WHOLE BODY PET-CT: M STAGING IN NON SMALL-CELL LUNG CANCER*

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FDG PET has been used for years in the diagnosis and recurrence of non small cell lung cancer (NSCLC). It has an important impact on patient management, and its coupling with CT for immediate fusion allows immediate localization and characterization of uptake. This article reviews the role of FDG PET-CT in the staging of NSCLC for the detection of metastatic disease.

Key-words: Lung neoplasms, CT – Lung neoplasms, emission CT (ECT).

The Belgian cancer registry estimates the newly diagnosed cases of lung cancer in 2009 at 7572 in Belgium (2077 females and 5495 males). It represents the third incidence of cancer after breast and colon cancers, but remains the first cause of cancer-related death (1). Accurate staging of cancer prior to therapy is critical to patient management. In this field, FDG PET represents a non-invasive metabolic imaging procedure allowing both nodal and distant metastatic staging, and as such, is recommended by the 2007 ACCP guidelines as first staging procedure when NSCLC is diagnosed, for both mediastinal and distant metastases detection (2, 3).

Nuclear medicine imaging is based on the tracer principle, defined by Hevesy (4) as the in vivo use of a very small amount of radioactive isotopes showing identical chemical properties as biological compounds to analyze a particular metabolic pathway. PET imaging is based on positron-emitters such as ^{18}F, ^{15}O or ^{82}Rb, among others. The annihilation of the positron emitted leads to the emission of two 180°-sided 511 kev photons, detected by a full crystal ring (5). Radiochemistry and radiopharmacy both represents an important prerequisite to molecular imaging, as they allow the incorporation of the positron emitter in a chemical structure suitable for injection and further, to the analysis of a precise physiological pathway. Integrated in glucose (as ^{18}F-fluorodeoxyglucose, FDG), fluorine-18 allows the metabolic imaging of increased glucose metabolism (6) – or its reduction or absence (in therapy monitoring, in cysts or in particular epilepsy indications).

Current PET-CT cameras show a typical resolution (full-width at half-maximum, FWHM) of about 5 mm (7-9). There is an ongoing research on crystals or semi-conductor detectors to improve both sensitivity and time resolution, the last showing great importance for time-of-flight imaging (10-12).

The main advantage of PET-CT cameras compared to single PET detection is the instantaneous fusion with anatomical data, leading towards better spatial localization of hot spots, increasing specificity (13). In addition, the density map offered by CT images can be used for attenuation correction after little adaptations related to the difference in energy between 511 kev radiation from annihilation, and X-rays (14).

On the clinical side, the effect of FDG PET-CT imaging on NSCLC patient management is widely documented in the literature. An interesting and recent study by Gregory et al. (15) considered the change in treatment planning induced by FDG PET-CT and its effect on a 5-year survival period. In 42.3% of the 168 cases, a change of treatment modality or curative intent was induced by FDG imaging. Furthermore, FDG PET-CT staging was highly predictive of Overall Survival (OS). Another study evaluated at 34% the change in therapy planning related to M-staging from FDG PET-CT data compared to conventional imaging (16) Finally, FDG PET-CT imaging leads also to a reduction of futile thoracotomies (17) compared to conventional imaging.

Global sensitivity and specificity

In a recent meta-analysis including 13 studies and 2873 patients, sensitivity and specificity of PET-CT in the detection of extrathoracic metastases were estimated respectively to 77 and 95% (18). These numbers include the detection of brain metastases, were there is a known lack of sensitivity du to the high physiological uptake of FDG in the cerebral cortex. PET-CT sensitivity for the detection of brain metastases is about 27% with a very high specificity of 98%. (19). Therefore, when combining PET-CT with MRI for the detection of brain metastases, the global sensitivity for the detection of extra thoracic metastases from NSCLC rises to 84% according to Lee et al. (20).

Cost-effectiveness

Alongside with the clinical efficiency of PET-CT in the staging of NSCLC, the cost-effectiveness from an economical point of view has to be discussed (21). An interesting study from Sogaard et al. (22) analyses the potential economical spare by the reduction of futile thoracotomies and subsequent morbidity. Although, if the cost-effectiveness remains an important point from a payer's perspective, the societal cost as further discussed by Schreyogg and colleagues (23), should also be taken into account. Finally, there is an increasing amount of publications from China (18, 24), where an increased incidence of NSCLC is expected in the next years due to the high prevalence of smoking (25).

Primary diagnosis and M staging

Whole-body PET-CT allows the staging of NSCLC in one procedure: the size of the primary, the involvement of mediastinal nodes and extra-thoracic spread assessment naturally leads to a TNM staging. However, as T staging relies more on size and anatomical relation with mediastinum or chest wall, a high resolution CT or in some cases chest MRI are better suited to a precise T staging. The metabolical information given by the primary (intensity of uptake) was investigated as a prognosis factor of survival in stage I and II NSCLC (26, 27). In addition, the assessment of global tumor burden (using metabolic tumor volume, MTV) was also investigated as prognosis factor (28-31).

The involvement of mediastinal node metastasis (N staging) is detailed elsewhere in this issue of the
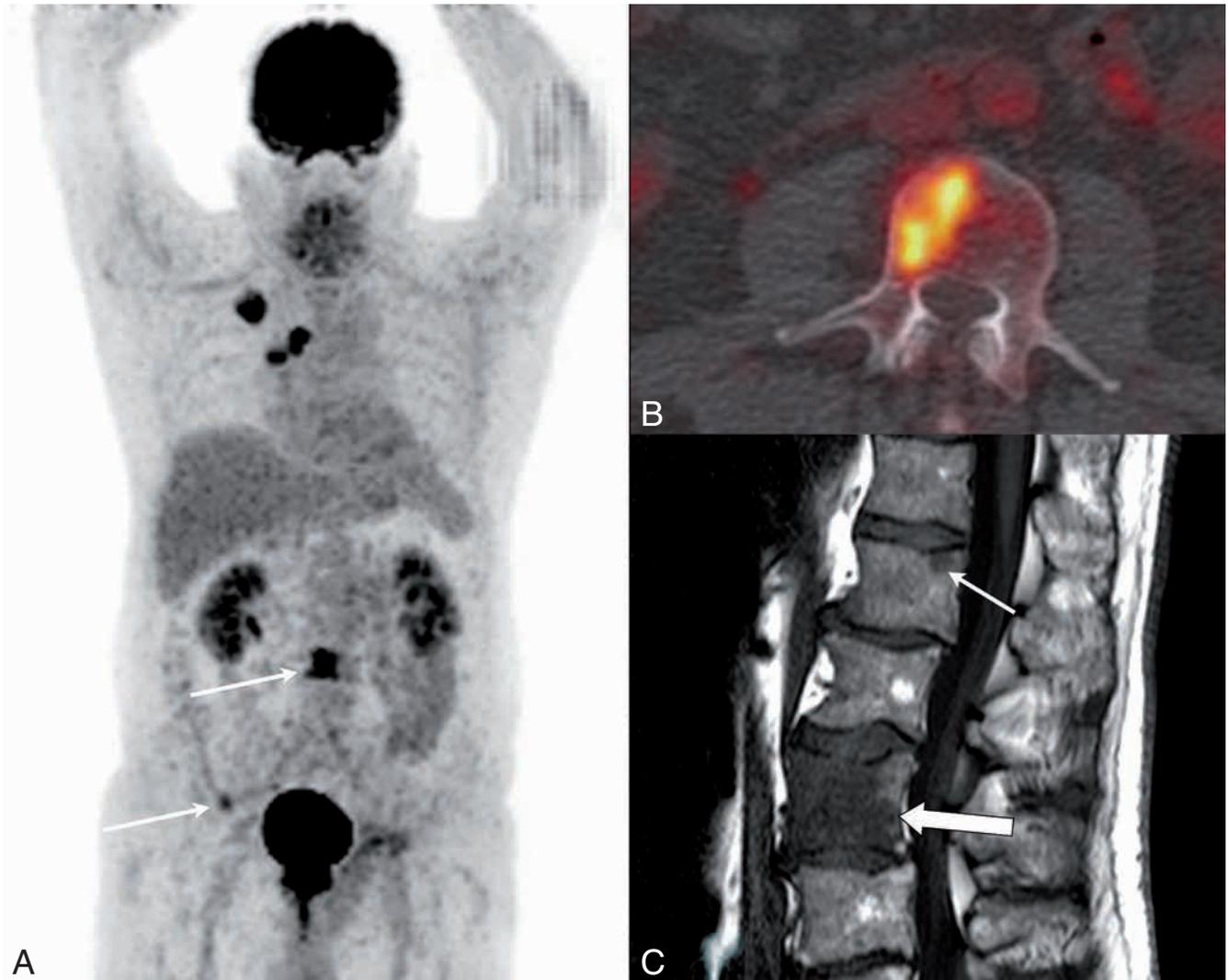

Fig. 1. — Primary staging of a right lung mass in a 66 year-old patient. A. Maximal Intensity projection (MIP) of whole-body 18F-FDG-PET showing the primary lung tumor in the right superior lobe, and both right hilar and right mediastinal invaded lymph nodes. The analysis of the lumbar region reveals a high uptake of FDG in the right part the body of the third lumbar vertebrae; a small focus is also noted in the region of the right coxa (arrows). B. Axial fusion PET-CT revealing a high focus of FDG in L3, raising suspicion for metastatic disease. C. T1-weighted MR image of the lumbar spine shows a large area of low signal intensity resulting from a marrow replacement in L3 (thick arrow), and other small areas in L1 (thin arrow) and in the right coxal bone (not shown). The TNM staging according to AJCC 7th edition was T2a (tumor larger than 3 cm) N2 (homolateral mediastinum invasion) M1b (bone metastases).

Belgian Journal of Radiology, and will therefore not be discussed.

M1a: pleural effusion

According to the 7th edition of the AJCC cancer staging manual (32), and since January 1, 2010, pleural effusion is considered as M1a staging. Pleural effusion in FDG PET-CT can be assessed by the maximal Standardized Uptake Value (SUVmax) of pleural lesions, but a ratio to the SUVmax value of the primary was reported to be the best predictive factor of malignancy (33). It must be kept in mind that pleural inflammatory disease is a well known false positive, in particular after talc

pleurodesis (even years after the procedure). This particularly illustrates the increase in specificity of hybrid imaging, as higher density of the high-uptaking pleural lesion (calcifications) is in favor of benign inflammatory process (34).

M1b: bone

A recent meta analysis from Wu and colleagues pooled Six studies involving 1894 patients for the assessment of bone metastases, estimating the sensitivity at 91% and a 98% specificity (18). The most recent included in this meta-analysis is a study from Liu et al. including 362 patients and estimating sensitiv-

ity and specificity at respectively 93,9% and 98,9%, for a global accuracy of 97,8% (35). Figure 1 illustrates the high FDG uptake in metastatic bone lesions.

M1b: adrenals

The assessment of adrenal involvement is a challenge, since the prevalence of incidental discovered lesions ("Incidentalomas") is estimated at autopsy ranging from 1.4% to 2.9% (36). In lung cancer patients in particular, this issue remains important as adrenals are common site of secondary lesions (37). Therefore, several authors have investigated potential parameters to distinguish
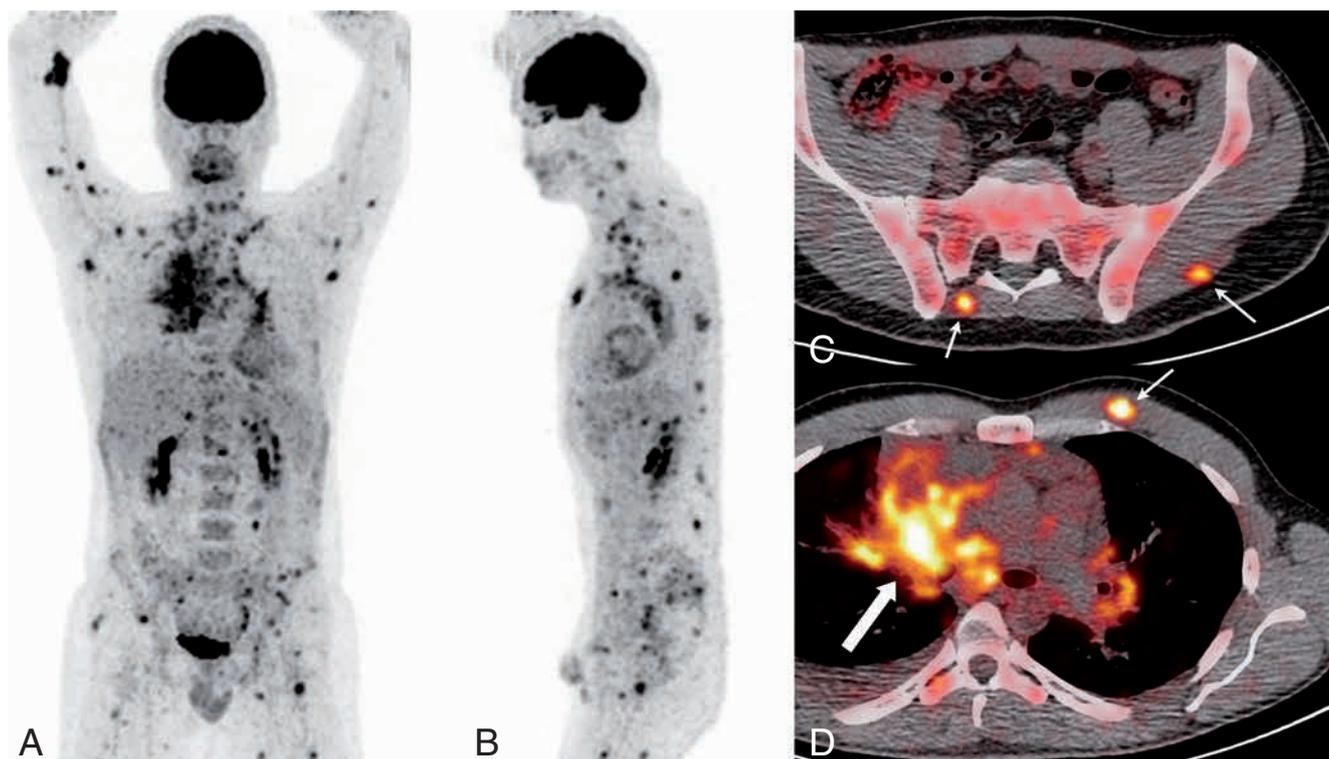
Fig. 2. — Coronal (A) and sagital (B) maximal intensity projections of FDG PET in a 36 years old patient referred for staging of squamous cell carcinoma of the right lung. In addition to the right hilar lesion, the whole-body analysis reveals multiple foci of uptake. C & D. The PET-CT fusion reveals the muscle location of the lesions (thin arrows), in addition to some bone lesions (not shown). Notice the primary right hilar lesion (thick arrow, D).

benign from malignant lesions (38-45). A study from Sweden about 534 patients (41) estimated that about only one fourth to one half of the adrenal lesion in cancer patients are actually from malignant origin. Authors recommend using dedicated adrenal imaging with CT attenuation measurements including washout, and biological testing for primary adrenal lesions. Other authors recommend the use of lesion-to-liver SUVmax ratio, as it appears to be more discriminating than SUVmax alone (40, 44).

The interpretation of increased uptake in the remaining adrenal gland after adrenalectomy has to be performed carefully, as physiological increase in FDG uptake might be seen in the remaining adrenal gland (46).

M1b: other - second malignancy

In rare cases, PET can discover unusual sites of metastases, such as muscle metastasis (47). Figure 2 shows a rare case of widespread muscle and bone metastases from lung primary in a 36 years-old patient.

Another incidental finding in addition to adrenal incidentalomas is the fortuitous discovery of another primary. This is not as rare as expected, as lung cancer shares its main risk factor (smoking) with other malignancies – head and neck squamous cell carcinoma, or esophageal carcinoma, among others. Lin and Ambati (48) estimate the prevalence of such unexpected primary between 1,2 and 4,2%, which as expected has high impact on patient management. Figure 3 shows a head and neck squamous cell carcinoma discovered by PET performed for the staging of lung cancer.

Recurrence

There is at the time no clear guidelines consensus for the timeline of FDG PET-CT to be performed after surgery for the detection of recurrence in asymptomatic patients. However, there is a clear role for PET as recently summarized and investigated by Toba and colleagues (49). This group from Japan estimated sensitivity and specificity at 94,4 and 97,6%, respectively, in a 101 patients cohort. These patients were elected for surgery, with a pathological stage ranging from 0 to IIIa. The authors conclude to the usefulness of PET-CT in this indication, but requiring larger studies especially from the cost-effectiveness point of view.

Future: PET-MRI?

In the last decade, all manufacturers of PET scanners moved to the hybrid PET-CT camera: there is on the market no more PET-alone available camera. This trend in hybrid imaging leads the major actors in industry to develop SPECT-CT scanners for monophotonic imaging, and beyond, PET-MRI. Technically, this integration must overcome many issues, mainly du to the magnetic field, by removing photomultiplier tubes in favor of semi-conductor detectors. This solution is not perfect, as it must compromise on both PET and MRI detection quality. Another option is to separate both the MRI and PET gantries, at the cost of a longer time examination, one of the gantries remaining unused. In addition, further research is required to maintain a high quality for attenuation correction (50), in order to maintain the semi-quantitative information of PET.

Fig. 3. — 60-year-old woman referred for PET-CT in the context of a left hilar mass. In addition to the primary directly invading the left hilum, (thin white arrow), an intense FDG uptake is noticed in both adrenal glands. The metabolic staging of the lung cancer concludes to a stage IV (M1b). In addition to the lung cancer, a clear focus of uptake in the right part of the floor of the mouth, associated with a lymph node in left level II cervical area, revealed a primary head and neck squamous cell carcinoma.

There is at the time no clinical data available to assess both usefulness and cost-effectiveness of PET-MRI in NSCLC patients.

Conclusion

PET-CT in NSCLC patients is a cost-effective and powerful tool in TNM staging, and in the detection of recurrence. It has to be coupled to brain MRI in the staging process due to its low sensitivity in brain metastases detection. Further studies a still required to evaluate the optimal timing of imaging after surgery, and the role of PET-CT in therapy response assessment. PET-MRI remains at the time in an early phase in development and no valid clinical data is yet available to evaluate its potential role in patient management.

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