# Detection, staging and follow up of lung cancer with positron emission tomography

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# 5 SUMMARY

**Chapter 1** explains lung cancer in terms of epidemiology and current diagnostic management with its drawbacks. Lung cancer is not only the most common cancer in man but also one of the leading causes of cancer death in the world today. Accurate staging of NSCLC is essential in the decision making of appropriate treatment since surgery is the treatment with the highest benefit. Besides assessment of mediastinal lymph node metastases, pre-operative screening focuses also on the detection of distant metastases. Current morphological imaging techniques lack accurate detection of lung cancer metastases. Therefore, diagnostic strategies with mainly these techniques result in performing unnecessary surgery in case of metastasized disease but also in denial of potentially curative surgery. PET is unique as it exploits a different angle in differentiating benign from malignant tissue using metabolic alterations in diseased tissue. Exploring the possibilities of PET in NSCLC is the basis of this thesis. The aims of the thesis conclude chapter 1.

In **chapter 2** three radiopharmaceuticals that have been studied with PET for their feasibility in imaging malignancies are briefly outlined: FDG, TYR, and CHOL. The most widely applied PET radiopharmaceutical in oncology is the glucose analogue FDG. NSCLC cells avidly incorporate FDG because they have an increased rate of glycolysis and overexpression of the glucose transporter. The metabolic pathway of FDG and the normal FDG body distribution is discussed. Although FDG PET may prove to be an accurate non-invasive imaging test for detecting malignancies, we should remember that FDG is not tumor specific. Macrophages, granulation tissue and necrosis may also show FDG accumulation. Therefore, PET measuring altered substrate requirements other than glucose is interesting. TYR has proven to be an appropriate radiopharmaceutical not only for the detection but also of the quantification of protein synthesis of malignant lesions. More recently, CHOL has been described as a PET radiopharmaceutical for tumor detection. As with FDG, the metabolic pathways of TYR and CHOL and their distribution within the body are discussed. Chapter 2 ends with a brief explanation about qualitative and quantitative PET data analysis. In most clinical situations, pure lesion detection rather than

quantification of the malignant metabolic rate is the main issue of whole-body PET.

Given the moderate performance of conventional methods for the staging of NSCLC, we have compared in **chapter 3** the ability of FDG PET and conventional methods to stage NSCLC in 102 patients with potentially resectable NSCLC. We have shown that FDG PET improves the detection rate of both mediastinal lymph node metastases and distant metastases. Of special interest is the high negative predictive value of FDG PET for detecting both mediastinal lymph node metastases and distant metastases. This can be used in advantage of patients with NSCLC; with negative mediastinal and distant FDG PET findings the surgeon may directly proceed to thoracotomy. The advantage of whole-body PET is not only to evaluate the primary tumor together with local metastases, but also leads to the correct identification of patients with unsuspected metastases. Although FDG PET, as compared to conventional methods, improves the staging of NSCLC patients, it has its limitations. Sensitivity and specificity of FDG PET are affected by metabolic activity and volume of malignant lesions, tumor to background contrast, PET image resolution and the presence or absence of inflammation. Knowledge of these effects is necessary for correct interpretation of FDG PET studies. Bearing this in mind, we suggest that implementing FDG PET as the initial investigation may improve the efficacy of the diagnostic workup in patients with NSCLC.

In the search for more specific PET radiopharmaceuticals, we have investigated whether whole-body CHOL PET has advantages over whole-body FDG PET in patients with thoracic cancer. Although the short half-life of CHOL could limit the applicability of whole-body scanning, in practice CHOL PET is feasible to obtain images from crown to femur in patients with thoracic cancers. This is appealing considering the ability of thoracic cancers to metastasize locoregionally and hematogenously. CHOL PET gives clear images with good contrast and can certainly be used to visualize malignant tissue. However, as compared to FDG PET it is less accurate due to lower accumulation of CHOL in malignant tissue. The inferiority is most notable in the detection of lymph node metastases. CHOL PET

shows superiority as compared to FDG PET in detecting brain metastases, however, this is not surprising considering the physiological glucose uptake by the brain. On the other hand, for CHOL PET normal tracer accumulation hampers detection of metastases in liver and kidney since these organs are major sites for choline oxidation.

Most publications dealing with FDG PET in NSCLC are based on studies with attenuation correction. Attenuation correction improves anatomic orientation (e.g. discrimination of lung tissue from mediastinum or liver) and attenuation corrected images may be evaluated quantitatively (e.g. research purposes to provide a quantitative parameter from the study). However, such acquisitions are time consuming and the vast majority of clinical FDG PET studies are made for staging purposes, i.e. lesion detection rather than tracer uptake quantification. Consequently, the relevance of performing a transmission scan for attenuation correction can be questioned if only visual evaluation is needed for the staging of NSCLC patients. Two independent observers blinded for clinical results studied non-attenuated and attenuated corrected whole-body FDG PET images in 23 consecutive patients with NSCLC. Comparing both types of scans, attenuated corrected scans show better delineation of internal organs. But in the assessment of hot spots no difference was observed between both scanning methods. In other words; attenuation correction may not be necessary for clinical staging purposes in patients with NSCLC. Considering the significant growth in the number of clinical FDG PET studies, scanner time is precious and elimination of attenuation correction seems justified in cases of pure FDG PET lesion detection.

In **chapter 4** we discuss the use of PET for post-treatment evaluation of tumor metabolism. Post-treatment analysis of tumor metabolism by PET may be of interest since anatomical imaging modalities provide only a moderate correlation with survival in lung cancer. We evaluated tumor response measurements with FDG PET and CT in 75 lung cancer patients treated with chemotherapy. PET and CT studies were performed within 2 weeks before start of treatment and approximately 6 weeks after the end of the last cycle of treatment. Both imaging techniques were independently, visually

scored. In a limited number of patients quantitative analysis with PET was performed of the primary tumor. It was shown that tracer uptake of the primary tumor significantly decreases after treatment. In 64% of the patients PET and CT showed both the same response rates. Using Kaplan-Meier and Cox regression analysis prognostic impact of tumor response as measured with PET was significant when adjusted for CT, while the impact of CT tumor measurements could not be demonstrated.

Increased amino acid utilization for protein synthesis is also a feature of malignancy. It is suggested that amino acids, as compared to FDG, play a minor role in the metabolism of inflammatory cells. In the post-treatment evaluation of tumor metabolism this may be of importance since treatment may induce inflammatory hypermetabolism causing an overestimation of FDG uptake and thereby misinterpretation of tumor response. Therefore, we evaluated the potential role of TYR PET for the visualization and quantification of protein metabolism of tumor tissue and normal lung tissue before and after chemotherapy or radiotherapy. First, TYR appeared to be a good tracer for the visualization and quantification of lung cancer. Second, PSR as well as SUV, both measures of quantifying tracer uptake, of tumor tissue decreased during the treatment course. Persistent low uptake was observed in normal lung tissue, during and after chemotherapy or radiotherapy. It should be noted that the PSR reflects a dynamic measurement over time after injection of the tracer, whereas the SUV reflects a static measurement of uptake at a certain chosen time point after tracer injection. Therefore, PSR may be of greater value for monitoring tumor responses to treatment. Since this study was set up as a feasibility study, other studies are needed to ascertain whether TYR PET for the quantification of the PSR will provide us with additional information with treatment implications in patients with lung cancer.

In conclusion, we have shown that FDG PET as compared to conventional staging methods improves the detection rate of both mediastinal and distant metastases in patients with NSCLC. For accurate measurements of radiopharmaceutical uptake attenuation correction of the PET signal is obligatory, however, attenuation correction may be omitted for purposes of pure clinical staging in

proven NSCLC patients. Comparing anatomical and metabolic tumor dimensions and their changes due to chemotherapy, visually evaluated FDG PET scans perform better than CT in response measurements. Tumor response measured with FDG PET had also more prognostic impact than CT measurement. In the search for more specific PET radiopharmaceuticals, CHOL and TYR were investigated for its potential advantages over FDG in patients with thoracic cancer. CHOL PET can be used to visualize thoracic cancers and the detection of brain metastases was superior. However, for the detection of lymph node metastases CHOL PET was inferior compared with FDG PET. TYR appears to be a good tracer for visualizing lung cancer and PSR of tumor tissue can be used to quantify reduction in the metabolic rate of the tumor.