imaging, usually after 180 min-post-FDG injection uptake time.

The rational for this protocol is based on the knowledge that FDG lung lesion uptake is a dynamic and progressive process that is continuously occurring, and the plateau uptake might not be reached until a maximal period of 5h post-FDG injection.

For a lung lesion, an increase in the SUV_{max} of delayed imaging acquisition, an absolute value of SUV_{max} superior to 2,5 or if an increase of 10% or more in SUVmax occurs between the initial and delayed image, can be an indication of malignancy.

This Dual time lung imaging protocol is particularly useful for solitary lung nodule study with marginal FDG uptake of SUV_{max} 2,5.[5]

Histologic and anatomic consideration in lung cancer:[6]

Non-small cell lung cancer (NSCLC) can be further categorized into several different types of epithelial malignant tumours, namely:

- Adenocarcinoma (ADC): comprises 40% of all lung cancers, is a malignant epithelial tumour with glandular differentiation, mucin production or pneumocyte marker expression. These tumours have particular growth patterns: lepidic, acinar, papillar, micropapillary and solid.
- Other variants of ADC are: invasive mucinous, colloid, fetal, enteric, or minimally invasive carcinoma.
- ADC typically will form a peripherally located mass that exhibits both central fibrosis and pleural puckering. But other appearances might occur and an ADC could be a centrally located mass, a diffuse lobar consolidation, or may express itself as multiple lobe lesions distributed bilaterally, and even pleural thickening.
- Squamous cell carcinoma (SCC) comprises approximately 20% of all lung cancers. It is a malignant epithelial tumour with 3 subtypes: keratinizing, non-keratinizing, and basaloid SCC can also be present in various places throughout the lungs, but the most common include the central portion, along major airways forming cavities when present in larger sizes.
- Large cell carcinoma: diagnosis cannot be done in a biopsy sample, but only be achieved with tumour surgical resection. There are several different subtypes of large cell carcinoma including; large cell neuroendocrine carcinoma (LCNEC), basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, and large cell carcinoma with rhabdoid phenotype.
- Other less common types of NSCLC include adenosquamous, pleomorphic, spindle cell, and giant cell carcinomas, as well as pulmonary blastoma, neuroendocrine tumours, and several others.

Neuroendocrine Lung Tumours (NET): Approximately 20% of all primary lung tumors are neuroendocrine including:

- Small cell carcinoma (SCC) comprises about 13% of all lung cancer and is a very aggressive type of NET.
- Large cell NE carcinoma (LCNC) is an aggressive type of cancer, four times as frequent in men as in women, it is quite rare in general.
- Carcinoide Tumour is a well-differentiated lung NET, which includes:
  - Low-grade, Typical carcinoids with a very slowly growth rate. Advanced disease, with malignant progression is very rare.
  - Intermediate grade, Atypical carcinoids with a faster growth rate, but not nearly as fast as other major types of lung cancer.
- Since lung NETs develop in hormone-producing cells, a few patients experience paraneoplastic symptoms unrelated to the lungs, such as diarrhoea or flushing in the face.

FDG-PET/CT scan and anatomic extension of Distant Metastasis (M) staging:

Distant metastasis detection is crucial in staging since it will include the patient in stage IV.

Among 813,302 NSCLC patients eligible for final analysis diagnosed between 1998 and 2006, approximately two thirds of patients had locally advanced (27.6%) or metastatic (38.1%) disease.[7]

FDG-PET/CT scan is a highly efficient way to detect metastasis due to the fact that it is a whole body and a multiorgan evaluation, and uses a radiopharmaceutical (FDG) with high detectability of the neoplastic tissue with cellular glycolic activity.

Also, since commercial PET scanners provide spatial resolution of 4.5 to 6.0 mm , even lesions smaller than 1 cm in diameter can be detected on the basis of an increased uptake of FDG.

The ability to detect a metastatic lesion is not directly dependent on the lesion dimension, but much more related with the metabolic contrast between the metastatic lesion and the normal surrounding tissue where it is implanted.

For example, normal bone tissue presents low FDG uptake but bone metastasis usually affords a high metabolic signal, causing a high metabolic contrast with surrounding tissue. In fact, a bone metastasis could be FDG positive with a small volume well before bone density and architecture defect can be detected on anatomic CT imaging.

The same applies for a lung or a subcutaneous metastasis, where a high metabolic contrast between the metastatic lesion and the normal surrounding tissue is possible.

Pleural metastasis from lung cancer could be present with or without pleural effusion.

FDG pleural uptake is always abnormal, even with low intensity. In a lung carcinoma patient, pleural uptake is highly suspicious for metastatic pleural disease. In case that this is the only site for metastatic disease finding, a histologic diagnosis is recommended and pleural FDG uptake location should be used to guide biopsy.[8]

Hepatic and kidney metastatic lesions are usually well detected, because of the fact that these two organs show a moderate physiologic FDG uptake, and the metastatic detection is dependent on metabolic rate and lesion volume.

For brain metastasis detection, FDG sensibility is reduced (60%), because normal brain cortex has a high glycolytic rate and a physiologic high FDG uptake. Contrast-enhanced MRI has a higher sensitivity for assessing brain metastasis than PET-CT.

Besides this fact, if FDG brain imaging is included in whole body imaging, it should always be analysed with the purpose of searching for metastatic brain lesions with FDG uptake higher than normal brain cortex or searching for special cases with brain focal areas of no FDG uptake, that could be a signal of brain oedema, secondary to brain metastatic disease.

Adrenal gland metastatic disease is able to be detected by FDG uptake, even with a small volume, but for this anatomic site the specificity for metastatic detection with FDG is lower (90%) than for the other sites (96%). The reason for that is dependent on the fact that some benign adrenal adenomas (or adrenal tuberculosis) might show FDG uptake.[9]

The important message is that, an adrenal gland nodule FDG positive, needs to be conjugated with diagnostic CT information. It may then be clarified if it is a benign adenoma (hypodense and with a regular contour) or a metastatic lesion with visible capsule invasion. If diagnostic CT information cannot clarify the nodular aetiology, and if the adrenal gland is the only site of metastatic disease, than a histologic diagnosis confirmation is recommended, because a false FDG positive result could be upstaging the patient and compromising the treatment strategy.

FDG-PET/CT could identify unsuspected extra thoracic lymph node metastasis, with normal size («1cm at CT). Nodal FDG uptake higher than blood pool is criteria for suspicious nodal metastasis, and nodal FDG uptake higher than liver uptake is highly concerning for nodal metastatic disease.

Detection of a second primary malignancy could happen in particularly because FDG-PET/CT is a whole body examination, and is estimated to occur in about 3% of lung NSCLC patients. Histologic diagnosis is always necessary, and this finding will impact on that patient management.[10]

In general any potential false FDG-positive lesions should be confirmed by biopsy if it could cause an upstaging, with implication on therapy strategy.

FDG-PET/CT scan and Regional Lymph node (N) staging:

Morphologic nodal staging with CT is based on lymph node size, were a node with a short axis diameter bigger than 10 mm is suspect of metastatic lymph node.

Metabolic nodal staging with FDG has a significantly higher sensitivity and specificity than morphological nodal criteria of CT in the detection of malignant involvement of mediastinal lymph nodes.

In a meta-analysis study, the sensitivity of PET/ CT for nodal metastasis was 85% and the specificity was 95% as compared with a CT sensitivity of 61% and specificity of 79%.[11]

The clinical importance of FDG-PET is the high negative predictive value in lymph node staging, which has been estimated to be higher than 90% in several studies.

However, it is important to be aware that there are cases of FDG-PET/CT nodal false negative results for small nodes <10-15 mm diameter, due to microscopic nodal metastases occurrence, only detected by post-operative histopathology.

Also, for central primary tumours might be not possible to distinguish between the primary lesion and the adjacent hilar nodes.[12] On the contrary, false positive nodal disease may occur with granulomatous disease (tuberculosis or sarcoidosis).

In view of the diagnostic accuracy recorded with PET--CT, when there is suggestion of malignant involvement of mediastinal lymph nodes by FDG-PET/CT, complementary invasive diagnostic assessment (EBUS or other) might be necessary for histological confirmation (Figure1), in order to accurately stage the patient.[13]

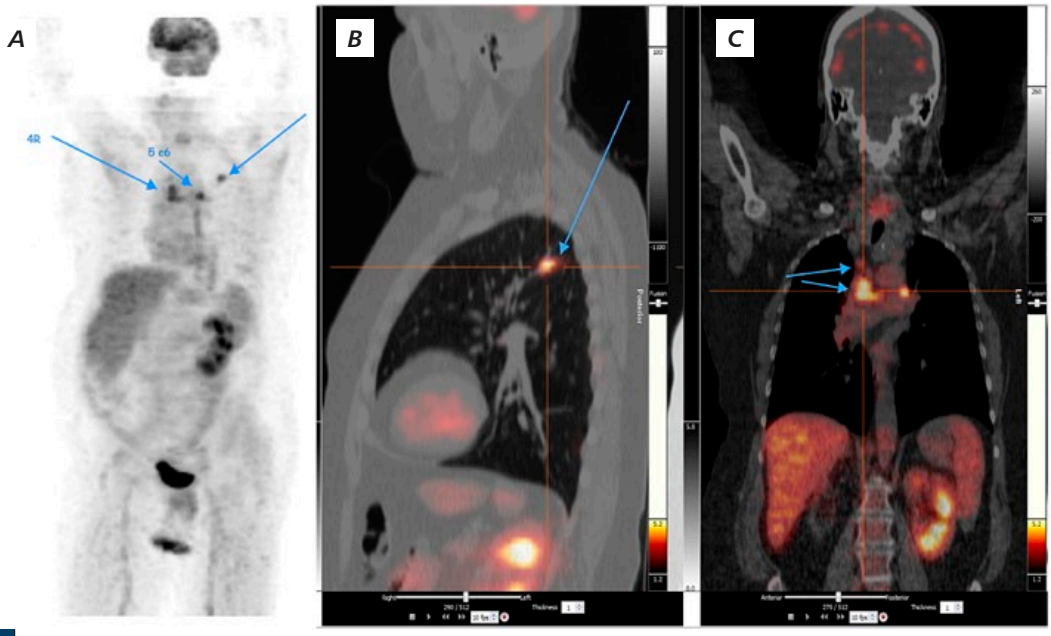

Figure 1

(A) A 68-yr-old asymptomatic male, with a CT finding of a solitary lung nodule on left superior lobe, with largest diameter of 18mm. (B) FDG-PET/CT shows positive uptake with SUVmax of 4,9. (C) At hilar region FDG uptake was not found. In the mediastinum nodal uptake was present: at sub- and para-aortic nodes (station 5-6), and at right upper paratracheal nodes (4R). No extra-thoracic FDG-uptake was present (cM0 stage). The contralateral mediastinal nodal FDG positive disease, was histologically confirmed by minimally invasive methodology, EBUS.

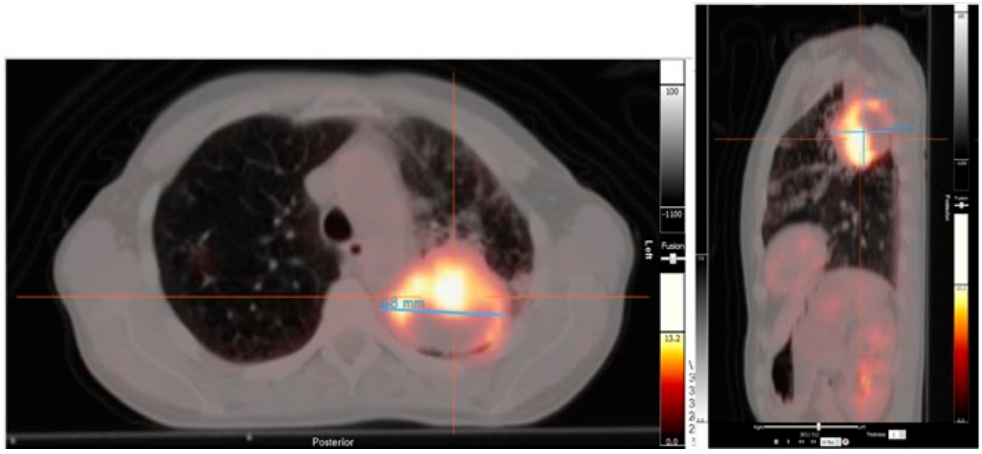

Figure 2 *59-yr-old female, with a lung mass (68mm) on the left superior lobe, with pleural contact. FDG-PET/CT imaging shows lung mass with positive uptake (SUV_{max} of 14), mainly peripheral, and a large intra-lesion necrosis. The transthoracic biopsy performed before PET/CT was non-diagnostic, because of necrotic sample.*

FDG-PET/CT SCAN AND PRIMARY TUMOR (T) STAGING

Lung carcinoma is a bronchogenic neoplasm arising from epithelial cells of the bronchial mucosa or from the cells lining the alveoli.

Although lung carcinomas may arise in any part of the lung, **Squamous cell** and **Small cell carcinomas** tend to arise from mucosa of **more central bronchi**, involving the lobar origin and the main bronchi. This more frequent central location often is the cause of obstruction and secondary atelectasis, invasion of bronchial wall and of mediastinal structures.

On the other hand, **Adenocarcinoma** tend to more often located in the **periphery of the lung**, with extension to visceral pleura, more often causing pleural invasion, pleural effusion and chest wall invasion.

Since 2011, adenocarcinoma was reclassified to reflect invasiveness and growth characteristics, into:

a) adenocarcinoma in situ,

b) minimally invasive adenocarcinoma,

c) invasive adenocarcinoma

The 8th Ed. of AJCC for lung carcinoma staging reflects this pathologic reclassification of adenocarcinomas (including the new Tis and the T1a (mi)) and also includes different T descriptors, according to new size cut-off of T category.

These two new T categories, Tis and T1a (mi), are particularly important for imaging diagnostic CT and FDG-PET/CT, because these two categories will manifest as ground-glass or partial-solid ground-glass nodules.

- Tis - carcinoma *in situ*- is a pure ground-glass lesion with a diameter «3cm, without CT imaging of solid component (and without invasive component at histopathologic evaluation).
- T1a (mi) - minimally invasive adenocarcinoma is a ground-glass lesion with a diameter «3cm, with a solid CT solid component «5mm (the invasive component at histopathology evaluation also «5mm).

It is interesting to note that, for cases of early T category (cT1b, cT1c and cT2) FDG-PET/CT scan is usually performed under the work-up of solitary lung nodule, before histology lung cancer confirmation.

For large primary lung lesions (highly suspected of cT3 and cT4), FDG-PET/CT is advised and, if possible, should be performed before lung lesion biopsy, for it will reduce the risk of unsuccessful biopsy of necrotic sample (Figure2).

Table 1 **FDG-PET/CT indication according to the 8th Ed. of TNM staging[1]:**

cTcategory	Clinical stage	FDG-PET/CT indication
Ground-glass opacities cTis		FDG-PET/CT is NOT required
cT1a (mi) cT1a (larger diameter of the solid component on CT < 1cm). Without other abnormality on chest CT.	stage IA1 cT1(mi) cN0 and cT1a cN0	FDG-PET/CT is NOT required for evaluating metastatic spread.
Candidates for treatment with curative intention.		FDG-PET/CT is indicated for evaluating metastatic spread (except for brain). FDG-PET/CT should categorize TNM uptake, with location and SUVmax quantification.

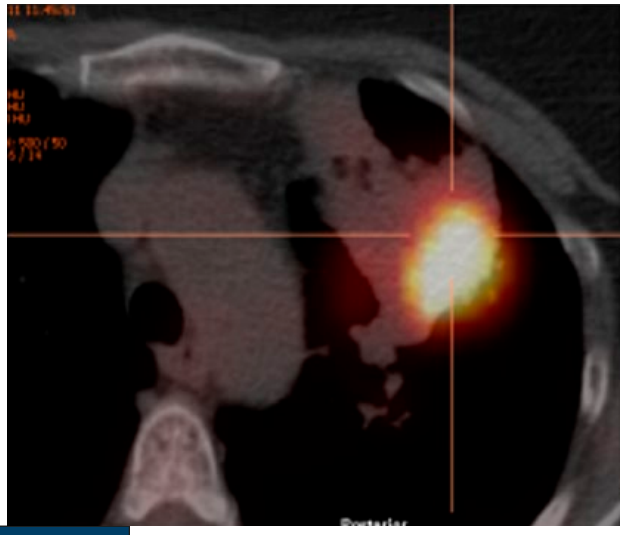

Figure 3 *Retro-obstructive atelectasis without FDG uptake in an Upper left lung FDG positive tumour.*

Also, because the whole body FDG-PET/CT imaging will detect FDG positive mediastinal nodal disease and/or unexpected distant metastasis, that information might introduce a different choice for biopsy location.

For individuals who have a solitary extra thoracic site suspicious of a metastasis, tissue confirmation of that M1 site is recommended if a fine-needle aspiration or biopsy is feasible.

Another important attribute of FDG-PET/CT is the ability to distinguish between tumour and distal atelectasis (Figure 3), secondary to tumour obstruction.

This information might have important impact on cT staging diameter and cT staging atelectasis or obstructive pneumonitis extending to the hilum and finally the tumour, but also for radiotherapy planning, this atelectasis information might significantly adjust and improve radiotherapy planning field. Changes of the therapeutic strategy due to PET/CT are especially seen in cT3 and cT4 tumours.

Another particular information of metabolic imaging is the clarification of parietal tumour invasion (figure 4), with special relevance for treatment planning of surgery and radiotherapy.

A prospective study where the accuracy of the preoperative staging of non-small cell lung cancer was evaluated comparing stand-alone CT and integrated FDG--PET/CT, the primary tumor was correctly staged in 84 patients (79%) at stand-alone CT and in 91 patients (86%) at integrated FDG PET/CT.[14]

Lymphangitic carcinomatosis, when present, can be seen on FDG-PET/CT images as a diffuse peritumoral uptake.

Work-up of solitary lung nodule /of a potencial lung cancer lesion (T):

A small note about this process at this time seems to be important since with the programmes for lung cancer screening, this investigation will be more and more frequent.

The aim of the screening procedure is to diagnose lung cancer lesions at an initial T staging level, ideally before cT2.

For indeterminate pulmonary nodules at diagnostic lung CT, and according to patient risk factor and pulmonary nodule characteristics (solid vs subsolid, dimension, unique vs multiple) a decision needs to be made between no routine follow-up required, routine CT follow-up, indication for FDG-PET/CT or tissue sampling.

The state of the art seems to be to follow the Fleischner Society's pulmonary nodule recommendations, where the ground glass lesions surveillance method is clearly indicated.[15]

FDG-PET/CT scan will contribute to the risk calculation of malignancy with the metabolic characterization of solid pulmonary nodules, following the rule (using an uptake time of 50 to 60 min):

- A nodule is positive for malignancy if SUV_{max} is higher than 2,5 » biopsy,
- If a nodule less than 1cm diameter demonstrated any FDG uptake, should be considered potentially malignant » biopsy,
- Dual point image at 1 and 3 hours uptake time) improves accuracy, because malignant lesions show increased uptake on delayed images (using a threshold of 10% SUV increase) whereas benign

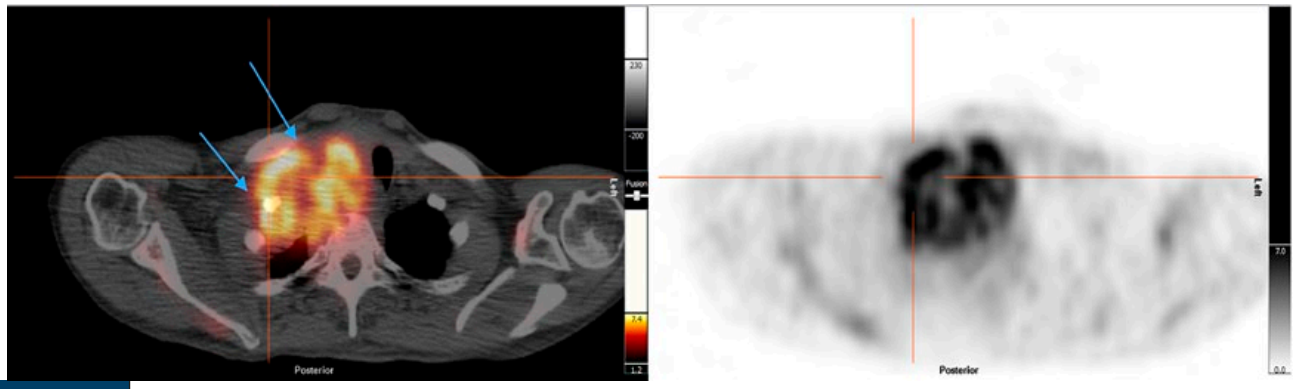

Figure 4 *Metabolic imaging of an apical right lung tumour with thoracic chest wall invasion. At functional imaging with FDG, the high tumour metabolic signal is integrated with the anatomic references.*

inflammatory lesions are stable or less active on second scan.
- Round atelectasis usually does not have FDG uptake.

Even though we should be aware that **lung nodules false positive** results might be related with benign tumours of inflammatory disease such as benign sclerosing haemangioma, leiomyoma and inflammatory pseudotumour or active granulomatous /inflammatory process (tuberculosis, fungal infection, rheumatoid nodule, sarcoid, lipoid pneumonia, talc granuloma, necrotizing pneumonia), **Lung nodules false negative** results will be present with some tumour tissue that shows no or little FDG uptake, like microscopic tumour deposits, mucoepidermoid carcinomas and biologically weak tumours (pure lepidic adenocarcinoma and carcinoid tumours).

FDG-PET/TC response criteria in solid tumours (PERCIST) vs response evaluation criteria in solid tumours (RECIST) [16,17]

Tumour progression during first-line chemotherapy occurs in approximately one-third of patients with lung cancer and this high frequency of progression emphasizes the need for monitoring treatment response with advanced imaging modalities, to adopt new treatment regimens and predict outcomes.

Currently, there is no agreement on the optimal imaging modality for post-treatment assessment in lung cancer.

Tumour measurements before and after treatment are considered appropriate criteria for evaluating T response.

The two uniform standardized response assessment criteria in solid tumours are the World Health Organization (WHO) criteria and the Response Evaluation Criteria in Solid Tumours (RECIST).

These criteria depend largely on size measurements, including bidimensional tumour measurements (the longest perpendicular diameters in the axial plane) by WHO and the one-dimensional diameter (longest tumour diameter in the axial plane) by RECIST.

Changes in cellular metabolism occur more rapidly than do changes in tumour size, and FDG PET has become a powerful tool in assessing treatment response, by providing information on the metabolic activity of tumour cells.

PET metabolic response using the PET Response Evaluation Criteria in Solid Tumours (PERCIST) has been shown to be a better predictor of histopathology response than anatomic response metrics, such as WHO criteria and RECIST 1.1

Several studies have reported significant differences in tumour SUV_{max} found on pre- and post treatment FDG--PET scans of patients who responded to therapy treatment versus the scans of patients who did not have a response.

When assessing response to therapy, the tumour standard uptake value (SUV_{max} or SUV_{peak} or SUL_{peak}) is used to measuring CHANGES in metabolic rates before and after treatment (table 2).

In this situation only an intra-individual comparison is done and that excludes the problems of variability of absolute metabolic rates errors, several times pointed as different body composition and glucose and FDG plasma clearance.

Neuroendocrine Lung Tumours (NET) metabolic particularities:[18]

Neuroendocrine tumours (NETs) were first described in 1907, and were initially named as carcinoid, because of their ability to become a malignant disease. As they arise from the enterochromaffin cells of the neuroendocrine system, more recently were named neuroendocrine tumours.

NETs may arise from a wide variety of primary organ sites, but are most often found in the gastroenteropancreatic system (57%) and in the lungs (27%).

Ki-67 index and mitotic count, adopted by 2010 WHO histological grading system plays an important role in NETs compared to other tumours, and is the primary determinant of grade in bronchial NETs (table 3).

Ki-67 is present in cells undergoing all parts of the cell division cycle (G1, S, G2 and mitosis) **but not in G0**, so the percentage of cells Ki-67 antigen positive reflects the growth fraction of a cell population.

NET lesions with avidity for FDG highlights patients with aggressive clinical behaviour, high proliferative rate and a shorter median survival, compared to those who did not (figure 5).

Table 2 **Objective therapeutic responses according to PERCIST 1.0**

PERCIST PET response criteria in solid tumours	$SUV_{peak}1$ (SUV before treatment); $SUV_{peak}2$(SUV after treatment); $\Delta SUV\% = (SUV1 - SUV2) / SUV1 \times 100\%$.
Complete Metabolic Response (CMR)	Complete resolution of 18F-FDG uptake within the measurable target lesion. Less than mean liver activity and indistinguishable from surrounding background blood-pool levels. No new 18F-FDG-avid lesions.
Partial Metabolic Pesponse (PMR)	Reduction of a minimum of 30% in the target tumor ^{18}F-FDG SUV value.
Stable Metabolic Disease (SMD)	Disease other than CMR, PMR, PMD. Equal to a differential of SUV value in between -29% and +29%.
Progressive Metabolic Disease (PMD)	30% increase in ^{18}F-FDG SUV value. Or any new 18F-FDG-avid lesion that are typical of cancer.

Table 3 **Ki-67 index and mitotic count in Lung NETs related with proliferation grade.**

Grade	Mitotic count per 2 mm^2	Ki-67 index	NET lung
Gx	Grade cannot be assessed		
G1	« 2 mitotic count	« 3%	Typical carcinoid Tumour
G2	2-20 mitotic count	3-20%	Atypical Carcinoid Tumour
G3	» 20 mitotic count	»20%	NE Carcinoma

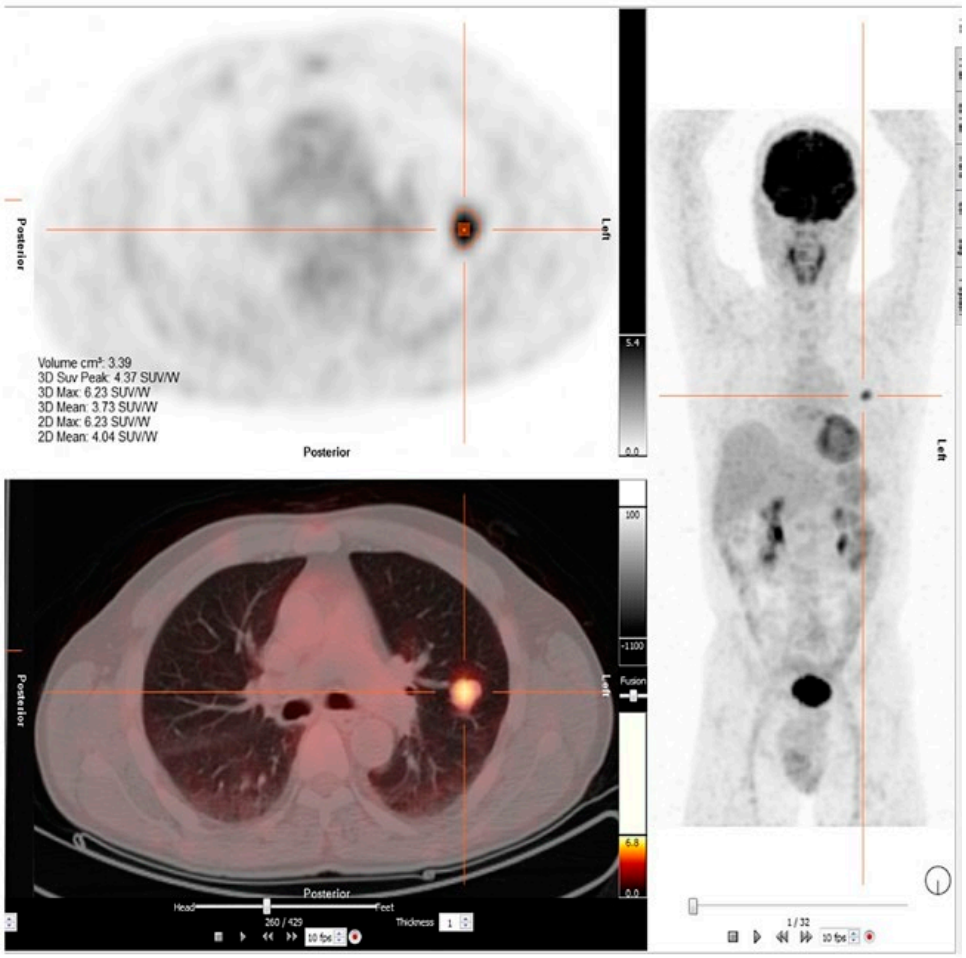

Figure 5 *A 55 year-old male, with an upper left lung lobe solid 23 mm nodule, surrounded by normal lung parenchyma. Lesion biopsy revealed a large cell neuroendocrine carcinoma, G3, Ki67>90%. FDG-PET/CT shows lung lesion FDG uptake with SUV_{max} of 6, and no other FDG uptake according to a metabolic stage of (cN0 cM0).*

Most NETs have high expression levels of transmembrane Somatostatin (SST) receptors (SSTRs), which opens the possibility for tumour imaging and therapy with radiolabeled SST peptide analogs.

Five distinct receptors subtypes (termed SSTR1-5) have been identified, with SSTR2 showing the highest affinity for natural SST and synthetic SST analogs.

A number of slightly different positron emission SST peptide tracers (Table 4) have been developed. These SST peptide tracers will allow a whole body in vivo imaging of somatostatin receptors to be performed.

These ^{68}Ga-DOTA-peptides for PET imaging will be used for diagnosis, staging and radioactive treatment of NETs, comprising the concept of theranostics (diagnostic techniques directly linked to the application of specific therapies).

Currently, there is no recommendation on which type of 68GaDOTA-peptide is preferred and logistic reasons such as availability of the precursor peptide will guide the choice in clinical practice, and the implementation of ^{68}Ga--DOTApeptide PET that may differ from country to country, mostly related with ^{68}Ge/^{68}Ga generators availability and reimbursement.

Table 4 **The affinity profiles of ^{68}Ga-DOTA-peptides differences**

^{68}Ga-labeled SST peptide analogs	Different affinities for the five SST Receptors subtypes
^{68}GA-DOTA-NOC (currently in use in Portugal)	Wide receptor binding profile, able to specifically bind to SSTR2, SSTR3, and SSTR5
^{68}GA-DOTA-TOC	High affinity for SSTR2 and SSTR5
^{68}GA-DOTA-TATE	Binds only to SSTR2, presenting 10-fold higher affinity for SSTR2 in vitro than that of the other 68Ga-DOTA-peptides

The optimal selection of therapies in a given NET patient at a given point in their clinical course remains an unanswered question. Initial anti-proliferative therapy tends to be with somatostatin analogues, with other therapies (such as peptide receptor radionuclide therapy (PRRT), tyrosine kinase inhibitors, or chemotherapy) chosen upon failure of these therapies.

The use of standardized staging criteria in NETs, as in other malignancies, has helped in categorization of patients for research purposes and to aid in prognostics. However, the use of serial anatomical imaging to determine response in NETs is complicated by the often indolent course/slow-growing nature of low-grade tumours.

Progressive disease, defined by RECIST criteria (as an increase in the sum of diameters of at least 20%or appearance of new lesions), may take years if not decades to manifest.

Even though the widespread adoption of ^{68}Ga-DOTA-peptides PET/CT has revolutionized NET imaging, CT and MRI remain the most common imaging modalities.

Functional (nuclear) imaging: ^{68}Ga-DOTA peptide - PET tracers:

The SUV_{max} of a patient's ^{68}Ga-DOTA peptide PET correlates to expression of SSTR on their NET pathology.

Consider that the well-differentiated NET lesions have more SSTRs expression, are mainly low-grade tumours and have a better prognosis, it is not surprising that avidity on ^{68}Ga-DOTA peptide PET uptake predicts improved overall survival in metastatic NET.

Although interpretation of uptake ^{68}Ga-DOTA peptide tracer changes, on serial ^{68}Ga-DOTA peptide PET scans, during treatment, is of undetermined clinical significance since

- a decrease in the SUV_{max} of a lesion could represent either response to therapy or de-differentiation of a tumour into high-grade NET (with lower expression of SST membrane receptors and a worse prognosis).
- an increasing of SUV_{max} of a lesion may either signify conversion of a signal well-differentiated tumour (with better prognosis) or alternatively

Table 5 **Biologic cellular information of dual 68Ga-DOTA-peptides/18F-FDG PET imaging**

^{18}F-FDG PET uptake in a NET lesion	• Identifies high proliferative rates • More likely present on G3 NET
^{68}Ga-DOTA-peptides uptake in a NET lesion	• Identifies expression of membrane somatostatin receptor (SSTRs) • Higher on well-differentiated, G1/2 NET

Table 6 **Dual ^{68}Ga-DOTA-peptides/^{18}F-FDG PET imaging)**

^{18}F-FDG PET NET lesion uptake	^{68}Ga-DOTA-peptides NET lesion uptake	Peptide receptor radiotherapy (PRRT) indication
Positive	Negative	PPRT contraindication. Tumour with negative or weakly positive SSTRs expression. Probable presence of de-differentiated tumour with no treatment efficacy.
Negative or weakly Positive	Positive	PRRT indicated, with ability of disease control (Kashyap et al., 2015)

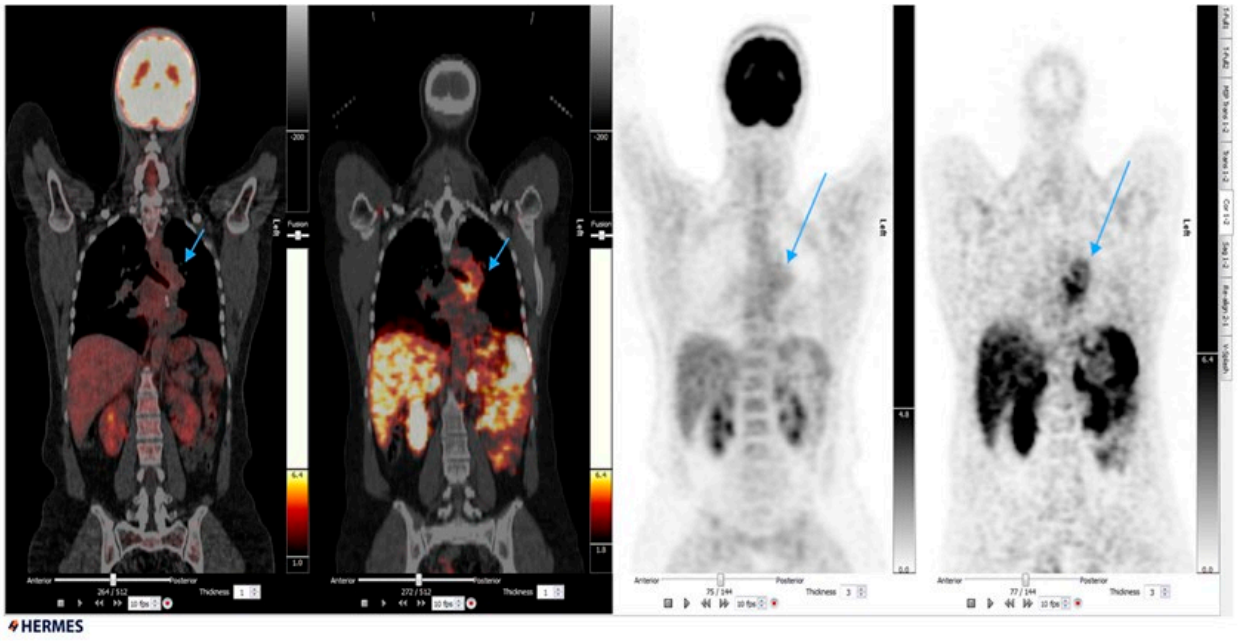

Figure 6

40 year-old female with left hilar recurrence of atypical carcinoid tumour (Ki67>5%), six years after a lobectomy for central typical carcinoid tumour. (pT2a pN0). A Dual ^{18}F-FDG PET /^{68}Ga-DOTA-peptides imaging performed at recurrence revealing a left hilar lesion DOTA-peptides positive and FDG-negative, supporting use of maintenance therapy with cold somatostatin.

tumour progression with increasing number of cells still expressing the receptors).

Dual ^{68}Ga-DOTA-peptides/^{18}F-FDG PET imaging

Dual PET imaging technique, ^{68}Ga-DOTA--peptides/^{18}F-FDG PET imaging is of potential value in NET work-up because the two scans are complementary.

In large volume lesions it is possible to find intra--lesions heterogeneous disease, , with areas of FDG avidity and others areas with ^{68}Ga-DOTA-SST peptides uptake. In this case the information might be used to indicate tissue sample collection.

The somatostatin imaging (^{68}Ga-DOTA-SST peptides uptake) is also indicated to predict peptide receptor radiotherapy (PRRT) delivery (and therapeutically efficacy) in the individual lesions/patient (figure 6).

CONCLUSION

Nowadays lung cancer is the leading cause of cancer related death.

In the near future lung cancer screening programs will bring to the daily-clinical activity a huge amount of undetermined lung nodules to deal with, promising early--diagnosis and early-stage lung cancers coming under the aim of improving overall lung cancer survival.

Emerging new lung cancer therapeutic opportunities is a new reality, that needs a more complete tumour characterization.

The tumour, the patient and the disease stage, need to be connected to the best therapy deemed fit!

Avoiding a therapy of unproven benefit is as important as missing a beneficial one.

We have more information on molecular tumour analysis and specific genetic mutations, more accurate histological discrimination, better ability of minimally invasive diagnostic and therapeutic approach, and more in vivo functional imaging ability.

How to deal with all this complexity? The answer might to be connected with the highlight knowledge of all related fields (pathology, molecular genetics, functional and anatomic imaging, minimally invasive diagnostic and therapeutic procedure, …) maintain multidisciplinary discussion, be persistence … and don't lose curiosity!

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