

Sigrid Stroobants (Catholic University Leuven, 2002): *Role of positron emission tomography with F-18-fluorodeoxyglucose in the diagnosis, staging and chemotherapy evaluation in patients with non-small cell lung cancer.*

Summary

Lung cancer is by far the most frequent cause of cancer related death in the Western world. A rational management combining the best possible care with the existing financial resources is thus of great importance. Imaging techniques such as chest X-ray, CT, US, and sometimes MRI are essential in the diagnosis, staging, and follow-up of patients with lung cancer. These imaging tests are based on differences in *density* of tissues. Although current imaging technology allows exquisite anatomic detail, the density differences often don't allow a definitive diagnosis and staging, and more invasive tests with tissue sampling are required.

PET has been used over the last decades mainly as a research tool for brain function studies and for the assessment of cardiac metabolism. In the last years, it has gained widespread enthusiasm as an innovative technique in oncology, based on its ability to visualise differences in *metabolism* of tissues. The role of FDG-PET in the diagnosis, staging and treatment evaluation was the scope of this thesis.

Role of FDG-PET in the differentiation of solitary pulmonary nodules

SPNs are an important diagnostic dilemma. The differential diagnosis of a SPN is between malignancy, benign tumour and infection. Bronchoscopic samples yield a pathologic diagnosis in only a minority of the cases. Treatment strategy depends on the probability of malignancy. Certain clinical factors (e.g. age, smoking behaviour, ...) and radiological characteristics (size, change over 2 year, presence of calcification, cavity formation, spicular delineation, ...) can be of use in this decision making, but often more invasive tests are needed to come to a firm diagnosis. In this study we wanted to examine the value of FDG-PET in the characterization these SPNs. Fifty-two patients with small non-calcified undetermined lesions on CT with a mean size of 1.96 ± 0.79 cm (range: 0.4 – 3 cm) were evaluated. The final diagnosis was determined by histopathology on the resection specimen in 40/52 patients. Thirty-five nodules proved to be malignant and 5 lesions was found to be benign. In 12 patients, radiological follow-up examinations showed the benign character of the lesion (mean follow-up 20.1 ± 9.5 months).

Malignant SPN were found to have much higher FDG uptake compared to benign lung nodules (SUV of 7.52 versus 1.56, $P < 0.0001$). When a SUV cut-off of 2.5 is used to discriminate malignant from benign nodules, as often used in literature, an accuracy of 90% is obtained. FDG-PET was false negative in two patients (1 carcinoid tumour, 1 adenocarcinoma of 0.9 cm). The lower sensitivity in lesions < 1 cm can be explained by partial volume effect. False negative PET results in carcinoids are probably related to the low metabolic activity of these slow growing tumours. PET was false positive in three cases (2 tuberculomas, 1 benign lesion on radiological follow up). It is known that inflammatory processes can have similar FDG uptake than neoplastic tissue. Therefore the specificity is related to the prevalence of inflammatory (granulomatous) disease. In Belgium, this is mainly due to tuberculosis and anthracosilicosis. We analysed the data further by calculating LRs and P_{ca} . The influence on the clinical decision was the highest when an SUV threshold < 1.5 or > 3.5 was found, since the P_{ca} was $< 0.5\%$ or $> 99.5\%$ respectively. An SUV between 1.5 and 3.5 was of little diagnostic help since the P_{ca} of cancer was around 50%.

We concluded that FDG-PET is an accurate tool in the differentiation of SPN. Since the P_{ca} of a SPN with a SUV < 1.5 was found to be less than 5%, expectation is justified. PET is however less sensitive in very small lung nodules or slow growing tumours.

Mediastinal staging with FDG-PET in NSCLC patients

In patients without distant metastasis, the involvement of the mediastinal lymph nodes proves to be an important prognostic factor. Patients without metastatic lymph nodes (N0-disease) or with only intrapulmonary or hilar ones (N1) are generally considered for straightforward resection. Those with ipsilateral (N2) or contralateral (N3) metastatic mediastinal lymph nodes, however, have so-called locally advanced disease, and are usually not considered for primary surgical treatment. It is therefore of considerable clinical interest to evaluate these mediastinal lymph nodes as accurately as possible before and during treatment. CT is the most commonly used non-invasive staging method of the mediastinum but is far from satisfying and less accurate than invasive surgical staging. On CT, lymph nodes are considered to be metastatic when they are enlarged. Size is however a relative criterion since lymph nodes can be enlarged due to infectious or inflammatory causes, and small-sized nodes can nonetheless harbour metastases. Given the low accuracy of current imaging techniques, invasive surgical staging, either cervical mediastinoscopy and/or anterior mediastinotomy, remain the gold standard for mediastinal staging.

In this work, we investigated the value of FDG-PET in the initial mediastinal lymph nodes staging in NSCLC. Different acquisition protocols and interpretation algorithms were tested prospectively.

The first part is a **prospective study comparing the accuracy of CT scan and FDG-PET in the locoregional lymph node staging of NSCLC**. Thoracic CT, PET, and invasive surgical staging were performed in 50 patients with potentially operable NSCLC. Abnormalities on each of these staging examinations were recorded on a standard lymph node map and correlated with the results of invasive surgical staging. The sensitivity, specificity, and accuracy in detecting N2 disease of CT was 67%, 59%, and 64%, respectively. Results of PET blinded to CT were significantly better ($p=0.004$): 67%, 97%, and 88%, respectively. Accurate localisation of hot spots was not always easy given the limited anatomic information incorporated in a PET image. A difference of one level can however be of critical importance is the distinction is to be made between hilar (and thus resectable N1-disease) and adjacent mediastinal nodes (or unresectable N2-disease). Lesion localisation was clearly improved if PET was visually correlated with CT. This resulted in a sensitivity, specificity and accuracy of 93%, 97%, and 96%, respectively. We concluded that PET was significantly more accurate than CT in the mediastinal lymph node staging in NSCLC. Both examinations were complementary, since visual correlation with the anatomic information on CT improved the reader's ability to discriminate between hilar versus adjacent mediastinal nodes. Especially the high negative predictive value of PET is important for implementation in clinical practice. Since only microscopic disease is missed, mediastinoscopy can be omitted in patients without mediastinal invasion on PET. We believe that all patients with an abnormal mediastinal PET still should proceed to invasive surgical staging, to be sure that no patient with N0-N1 disease is denied the chance of cure by direct surgical resection based on a false positive PET.

The second part prospectively examines whether the **use of anatomic-metabolic PET-CT fusion images improves the accuracy of localisation of regional lymph node metastases** on a preoperative FDG-PET in NSCLC. This was evaluated in 56 patients in whom, in addition to PET and CT images, also PET-CT fusion images were generated using a computer algorithm based on mutual information. In the evaluation per individual lymph node station, CT was accurate in 87%, isolated FDG-PET reading in 91%, visual PET+CT correlation and PET+CT fusion in 93%. In the correct identification of the nodal stage, CT was correct in 50% of the patients, FDG-PET in 66%, visual correlation in 71%, and fusion in 73%. It was concluded that in the exact localisation of metastatic lymph nodes, reading of FDG-PET becomes more accurate if the FDG-PET images can be visually correlated with CT images, and that PET+CT anatomic-metabolic fusion images add only a marginal benefit compared to visual correlation.

The third part examines **the influence of attenuation correction on the accuracy of detection of metastatic lymph nodes**. Most studies that evaluated the performances of PET for mediastinal staging used attenuation corrected images. Since this is time-consuming, we wanted to evaluate in the next study if the faster whole-body scan (WB-PET) was as accurate as the attenuation corrected scan (AC-PET). Ninety-two patients who underwent both AC-PET and WB-PET were analysed, and the results of the 2 PET-modalities were confronted with final pathology findings of the lymph nodes. Attenuation correction had no impact on lesion detection. It resulted, however, in better localisation of hot spots. Ten of 74 metastatic lymph nodes were incorrectly localised in an adjacent lymph node station on WB-PET, resulting in an incorrect N-stage determination in 2 patients.

Can PET omit the need for invasive surgical staging? The answer is a conditional YES.

Especially the very high negative predictive value of FDG-PET for excluding N2/N3 disease (>95%), which is in fact higher than the negative predictive value for mediastinoscopy, is attractive for implementation in clinical practice. False negatives are mostly related to minimal N2-disease and straightforward thoracotomy is in rewarding in these patients since a reasonable prognosis after surgical resection can be expected. In some cases a false negative result is obtained by mislocalisation of a mediastinal lymph nodes (N2) to the hilum (N1). In order to reduce the number of futile thoracotomies based on unsuspected N2-disease secondary to mislocalisation of a hilar hot spot, mediastinal involvement should be excluded by invasive surgical staging in hilar PET-N1 disease. Therefore we advise to only omit mediastinoscopy in patients with N0-disease on PET. Finally, because of the low spatial resolution, PET is not able to distinguish mediastinal lymph nodes adjacent to the primary tumour. Therefore we advise to always perform invasive surgical staging in patients with central lung tumours.

Although the positive predictive value is also high, we would still advise mediastinoscopy in patients with positive mediastinal lymph node on PET, since some inflammatory conditions can cause false positive FDG uptake and we want to be sure that no single patient with N0 or N1-disease is denied the chance of cure by direct surgical resection based on a false positive PET.

Which acquisition protocol should be used? If invasive surgical staging is only omitted in PET-N0 patients, proper localisation of affected nodes becomes irrelevant. Since the sensitivity for detecting metastatic deposits is equal for all tested protocols, a fast and easy WB-PET is sufficient. From October 1998, this strategy was implemented in clinical practice and resulted in a nearly 50% reduction of the number of mediastinoscopies.

Additional value of FDG-PET in the detection of distant metastases

The finding of extrathoracic metastases implies that a patient is no longer amenable to long-term remission or cure. Therefore, accurate detection of metastatic spread is of paramount importance. Standard staging is based on a battery of diagnostic test including ultrasound, CT, MRI and bone scintigraphy. The current standard staging is however far from perfect. Since the structure-based staging modalities cannot accurately differentiate between benign and malignant lesions, a substantial number of detected abnormalities will remain equivocal and additional, often more invasive tests are needed to exclude or confirm metastatic disease. Furthermore, an important number of distant metastases are not picked up with the current staging procedure since approximately 20% of the patients, who underwent radical treatment for apparently localised disease, will nonetheless have a distant relapse.

The aim of this study was to evaluate the additional value of WB-PET in the detection of occult distant metastasis in potentially operable NSCLC patients in whom the conventional staging (CS) was negative (M0) or equivocal (Mx) for metastasis. In the 144 patients that were retrospectively evaluated, conventional staging was strictly negative for distant metastases in 123 patients (CS-M0-group) and equivocal in 21 patients (CS-Mx-group).

In 10 of the 123 CS-M0 patients, one or more lesions suspected for malignancy were observed on PET. Malignancy could be confirmed in 7 patients: unsuspected distant metastases were found in 5 patients (bone (n=3), retroperitoneal lymph node (n=1) or lung (n=1) and in the other 2 patients focal FDG uptake was related to a secondary primary tumour in the colon. In three patients, FDG uptake was related to false uptake in benign (colon polyp but with severe dysplasia) or inflammatory (fibrocystic mastopathy and bowel) disease.

Twenty-four lesions in 21 patients remained equivocal after thorough non-invasive staging (10 lung, 8 bone, 4 adrenal, 2 liver). PET correctly characterised 19/24 lesions (79%) in 18 patients as true positive (n=1) or true negative (n=18). False positive uptake was observed in 1 patient with an adenoma in the adrenal gland. In 2/21 patients, follow-up proved that PET was false negative (bone and lung).

Based on these results, it was concluded that additional value of PET for detecting occult distant metastasis is marginal when a thorough conventional staging is performed. Unsuspected metastases are mostly found in clinically hidden or difficult areas (bone, soft tissue, lymph nodes). Since false positive FDG uptake can occur, isolated positive PET finding that alters patient management should be confirmed by other methods (either additional imaging or tissue sampling). PET is able to exclude malignancy in the majority of lesions that are equivocal on conventional imaging. Exclusion of malignancy by FDG-PET should be done with caution in case of small lesions (e.g. adrenal nodules of less than 1 cm).

Use of FDG-PET in the evaluation of induction chemotherapy in stage III-N2 NSCLC

Although complete surgical resection is technically feasible in case of ipsilateral mediastinal lymph nodes involvement (stage IIIA-N2), the 5-year survival rate is only marginal. Since the majority of relapses occur at distant sites, systemic approaches with chemotherapy are necessary to improve cure rates. Over the last years, evidence is growing that cisplatin-based chemotherapy given prior to local treatment (either radical surgery or radiotherapy) is able to eradicate this subclinical metastatic disease, so that long-term survival can be achieved in one third of the patients. During this treatment, the clearance of viable tumour cells in the mediastinal lymph nodes by induction chemotherapy - so-called downstaging- is a very important aspect for the prognosis. Unfortunately, there are no reliable tools to examine this downstaging. Reassessment after chemotherapy by CT is far from accurate, while re-mediastinoscopy is often technically difficult. In this study, we want to evaluate the accuracy of FDG-PET in assessing the efficacy of induction chemotherapy in stage IIIA-N2 NSCLC in terms of response and downstaging after induction chemotherapy and in predicting long-term treatment outcome and survival after combined treatment. Forty-five patients were prospectively evaluated. CT and AC-PET were prior to and after 3 cycles of platinum-based induction chemotherapy.

In the subgroup of patient who underwent surgery as definitive local treatment (n=30), mediastinal findings on CT and PET were compared with pathology of the resection specimens. PET was significantly better than CT in detecting residual mediastinal disease with an accuracy of 73% and 57%, respectively. Compared to the results obtained during the initial staging, the lower accuracy is due to a loss in sensitivity from more than 80% when FDG-PET is used prior to treatment, to only 54% after induction chemotherapy. Whereas in the chemo-naïve patient only microscopic nodal involvement is missed, after induction chemotherapy also lymph nodes with obvious macroscopic disease and extracapsular extension were found to be false negative.

Reassessment with PET after induction chemotherapy was correlated with the outcome after the combined modality treatment in the whole group (n=45). Survival was significantly better in patients with mediastinal clearance on PET (P=0.02) or with more than 50% decrease of the SUV_{max} of the primary tumour (P<0.001) after induction chemotherapy. The combination of both findings, here called overall FDG-PET response, proved to be the best predictor of a favourable outcome (2-year survival of 70% versus 18%, P<0.0001). All PET response parameters were better predictors of survival than the currently used CT-response (2-year survival rate 49% versus 21%, P=0.0426). If these findings can be confirmed in larger clinical trials, FDG-PET after induction chemotherapy could become an accurate non-invasive method to predict therapeutic outcome, and

to separate patients with a good prognosis from those with a poor one. This in turn could help to select potentially curable patients for intensive locoregional treatment after induction chemotherapy, while avoiding the potential toxicity of it from the others.