INTRODUCTION
Lung cancer is the global leading cause of cancer related mortality in men and second leading cause of cancer related mortality in women. Lung cancer occurs in two different forms, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), respectively. Of all lung cancer patients, 80-85% are diagnosed with NSCLC, which is the subject of this thesis. At presentation, close to 70% of patients with NSCLC have locally advanced (stage III) or metastatic (stage IV). Median overall survival rates are between 10 to 14 months for stage III and 6-8 months for stage IV patients. To improve survival and quality of life for these patient groups, novel diagnostic targets and personalized therapies are necessary.

The choice of therapy is largely depending on the stage of the disease and performance status. Staging is the result of several diagnostic procedures that together determine the diagnosis and extent of disease. Currently, the diagnostic work up usually starts with the general practitioner who requests a chest X-ray in case of suspicious complaints or signs at physical examination. In case abnormalities are found, then patients are referred to a chest physician and a positron emission tomography (PET) with X-ray computed tomography (CT), a so-called PET/CT-scan, is performed using the radiopharmaceutical 2-deoxy-2-(18F)fluoro-D-glucose (18F-FDG). The uptake of 18F-FDG is increased in many cancers, and reflects tumor metabolic activity. Apart from a visual assessment, the maximum standardized uptake value (SUV\text{max}) is used as a measure of tumor activity and is of value because of its prognostic and predictive abilities. However, SUV\text{max} is based upon a single voxel value (i.e. a very small tumor area) and does not take into account aspects such as total tumor volume, mean tumor glycolysis and tumor heterogeneity.

18F-FDG PET/CT can also be used to assess response to treatment. However, the various assessment criteria were developed in the chemotherapy era and may need to be adopted in targeted therapy or immunotherapy treated patients. Response assessment after chemotherapy is performed by the use of anatomic response criteria such as RECIST. This assessment is much less predictive in patients treated with immunotherapy and criteria have recently been adapted for this modality. Therefore new response assessment need to be introduced that can replace the classical RECIST criteria.

A better approach to evaluate NSCLC patients would be to take all tumor voxels into account. Previously, techniques such as the total lesion glycolysis (TLG)
and metabolic tumor volumes (MTV) have been introduced to take advantage of volumetric measurements of PET imaging. These two parameters have also been shown to be prognostic in all stages of NSCLC\textsuperscript{10-13}. The metabolic activity performs better in predicting survival as compared to the TNM seventh edition staging manual\textsuperscript{14}. Although these techniques have additional value compared to measuring SUV\textsubscript{max}, these volumetric techniques still do not take into account tumor heterogeneity. In this thesis we have studied tumor heterogeneity in advanced NSCLC.

\textsuperscript{18}F-FDG PET for therapy response assessment has shown promise, as previous studies have shown. Often, metabolic changes precede anatomic tumor lesion size alterations\textsuperscript{15-17}. Voxel-by-voxel analysis may provide more detailed information of tumors. Whether this technique actually provides an advantage in determining tumor response needs to be confirmed. Volumetric analysis of tumors is a technique in which a comparison is made of individual (tumor) areas within the same location on different types of images acquired at different time points. It is applicable for any intensity based mapping and has already been applied with other imaging modalities\textsuperscript{18}.

In chapter 2 we have studied detailed volumetric assessments of \textsuperscript{18}F-FDG PET/CT using voxel-by-voxel analysis in patients with advanced NSCLC at baseline and after 6 weeks of treatment. The question is whether such a technique produces robust and reproducible results and is applicable for measuring tumor response with \textsuperscript{18}F-FDG PET/CT.

Different tumor characteristics have been identified which causes resistance to treatment. One such characteristic is hypoxia, which is related to resistance to both chemotherapy and radiotherapy\textsuperscript{19, 20}. To image the distribution of hypoxia within patients, different hypoxia imaging PET tracers have been developed. These different tracers may be used as a biomarker. One of the questions in chapter 3 is whether we can reliably use a hypoxic biomarker in patients with untreated advanced NSCLC. In order to do this, we studied \textsuperscript{18}F-FAZA, a hypoxia specific PET tracer, and \textsuperscript{18}F-FDG concomitantly in 11 patients with untreated stage III-IV NSCLC. In chapter 4 we studied the use of \textsuperscript{18}F-FAZA PET/CT to determine whether the hypoxic biomarker is a reliable marker in 7 patients with advanced NSCLC who received chemotherapy.
Imaging Pi3K inhibition

In chapter 5 we studied the inhibition of phosphoinositide 3-kinases (PI3K’s) by \(^{18}\)F-FDG-PET imaging. PI3K’s are essential enzymes that regulate glucose uptake in normal and tumor tissue\(^{21}\). It is unknown how PI3K inhibitors influence metabolic effects in tumors and normal tissue. Previous animal studies have shown that metabolic measurement using \(^{18}\)F-FDG might be suitable for assessing response with treatment with a PI3K inhibitor\(^{22}\). With \(^{18}\)F-FDG PET imaging normal tissue metabolism can be measured in patients with advanced NSCLC when they are treated with PI3K inhibitors.

Imaging EML4/ALK inhibition

In chapter 6 we studied total metabolic tumor response in ALK positive patients with advanced NSCLC. Treatment with crizotinib for those patients with the anaplastic lymphoma kinase (ALK) translocation has shown significant clinical benefit\(^{23,24}\). Tumor measurements in these studies were performed with CT. We wondered whether \(^{18}\)F-FDG-PET/CT would improve imaging of tumor changes during crizotinib treatment. Furthermore, it is not known whether CT or \(^{18}\)F-FDG PET/CT are equally suitable for detecting disease progression during follow up in this particular group of patients, so this was subject of study as well.

Radiation therapy

For stage III NSCLC, the treatment consist of concurrent thoracic chemoradiation. The chemotherapeutic drug gemcitabine thereby enhances the radiation due to a phenomenon called radiosensitization. One of the strongest radiosensitizing drugs available is gemcitabine. The use of gemcitabine in NSCLC as a radiosensitizer has been limited due to substantial excess toxicity associated with the use of full dose or with large radiation fields (i.e. 2D radiotherapy)\(^{25-28}\). However, phase 1 and 2 studies showed the feasibility and effectiveness of low-dose gemcitabine combined with 3D radiotherapy for unresectable NSCLC\(^{29,30}\). In a prospective study we addressed the question whether proper staging followed by induction chemotherapy and weekly low-dose gemcitabine concurrently with 3D radiotherapy had a good efficacy in stage III NSCLC patients (chapter 7).
Targeted therapy

To apply targeted therapy in advanced NSCLC, sequencing technologies are needed to assess genetic aberrations. These technologies include high resolution melting and Sanger sequencing and the more recently introduced next generation sequencing. Different genetic aberrations, such as epidermal growth factor receptor (EGFR) mutations or ALK translocations, each require a tailored treatment. In the Northern Netherlands we studied the frequency of EGFR and Kirsten rat sarcoma (KRAS) mutations as well as the treatment effect of EGFR tyrosine kinase inhibitors (TKI). So the questions addressed in this chapter are: 1. what are the frequencies of these mutations within the Northern Netherlands? 2. What is the treatment effect of EGFR TKI? This study is described in chapter 8.
References


