Molecular imaging in the combined modality treatment of lung cancer

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PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
op gezag van de Rector Magnificus, Prof. mr. G.P.M.F. Mols,
volgens het besluit van het College van Decanen,
in het openbaar te verdedigen
op vrijdag 22 oktober 2010 om 12.00 uur

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Judith Gertruda Mechtilda van Loon

Promotores

Prof. dr. D. De Ruysscher

Prof. dr. Ph. Lambin

Copromotor

Dr. L. Boersma

Beoordelingscommissie

Prof. dr. E.F.M. Wouters (voorzitter)

Dr. B. Brans

Prof. dr. Y. Lievens (UZ Leuven)

Prof. dr. J.P.A.M. van Meerbeeck (UZ Gent)

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CHAPTER 1

General introduction and outline

1.1 Epidemiology

Each year, more than 3 million cancer cases are diagnosed in Europe, with over 1.5 million patients dying from this disease. The major cause of cancer death is lung carcinoma, accounting for almost 20% of all deaths due to cancer in 2008 ¹. It is the third common malignancy in Europe, after colorectal and breast cancer, accounting for more than 12% of all new cancer cases.

In the Netherlands, the age-standardised incidence of lung carcinoma is decreasing in men, but still increasing in women. These trends largely reflect the changes in the prevalence of smoking, which is the major cause of this disease ². Since 2006, more than 10,000 patients a year are diagnosed with lung carcinoma. Given the ageing of the population, lung cancer will remain an important health problem. The prognosis of the disease is poor, with a 1 year overall survival of 40% and a 5 year overall survival of only 14% ³.

Lung cancer is broadly divided in two main categories on basis of its histology: non-small cell lung cancer (NSCLC), accounting for 80-85% of cases, and small cell lung cancer (SCLC), accounting for 15-20% of cases. Approximately 40% of NSCLC and more than 70% of SCLC patients have distant metastases at initial presentation ⁴. Most of these patients are treated with palliative systemic treatment, together with analgesics and palliative radiotherapy to relieve symptoms. The remaining patients present with disease confined to the thorax. Those patients are generally offered curative intent therapy.

Non-small cell lung cancer (NSCLC)

NSCLC is divided in four different stages on basis of the anatomical extent of disease, which is classified according to the TNM classification. The TNM classification is used to define the extent of disease with respect to the primary tumour (T), involvement of regional lymph nodes (N) and the presence of distant metastases (M). Recently, the 7th edition of the TNM classification system has been introduced ⁵. With respect to NSCLC, this edition includes some changes in the T and M descriptors, as well as in the assigned stages on basis of the TNM ⁶.

The assigned stage is prognostic for survival, and it forms the basis for selection of the most appropriate treatment regimen (Figure 1.1). Of all patients with NSCLC, only 25% is diagnosed with stage I & II disease, which is considered as resectable. Early stage patients who are medically inoperable are commonly treated with radiotherapy. In particular, stereotactic radiotherapy has become an attractive treatment modality for this patient category, with a 3 year local control rate of more than 90% and a 3 year overall survival of 60% ⁷. Thirty-five percent of patients have locally

advanced (stage III) disease, for whom surgery is mostly not an option ⁴. For these patients, the current standard treatment consists of radiotherapy in combination with chemotherapy.

T	N	M	Stage	First choice treatment*
1	0	0	IA	Surgery
2a	0	0	IB	
1	1	0	IIA	Surgery + chemotherapy
2a	1	0	IIA	
2b	0	0	IIA	
2b	1	0	IIB	
3	0	0	IIB	
1	2	0	IIIA	Concurrent chemoradiotherapy
2	2	0	IIIA	
3	1 or 2	0	IIIA	
4	0 or 1	0	IIIA	
any	3	0	IIIB	
4	2 or 3	0	IIIB	
any	any	1	IV	Chemotherapy**

Figure 1.1 TNM staging (7th edition) for NSCLC and treatment of choice per assigned stage

* According to the American College of Chest Physicians (ACCP) guidelines

** In selected patients with oligometastasis: chemotherapy, high dose radiotherapy, surgery

Small cell lung cancer (SCLC)

SCLC is characterized by a rapid growth rate and early dissemination to lymph nodes and distant organs. SCLC patients are classically divided into limited and extensive stage disease ^{8, 9}. Recently, however, the use of the TNM staging system has been recommended for SCLC as well ^{10, 11}. Approximately 25% of SCLC patients present with stage I-III disease ⁴. Even in this patient group without distant metastases, surgery is rarely an option because of the advanced stage of locoregional disease. Furthermore, its benefit in the rare stage I patient is controversial ^{12, 13}. Therefore, combined chemo-radiotherapy is the first choice treatment for patients with stage I-III SCLC.

1.2 Imaging modalities for patient selection and evaluation of treatment

Traditionally, anatomical imaging modalities are applied for the diagnosis and staging, as well as in the follow-up of lung cancer patients. These modalities are based on contrast differences between normal and cancerous tissue. More recently, molecular imaging techniques have been developed, which allow the visualization of molecular processes inside tumour and normal tissues in a non-invasive manner.

Anatomical imaging

Chest X-ray and computed tomography (CT) are the most widely used anatomical imaging modalities in lung cancer. A chest X-ray is useful as a first-line tool to assess the indication for further imaging. The chest CT scan allows cross-sectional imaging of the body through rotational x-ray imaging. Modern CT scanners have a resolution down to less than 1 mm. For lung cancer, it is the imaging modality that provides best anatomic detail. It has a high sensitivity for the detection of the primary tumour, enabling its exact localization. The contrast between adjacent tissues can be further improved by the administration of intravenous contrast agents.

While CT is the most accurate imaging modality with respect to anatomical information in lung cancer, its limited potential to distinguish between vital tumour and non-malignant tissue prevents the use in certain areas of the TNM classification. Anatomic imaging modalities are compromised in their ability to define the exact tumour border in certain circumstances, such as in patients with atelectasis or tumours near the thoracic wall¹⁴. Furthermore, the accuracy to differentiate between malignant and benign lymph nodes is lower, with a sensitivity and specificity of CT for identifying mediastinal lymph node involvement of 51% and 85%, respectively¹⁵. Finally, the assessment of changes early during or after treatment with conventional chest X-ray and CT is limited by their poor discriminating capacity between residual tumour and treatment induced changes^{16,17}.

With respect to these issues, molecular imaging with positron emission tomography (PET), providing information on specific biochemical pathways, has additional value.

Molecular imaging with positron emission tomography (PET)

The principle of PET lies in the detection of positrons emitted by a radioactive tracer. In this way, three dimensional images can be obtained which show the distribution of the tracer throughout the body. Different radiopharmaceuticals have been evaluated for the imaging of malignant tumours, of which ¹⁸F-fluorode-

oxyglucose (FDG) is by far most commonly used. Like glucose, FDG is transported into the cell and subsequently phosphorylated by hexokinase. The fluorine atom of FDG, however, prevents it further metabolism, and hereby, FDG is metabolically trapped inside the cell. FDG-PET scanning utilizes the difference in accumulation of FDG between normal and cancerous tissues, based on an enhanced glucose metabolism in cancer cells owing to increased expression of the glucose transporter enzyme Glut-1. In this way, tumours can be imaged as focal accumulations of FDG. This makes FDG-PET scanning a sensitive method for the detection and visualization of tumour bearing areas, as well as for monitoring response to treatment.

The added value of FDG-PET in the staging of locally advanced lung cancer is beyond doubt, as it results in stage migration for up to 30% of stage III NSCLC and 6-33% of limited disease (LD) SCLC patients, which are diagnosed with distant metastases¹⁸⁻³⁰. This upstaging withholds toxic radical therapy in these patients who will not benefit from it. FDG-PET is more accurate than CT with respect to mediastinal lymph node staging as well, with a sensitivity and specificity of 74% and 85%, respectively¹⁵. At present, performing an FDG-PET scan is recommended as a routine clinical staging tool for assumed stage IB-IIIB NSCLC¹⁵.

There are certain limitations, however, to the use of FDG as a cancer imaging agent. One important limitation is the increased uptake in non-malignant areas with enhanced glucose metabolism, such as inflammatory regions³¹. These limitations have driven the search for tracers other than FDG that specifically visualize certain molecular characteristics. These include proliferation markers, such as ¹¹C-methionine, ¹¹C-choline and ¹⁸F-fluorothymidine and markers of hypoxia, of which ¹⁸F-FMISO is most commonly applied. Furthermore, tracers are being developed that visualize the expression of specific receptors at the surface of tumour cells.

Thus, molecular imaging with PET shows many advantages over anatomical imaging alone in the combined modality treatment of lung cancer. Especially the use of integrated PET-CT, combining anatomical information with functional information of the PET scan has great clinical potential.

1.3 Combined modality treatment for inoperable lung cancer

Radiotherapy (RT) in combination with chemotherapy is the treatment of choice for the approximately 35% of NSCLC patients presenting with locally advanced (stage III) disease, for whom surgery is mostly not an option⁴. It is also the first choice treatment for the approximately 25% of SCLC patients presenting with stage I-III disease.

Chemotherapy can be given either before the start of RT (sequential chemo-radiotherapy) or simultaneously with RT (concurrent chemo-radiotherapy). In NSCLC, concurrent treatment demonstrated superior outcome compared to sequential chemo-radiation with a 3 year survival of 24% with concurrent treatment, vs. approximately 18% with sequential therapy³². The same holds true for SCLC, in which a clear benefit of concurrent over sequential chemo-radiotherapy has been demonstrated³³.

1.4 Purpose and outline of the thesis

Although the survival of locally advanced NSCLC and stage I-III SCLC has significantly improved with combined chemo-radiotherapy, the majority of patients still show disease progression shortly after the completion of treatment. About one third of patients experience local tumour progression as their first site of relapse³⁴⁻³⁸. Furthermore, these combined treatment strategies are associated with higher toxicity rates than treatment with RT alone. Theoretically, locoregional tumour control could be improved by increasing the radiotherapy dose or intensification of the chemotherapy regimen. Because dose limiting toxicity already occurs with the presently applied combined treatment schedules, this is not straightforward, as further intensifying therapy would result in unacceptable toxicity.

Recently, more conformal radiotherapy techniques such as stereotactic body RT (SBRT), intensity modulated RT (IMRT) or proton therapy have been introduced, as well as targeted systemic agents, which increasingly allow for specific antitumour therapy. This provides opportunities to improve locoregional control without enhancing toxicity. The introduction of these techniques, however, emphasizes the need for imaging techniques enabling accurate definition of the presence and extent of tumour.

Another approach to optimize the treatment benefit in each individual patient can be found in strategies directed at an early adaptation of therapy dependent on the treatment response. Finally, the outcome after completion of curative treatment could potentially be improved by an early detection of local progression, increasing the opportunity to be offered salvage therapy. In view of the limited ability of anatomical imaging techniques to discriminate between active tumour and post-treatment changes, molecular imaging could play an important role in this respect.

The aim of this thesis is to assess the potential of molecular imaging with PET to optimize the combined modality treatment of lung cancer.

In regard to this aim the following aspects are addressed:

- FDG-PET-CT based target volume definition to optimize radiotherapy for locally advanced lung cancer
- The value of FDG-PET-CT in the follow-up of locally advanced NSCLC patients
- Development of novel PET tracers for the non invasive imaging of specific tumour characteristics

Part I: FDG-PET-CT based target volume definition to optimize radiotherapy for locally advanced lung cancer

No imaging technique allows a direct evaluation of the presence and extent of microscopic disease extension around the tumour visible on PET and CT. Therefore, in RT planning, a margin of tissue surrounding the macroscopic tumour (Gross tumour volume, GTV) is added in all patients to ensure that the area with potential microscopic spread is covered by the radiation field³⁹. The resulting volume is defined as the clinical target volume (CTV).

Microscopic disease spread, however, does not occur in all patients with NSCLC^{40, 41}. Hence, the ability to predict the presence of microscopic spread on the basis of pre-treatment PET or CT imaging could lead to tumour tailored margins, resulting in an optimal sparing of normal tissue in individual patients. In chapter 2, risk factors for the presence of microscopic disease spread were identified on pre-treatment PET-CT.

Traditionally, both in NSCLC and SCLC, prophylactic irradiation of clinically uninvolved mediastinal lymph nodes was performed. This resulted in large treatment volumes. Routine elective nodal irradiation is no longer recommended in NSCLC^{42, 43}, as both PET- and CT-based selective irradiation of involved lymph nodes have proven its safety⁴⁴⁻⁴⁷. The safety of selective nodal irradiation (SNI) in NSCLC, however, cannot straightforwardly be extrapolated to SCLC. This is illustrated by a study showing an unacceptable amount of 11% of isolated nodal failures outside of the treatment volume in SCLC with CT-based SNI in SCLC⁴⁸. As FDG-PET scanning is more accurate than CT in the primary staging of SCLC^{29, 49-51}, we hypothesized that PET based SNI would improve the coverage of involved lymph nodes compared to CT-based SNI^{29, 49-51}. Chapter 3 describes the results of a planning study in which the influence of selective irradiation of FDG-PET positive mediastinal nodes on radiation fields and normal tissue exposure in limited disease (LD) SCLC was investigated. A prospective study was subsequently performed to evaluate the safety of PET-based SNI in LD-SCLC, of which the results are reported in chapter 4.

Part II: The value of FDG-PET-CT in the follow-up of locally advanced NSCLC patients

Theoretically, early detection of progressive disease after curative intent therapy, at a time that radical retreatment is still an option, could improve survival. In NSCLC however, there are at present no convincing data supporting that early detection of progression with chest X-ray or CT scan results in survival benefit^{16, 52-54}. A major restriction of both modalities is the poor discriminating capacity between residual or recurrent tumour and post-treatment changes^{16, 17}. As repeated imaging is often needed to confirm progression, this delay could lead to missing the chance for salvage treatment. In this respect, FDG-PET scanning could have additional value, as PET is more accurate than CT in the distinction of tumour from post-radiotherapy effects⁵⁵⁻⁵⁷, and is known to be prognostic for outcome⁵⁸⁻⁶². In chapter 5, we evaluated whether a PET-CT 3 months after therapy can detect potentially curable progression in NSCLC patients treated with curative intent with (chemo-)radiation. Chapter 6 describes the results of an economic evaluation assessing the cost-effectiveness of a PET-CT based follow-up strategy.

Part III: Development of novel PET tracers for the non invasive imaging of specific tumour characteristics

Recent advances in molecular biology have revealed a number of biological characteristics of cancer cells that offer potential targets for imaging. Some of these characteristics, such as hypoxia, cell density and proliferation, are associated with tumour aggressiveness and response to anticancer treatment. These characteristics are known to be heterogeneous across the tumour⁶³⁻⁶⁵. Non-invasive imaging of those characteristics could have great clinical importance, as it would allow patient selection for targeted antitumour therapy as well as the identification of relatively treatment resistant areas within the tumour.

In part III of this thesis, two phase I trials are presented evaluating novel PET tracers. In chapter 7 the results of a phase I trial evaluating [¹⁸F]HX4, a novel marker of hypoxia, are reported. In chapter 8, the safety of Zirconium-89 (⁸⁹Zr) labelled cetuximab was evaluated. Cetuximab is a monoclonal antibody against the epidermal growth factor receptor (EGFR), a receptor which expression has been correlated with tumour aggressiveness and treatment resistance⁶⁶.

Part IV: Discussion

In part IV, the role of PET in the combined modality therapy of lung cancer is discussed. A review of the available literature regarding this subject is provided in chapter 9. In chapter 10, the major results of this thesis are described in the context of the currently existing evidence, and perspectives for future research are highlighted.

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Part

I

**FDG-PET-CT based target volume definition
to optimize radiotherapy for
locally advanced lung cancer**

CHAPTER 2

Microscopic disease extension in 3D for Non Small Cell Lung Cancer: development of a prediction model using pathology validated PET and CT features

Judith van Loon*

Christian Siedschlag*

Joep Stroom

Hans Blaauwgeers

Robert-Jan van Suylen

Joost Kneijens

Maddalena Rossi

Angela van Baardwijk

Houke Klomp

Wouter Vogel

Sjaak Burgers

Liesbeth Boersma

Kenneth Gilhuijs

*** Both authors contributed equally to this manuscript**

Submitted

Abstract

Background and purpose

One major uncertainty in radiotherapy planning of non-small cell lung cancer (NSCLC) concerns the definition of the clinical target volume (CTV), meant to cover potential microscopic disease extension (MDE) around the macroscopically visible tumour. The primary aim of this study was to establish pre-treatment risk factors for the presence of MDE. The secondary aim was to establish the impact of these factors on the accuracy of PET and CT to assess the total tumour-bearing region at pathology (CTV_{path}).

Methods and materials

34 NSCLC patients, who underwent CT and PET prior to lobectomy, were included. Specimens were examined microscopically for MDE. The gross tumour volume (GTV) on CT and PET was compared with the GTV and the CTV at pathology, taking tissue deformations into account. Using multivariate logistic regression, image based risk factors for the presence of MDE were identified and a prediction model was developed based on these factors.

Results

MDE was found in 17 of the 34 patients (50%). MDE did not exceed 26 mm in 90% of patients. In multivariate analysis, two parameters (mean CT tumour density and GTV_{CT}) were significantly associated with MDE. The AUC of the 2 parameter prediction model was 0.86. 13 tumours (38%, 95% CI: 24-55%) were identified as low risk for MDE, being potential candidates for reduced intensity therapy around the GTV. In the low risk group, the effective diameter of the GTV_{CT/PET} accurately represented the CTV_{path}. In the high risk group, GTV_{CT/PET} underestimated the CTV_{path} with on average 19.2 and 26.7 mm, respectively.

Conclusions

CT features have potential to predict the presence of MDE. Tumours identified as low risk of MDE show lower rates of disease around the GTV than high risk tumours. Both CT and PET accurately visualize the CTV_{path} in low risk tumours, but underestimate it in high risk tumours.

2.1 Introduction

Radiotherapy (RT) with or without chemotherapy is the current standard treatment in locally advanced (stage III) and inoperable stage I/II non-small cell lung cancer (NSCLC). Even with concurrent chemoradiotherapy, about one third of patients experience local failure as their first site of relapse¹⁻³. Improving locoregional tumour control by increasing the radiation dose is not straightforward, because dose limiting toxicity occurs, such as lung damage and severe esophagitis^{4, 5}. Technical improvements in radiotherapy, like respiration-correlated (RC) imaging, stereotactic body RT (SBRT), intensity modulated RT (IMRT) and the use of ¹⁸Fluoro-Deoxy-Glucose (FDG)-PET scans in RT planning have facilitated radiation dose escalation with acceptable side effects⁶⁻⁹. These techniques allow a more precise targeting of RT. As a result, accurate target definition becomes increasingly important. PET and CT imaging allow definition of the location and extent of the macroscopic tumour with growing accuracy^{10, 11}. However, large inter- and intraobserver variation exists in the delineation of the Gross Tumour Volume (GTV)¹². Even more uncertainty exists in the definition of the clinical target volume (CTV), which should include the GTV with a margin of surrounding tissue covering potential microscopic spread¹³. Current imaging techniques do not allow direct evaluation of the presence and extent of microscopic disease extension (MDE) around the tumour as seen on PET and CT. Hence, only population statistics on MDE are available, based on correlation of imaging with pathology. These studies report an average MDE from 1.5 mm to 8 mm¹⁴⁻¹⁷, with more extensive MDE in adenocarcinoma than in squamous cell carcinoma¹⁵. Considering tissue deformations between in-vivo imaging and ex-vivo pathology, it is likely, however, that these ranges are underestimated. When tissue deformations are not taken into account, underestimation of the extent of MDE may occur up to a factor 2^{18, 19}.

MDE, however, does not occur in all patients^{15, 18}. The ability to predict the presence of MDE on the basis of pre-treatment imaging could lead to tumour tailored CTV margins, resulting in an optimal sparing of normal tissue in individual patients. The aim of the current study was two-fold: first, to establish pre-treatment risk factors for the presence of MDE at pathology. Secondly, to establish the impact of these factors on the accuracy of PET and CT to assess the total tumour-bearing region at pathology ("CTV_{path}") in three dimensions.

2.2 Methods and Materials

Patients

Patients were included in the following participating hospitals: the Netherlands Cancer Institute (Amsterdam, the Netherlands, central approval from the medical ethical board), the Onze Lieve Vrouwe Gasthuis (Amsterdam, the Netherlands) and the Maastricht University Medical Centre (Maastricht, the Netherlands). All patients gave written informed consent.

Preoperative imaging and tumour delineation

All patients underwent a chest CT and ^{18}F FDG-PET scan within 8 weeks prior to surgery. The CT slice-thickness ranged from 1 to 5 mm, depending on whether the scan was made in the diagnostic process or for study purposes. The PET scan was performed during free-breathing with a voxel size of 5 mm, using attenuation correction based on low dose CT. On the CT scans, the lung lobes and the gross tumour volume (GTV) were delineated using lung window level settings (W=1600, L=600) by an experienced RT technician (MR) in consensus with a dedicated lung radiation oncologist (JK/JB). On the PET scans, the GTV was delineated automatically using a 42% threshold of the maximum standardized uptake value (SUV_{max}) as described elsewhere^{20, 21}. PET scanners were calibrated between participating institutes using a dedicated phantom^{22, 23}.

Pathology processing

A fixed protocol was used among participating centres to process the resected lung lobes¹⁸. In short, the lobe was inflated with 10% formaldehyde injected through the bronchial opening. After a minimum of 24 hours the specimen was sectioned into 0,5 cm slices in a region of 2 cm around the tumour, and of 1 cm thickness throughout the rest of the lobe. Sectioning was performed perpendicular to the longest axis of the lobe, which, in approximation, was parallel to the cranio-caudal axis of the patient. Hence, the orientation of the specimen slices was as close as practically possible to the orientation of the CT slices. A digital photograph was taken of each separate slice. Subsequently, microscopic thin sections covering the tumour and a 2 cm margin in three dimensions around the tumour were obtained.

Assessment of GTV and microscopic disease extension at pathology

All samples were microscopically analyzed by one observer (JvL) in consensus with an experienced lung pathologist (RvS). Both the gross tumour based on pathology

(GTV_{path}) and microscopic disease extension were delineated in each microscopic section. MDE was defined by the presence of microscopic tumour deposits beyond the GTV_{path} . Thus, the GTV_{path} did not include MDE.

The microscopic samples were scanned and loaded into image processing software (GNU Image Manipulation Program (GIMP), version 2.0). The volume of the GTV_{path} was calculated by multiplying the area of the index tumour in each microscopic slide with the thickness of the corresponding slice. The effective tumour diameter of this volume was computed as follows:

$$d = 2 \left(\frac{3V}{4\pi} \right)^{1/3}, \text{ where } V \text{ denotes the } GTV_{path}.$$

In addition to the GTV_{path} , the presence of MDE was recorded for each patient. When MDE was found, its shortest distance to the GTV_{path} was measured in 3-D. These distances were corrected for residual deformations between the in-vivo scans and the ex-vivo specimen using a previously described method¹⁹. Briefly, the deformations around the GTV at pathology are modelled by an ellipse, where the deformation factor varies between 0.7 and 3.1, depending on the angle relative to the direction of gravity during sectioning. All locations of MDE were corrected for deformation using the ellipse parameters for each separate lobe. Subsequently, a cumulative histogram of the maximum distances between MDE and the GTV_{path} (MDE_{max}) was obtained.

Analysis of risk factors for microscopic disease extension and development of a prediction model

Image, tumour and patient characteristics were evaluated for their potential association with the presence of MDE (Table 2.1).

Table 2.1 Variables tested for their association with the presence of microscopic disease extension

Variable	Description
GTV_{CT}	The gross tumour volume as delineated on the CT scan
CT_{mean}	The mean signal (in water units) observed in the delineated GTV on the CT scan
CT Circularity	The circularity of the delineated GTV_{CT} , defined as $\frac{\text{Volume of } GTV_{CT} \text{ within sphere of effective diameter}}{\text{Volume of } GTV_{CT}}$ <p>Here, the effective diameter is given by $2 \cdot \sqrt[3]{\frac{3 \cdot GTV_{CT}}{4\pi}}$</p>
SUV_{max}	The maximum standardized uptake value as measured on the PET scan
GTV_{PET}	The gross tumour volume on the PET scan (calculated using a 42 % threshold of the maximum SUV).
Tumour type	The histology of the tumour (adeno or non-adeno carcinoma)
Age	The age of the patient at surgery

The effective diameter of the GTV on CT and PET, the mean CT density of the GTV_{CT} and the circularity of the GTV_{CT} were automatically calculated using an adaptation of previously employed methods²⁴.

All statistical analyses were performed using SPSS version 15.0. The variables were tested for their association with the presence of MDE using the independent samples T-test for scale variables and the Chi-square test for nominal variables. Multivariate binary logistic regression was subsequently applied in combination with backward feature selection (p-to-entry 0.05 and p-to-remove of 0.1). The performance of the resulting prediction model was quantified using receiver operating characteristic (ROC) analysis. Based on the output of the model, the patients were categorized into a group at low risk of presence of MDE and a group at high risk.

Comparison of the GTV at PET and CT with the GTV and CTV at pathology

The effective diameter of the GTV at CT and PET was first compared to that of the GTV_{path} (i.e., not including MDE). Secondly, the effective diameters of the GTV_{CT} and GTV_{PET} were compared to that of the total tumour-bearing tissue at pathology (CTV_{path}). The latter was defined as the sum of the effective diameter of GTV_{path} and two times the maximum MDE (to convert radius to diameter). Thereafter, the accuracy of PET and CT to assess the CTV_{path} was established separately in the group of patients with MDE (MDE+) and without MDE (MDE-). The latter analysis was performed twice; once based on the presence of MDE at pathology, and once based on its presence according to the prediction model.

2.3 Results

Patient and tumour characteristics

From September 2006 to December 2008, 34 NSCLC patients (19 male and 15 female) scheduled for a lobectomy were included. The average age at surgery was 60.6 years (range: 42-80 years). PET and CT imaging were performed at a median of 19 days (range: 1-55 days) before surgery. The surgical specimen consisted of the left upper lobe (n=11), left lower lobe (n=5), right upper lobe (n=13), right middle lobe (n=2) and right lower lobe (n=3). Tumour histology was adenocarcinoma in 53% (n=18), squamous cell in 18% (n=6), large cell in 12% (n=4), mixed adenosquamous in 9% (n=3), bronchioloalveolar in 3% (n=1) and NSCLC, not otherwise specified in 6% (n=2).

Assessment of GTV and microscopic disease extension at pathology

1311 microscopic sections (median: 38 per patient, range: 17-103) were analyzed. MDE outside of the GTV_{path} was found in 17 of the 34 (50%, 95% CI: 34-66%) patients. The cumulative distribution of MDE_{max}, both with and without deformation correction, is shown in Figure 2.1. Without deformation correction, a CTV margin of 14 mm would be needed to cover MDE in 90% of the patients. With deformation correction the margin to cover MDE in 90% of the patients increased to 26 mm. The distribution of microscopic tumour deposits was found to be isotropic in the transverse plane: MDE medial of the GTV_{path} was seen in 26%, lateral in 29%, dorsal in 23% and ventral in 22%. With the current sampling method, no MDE was found in the cranial and caudal direction. No association was found between the location of the tumour in the lobe and the presence of microscopic tumour deposits. Furthermore, there was no correlation between the time interval between imaging and surgery and the extent of overestimation/underestimation with CT and PET.

Figure 2.1 Cumulative distribution of the distance of maximum microscopic disease extension (MDE_{max}) to the border of the GTV_{path}

Prediction of microscopic disease extension

The distribution of the potential predictive variables in the subgroups with and without MDE is shown in Table 2.2. Two features (CT_{mean} and GTV_{PET}) showed significant differences. Multivariate analysis yielded CT_{mean} and GTV_{CT} as significant factors in the logistic regression model (Table 2.2). The area under the ROC curve of this two-parameter prediction model was 0.86 (95%CI: 0.73-0.98, p=0.001) (Figure 2.2).

Table 2.2 Comparison of variables between the subgroups with and without microscopic disease extension (MDE)

	MDE absent	MDE present	UVA	MVA
	<i>Mean ± SD</i>	<i>Mean ± SD</i>	<i>p-value</i>	<i>p-value</i>
GTV _{CT} (cm ³)	22.9 ± 11.4	61 ± 21.1	0.14	0.03
CT _{mean}	787 ± 22.8	860 ± 24.1	0.04	0.03
CT Circularity	0.78 ± 0.02	0.71 ± 0.03	0.10	ns
SUV _{max}	9.7 ± 4.9	11.7 ± 1.4	0.28	ns
GTV _{PET} (cm ³)	9.8 ± 3.1	24.6 ± 5.7	0.04	ns
Tumour type**	58 %	35 %	0.18	ns
Age (years)	58.4 ± 11.4	62.6 ± 11.4	0.29	ns

SD: standard deviation; UVA: Univariate analysis; MVA: Multivariate logistic regression analysis; Ns: not significant

UVA: p-values ≤ 0,05 indicate a statistically significant difference of the predictor variables between the subgroups

MVA: p-values ≤ 0,05 indicate statistically significant factors resulting from backward logistic regression

*in water units

**percentage with adenocarcinoma

Figure 2.2 Receiver operating characteristic (ROC) curve of the two parameter prediction model

Multivariate regression analysis results in CT mean and GTV_{CT} as significant parameters in the prediction model. Area under the curve: 0.86

A cut-off value in the model was chosen corresponding to a sensitivity of 90% and a specificity of 64%. This operating point corresponds to a probability threshold for MDE of 30%. At this operating point, 13/34 patients (38%, 95% CI: 24-55%) were

assigned to the low-risk group for MDE. The cumulative distribution of the maximum distances to the GTV border for these two groups is shown in Figure 2.3.

Figure 2.3 Cumulative distribution of the maximum distance of microscopic disease extension (MDE_{max}) to the border of the GTV_{path} according to the risk of MDE
 MDE_{max} per patient in the group at low risk of MDE ($N=13$) and the group at high risk of MDE ($N=21$), as predicted by the linear regression model

Figure 2.4 Illustration of the difference in overall disease load around the GTV at imaging between patients at low and at high risk of microscopic disease extension (MDE)
 The difference in overall disease load between high and low risk patients is shown for the GTV_{CT} only to provide anatomical information. Colour represents the fraction of patients in whom disease extension was found at various distances from the GTV_{CT} . Only regions inside the lung are relevant
 A. Illustration in CT scan of a patient at low risk of MDE
 B. Illustration in CT scan of a patient at high risk of MDE

Of the 17 patients with actual presence of MDE, two were at low risk for MDE, according to the model, corresponding to a sensitivity of 88%. Of the 17 patients without actual MDE, 6 were at high risk of MDE, corresponding to a specificity of 65%.

The overall disease load, reflected in the total tumour bearing tissue at pathology, around the GTV_{CT} and GTV_{PET} was larger in the subgroup of patients at high risk for MDE compared to the subgroup at low risk. This difference in overall disease load between patients at low and high risk of MDE is graphically illustrated in Figure 2.4. Especially differences in prevalence of microscopic tumour deposits close to the GTV at imaging were evident.

Comparison of the GTV at PET and CT with the GTV and CTV at pathology

The mean GTV_{path} was 17.5 cm³ (range: 0.5 cm³ – 81.9 cm³). Overall, the effective diameter of the GTV_{CT} overestimated that of the GTV_{path} by 6.6 mm ($p < 0.001$). The effective diameter of the GTV_{PET} was 0.4 mm larger than that of the GTV_{path}, which was not statistically significant ($p = 0.63$) (Figure 2.5). Conversely, the effective diameter of the CTV_{path} (deformations included) was underestimated by CT with 13.4 mm on average, while the PET showed an even larger underestimation of 20.1 mm. Both underestimations were significant ($p = 0.008$ and $p = 0.0003$, respectively) (Figure 2.6).

Stratified according to MDE at pathology, the CTV_{path} was underestimated more on CT and on PET in the MDE+ subgroup than in the MDE- group (Table 2.3A). The underestimation on CT and PET was significant in the MDE+ group ($p < 0.001$), but not in the MDE- group. Stratification according to the risk of MDE according to the logistic model, demonstrated comparable results (Table 2.3B); both CT and PET underestimated the CTV_{path} in the subgroup at high risk for MDE ($p = 0.009$ and $p = 0.001$ for CT and PET, respectively), but the underestimations were not significant in the subgroup at low risk.

Figure 2.5 Comparison of the effective diameter of the GTV_{CT} and the GTV_{PET} with that of the GTV_{path}
Correlation coefficients: GTV_{CT} - GTV_{path}: 0.95; GTV_{PET} - GTV_{path}: 0.91

Figure 2.6 Comparison of the effective diameter of the GTV_{CT} and the GTV_{PET} with that of the CTV_{path}
Correlation coefficients: GTV_{CT} - GTV_{path}: 0.55; GTV_{PET} - GTV_{path}: 0.55

Table 2.3 Comparison of the effective diameter of the GTV at imaging and the effective diameter of the CTV at pathology (CTV_{path})

A) Comparison according to the presence of MDE found at pathology					
CT*	Mean ± SD (mm)	p-value	PET**	Mean ± SD (mm)	p-value
Overall	-13.4 ± 27.9	0.008	Overall	-20.1 ± 29.0	0.0003
MDE+	-30.6 ± 28.8	0.0005	MDE+	-39.9 ± 27.5	0.00002
MDE-	3.7 ± 39.5	0.229	MDE-	-0.3 ± 11.7	0.92
B) Comparison according to the risk of MDE according to the prediction model					
CT*	Mean ± SD (mm)	p-value	PET**	Mean ± SD (mm)	p-value
MDE+	-19.2 ± 30.6	0.009	MDE+	-26.7 ± 31.1	0.001
MDE-	-4.1 ± 20.6	0.482	MDE-	-9.4 ± 22.3	0.154

Stratified to patients with and without MDE at pathology (A) and according to the prediction model (B), respectively.

SD = standard deviation

*Effective diameter of GTV_{CT} minus that of CTV_{path}

**Effective diameter of GTV_{PET} minus that of CTV_{path}

2.4 Discussion

To ensure that all tumour bearing tissue is covered by the radiotherapy fields, an accurate knowledge of both the gross tumour volume (GTV) and the microscopic extension of tumour beyond the visible border on imaging (the margin to be included in the clinical target volume (CTV)) is essential. Accurate distinction between the location of macroscopic tumour and microscopic disease is of value as tumour control probability calculations suggest that the dose required to eradicate microscopic disease (thus, the dose in the CTV margin) is lower than the dose for macroscopic tumour^{25, 26}.

In the current study, MDE was found in 50% (95% CI: 34-66%) of patients. Mean tumour density on CT (CT_{mean}) and tumour volume on CT (GTV_{CT}) were found to be significant factors at multivariate analysis associated with the presence of MDE. The prediction model on basis of those two parameters had an area under the curve of 0.86. This model may be used to identify patients with higher overall incidence of disease at all distances around the GTV visible on imaging. These findings are encouraging as they could ultimately allow to adapt dose painting across the CTV margin according to subgroups of patients²⁷, thus optimizing local control while limiting toxicity in patients who are at low risk of microscopic disease extension. Therefore, validation of the prediction model in a larger patient population is strongly encouraged.

MDE showed an isotropic distribution around the GTV_{path}. This finding suggests that uniform CTV margins may be appropriate. It also supports the use of our CTV_{path} definition, being the GTV with a circumferential margin equal to the maximum ob-

served MDE. In this study, no MDE was found in cranial and caudal directions. This finding is most probably due to the incomplete histological sampling in these directions compared to the other directions. All pulmonary tissue ventrodorsal and mediolateral of the tumour was available for microscopic examination. In the cranio-caudal directions, histological information was only available from slices taken at 5 mm distance from each other. In this way, microscopic tumour deposits present in between two slices will have been missed.

Literature comparison

The current study shows that the GTV delineated on the PET scan using a fixed threshold (42% of $SUV_{max}^{20, 21}$) is better correlated with the GTV_{path} than the manually delineated GTV_{CT} . The latter overestimated the diameter of the GTV_{path} with 6.6 mm on average. Few reports of other groups are available comparing both PET and CT with pathology: With respect to CT, Grills et al. found an overestimation of the GTV_{path} by CT of 5.8 mm¹⁶, which is comparable to our study. Others, however, found a close approximation^{15, 17, 29}. Yu et al. reported a benefit of PET based delineation over CT mainly in patients with atelectasis²⁸. As the resolution of both imaging techniques is not sufficient to visualize microscopic disease, it may not be surprising that both the PET- and CT-based GTV underestimated disease extension when MDE is taken into account. In this study, we show however, that the overestimation of the GTV at CT and PET does not make up for the lack of coverage of microscopic disease. In patients without MDE, all tumour bearing tissue was covered by the CT- and PET-based GTV.

The margin of 26 mm found to cover MDE in 90% of patients is much larger than what is expected on basis of the literature. The extent of MDE found previously in studies correlating imaging with findings at pathology range from 0 to 12 mm^{14-16, 30}. It would appear, however, that the microscopic examination of the pathology specimen in the present study was more extensive than the methods applied in previous investigations. Secondly, deformation of the lung tissue between in-vivo and ex-vivo was not taken into account in these studies. Grills et al. concluded that a 9 mm CTV margin added to the CT-based GTV should cover MDE in 90% of cases. Taking into account that CT tends to overestimate the GTV_{path} by 7 mm on average, our results suggest that a CTV margin of 16 mm may still be required to cover 90% of MDE.

Nonetheless, the application of large CTV margins would inevitably lead to a considerable increase in normal tissue exposure. Tumour control probability models, however, indicate that only 70-80% of the prescription dose to control the macroscopic tumour may be needed to eradicate microscopic disease^{25, 26}. This suggests that MDE outside the macroscopic tumour would be largely covered by the beam penumbra of conventional RT fields. New RT technologies, however, are associated

with altered penumbra characteristics. Grills et al. investigated to what extent MDE would be covered with the use of SBRT¹⁶. Depending on the technique used, ≤ 6 -8.5 mm of MDE would be automatically covered by the 80% isodose line (dose considered by the authors to be adequate to control microscopic disease). This confirms that with the use of more conformal techniques, inadequate CTV margins increase the risk of underdosage to tumour-bearing tissue. Our results suggest that this risk is higher in patients stratified to the MDE-positive group by the prediction model than in patients stratified to the MDE-negative group.

Prediction model

Although the prediction model has a relatively high sensitivity, the specificity is lower (67%), indicating that only 2 out of 3 patients without MDE are correctly identified as low risk patients. Nonetheless, the model shows distinct differences in disease load around the GTV_{PET} and GTV_{CT} between the two groups, indicating that pre-treatment imaging features have the potential to discriminate between the presence and absence of microscopic extension. Validation of the prediction model in an independent patient cohort is required in order to become a valuable tool in clinical practice.

An explanation as to why higher CT density in the tumour is associated with a larger risk for microscopic disease extension is still pending. Theoretically, higher CT density could be caused by a higher tumour cell density, a higher fraction of necrosis and/or a lower fraction of stroma, but these hypotheses are currently unproven and subject of further research. Although MDE was present more frequently in squamous cell carcinoma than in adenocarcinoma ($p=0.18$), the histological subtype was not significantly associated with MDE in univariate and multivariate analysis. GTV_{PET} did not retain significance in multivariate analysis, likely due to its correlation with GTV_{CT}.

Study limitations

The methods used in the current study for the correlation of imaging with pathology have some limitations. Firstly, during PET scanning, no system was used to account for respiratory movements of the tumour. Therefore, the exact anatomical localization of the tumour is subject to some uncertainty. The role of PET as a predictor for the presence of MDE may have been underestimated for this reason. New technology, such as 4D-PET-CT scanners may further increase the accuracy of the correlation of the imaging characteristics with pathology. A second limitation is that potential differences in shape of the GTV at imaging and at pathology have not been taken into account. A third limitation originates from the inaccuracy at pathology to accurately achieve uniform slice thickness of 5 mm. It is theoretically possible that

thinner slicing at pathology would result in a higher detection rate of microscopic tumour deposits, but this was technically not feasible.

2.5 Conclusion

Multivariate analysis of tumour, patient and PET and CT characteristics shows that CT characteristics of NSCLC have the potential to predict the presence of microscopic disease extension (MDE) around the GTV at pathology. Patients at low risk of MDE show smaller rates of disease at all distances around the GTV than patients at high risk. Both CT and PET accurately visualize the CTV_{path} in patients at low risk of MDE, but significantly underestimate the CTV_{path} in high risk patients.

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CHAPTER 3

^{18}F FDG-PET based radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer changes radiotherapy fields: a planning study

**Judith van Loon
Claudia Offermann
Geert Bosmans
Rinus Wanders
André Dekker
Jacques Borger
Michel Öllers
Anne-Marie Dingemans
Angela van Baardwijk
Jaap Teule
Gabriel Snoep
Monique Hochstenbag
Ruud Houben
Philippe Lambin
Dirk De Ruyscher**

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Abstract

Background and purpose

To investigate the influence of selective irradiation of ^{18}F FDG-PET positive mediastinal nodes on radiation fields and normal tissue exposure in limited disease small cell lung cancer (LD-SCLC).

Methods and materials

Twenty-one patients with LD-SCLC, of whom both CT and PET images were available, were studied. For each patient, two three-dimensional conformal treatment plans were made with selective irradiation of involved lymph nodes, based on CT and on PET, respectively. Changes in treatment plans as well as dosimetric factors associated with lung and esophageal toxicity were analyzed and compared.

Results

FDG-PET information changed the treatment field in 5 patients (24%). In 3 patients this was due to a decrease and in 2 patients to an increase in the number of involved nodal areas. However, there were no significant differences in gross tumour volume (GTV), lung, and esophageal parameters between CT- and PET-based plans.

Conclusions

Incorporating FDG-PET information in radiotherapy planning for patients with LD-SCLC changed the treatment plan in 24% of patients compared to CT. Both increases and decreases of the GTV were observed, theoretically leading to the avoidance of geographical miss or a decrease of radiation exposure of normal tissues, respectively. Based on these findings, a phase II trial, evaluating PET-scan based selective nodal irradiation, is ongoing in our department.

3.1 Introduction

Small cell lung cancer (SCLC) is a tumour with a poor prognosis, with only one-third of patients presenting with limited-disease (LD-SCLC) ^{1, 2}. In LD-SCLC, long-term survival has improved with chemo-radiation and this is, therefore, currently the first choice treatment. This is at the expense, however, of severe reversible esophagitis and lung damage ³⁻⁶. Moreover, over 30% of patients still fail locally with this treatment ⁷. Therefore, in the subgroup of patients with limited disease, strategies to reduce toxicity and increase local tumour control would be of great clinical value. A straightforward strategy to reduce toxicity is to diminish the radiation fields, which could be done by omitting routine elective nodal irradiation. In case of non-small cell lung cancer (NSCLC) elective nodal irradiation is no longer recommended ⁸. In NSCLC, radiation fields could be safely reduced by selective nodal irradiation, based on CT, and even further based on FDG-PET (¹⁸F-fluorodeoxyglucose-Positron Emission Tomography) scans ⁹⁻¹². Treating only FDG-positive mediastinal areas decreased radiation exposure of the lungs and the esophagus sufficiently as to allow for radiation dose-escalation in NSCLC ^{13, 14}. However, contrary to NSCLC, in a phase II study in LD-SCLC, we observed isolated nodal failures outside of the clinical target volume (CTV) in 11 % of cases with selective nodal irradiation, based on CT ¹⁵. This finding illustrates that the positive results obtained for selective mediastinal node irradiation in NSCLC cannot straightforwardly imply the same results in SCLC patients. To our knowledge, no clinical data are available on PET-based selective mediastinal irradiation in SCLC.

The available literature suggests that FDG-PET scan has diagnostic value in SCLC ¹⁶⁻²². SCLC shows high uptake of FDG, with a mean SUV_{max} (maximal Standardized Uptake Value) for primary and mediastinal nodal lesions similar to that seen in NSCLC ¹⁶. In the largest reported series of 120 patients with SCLC, FDG-PET resulted in a stage migration for 14 patients, upstaging 10 patients to extensive disease and downstaging 3 patients ²⁰. In a retrospective analysis of 46 patients with SCLC, Pandit et al. described a 100% sensitivity of PET for detection of disease, based on pathologic correlation ²¹. It has been suggested that an FDG-PET scan can identify metastases to regional lymph nodes in 15-25% of patients whose mediastinal CT scan was negative ^{16, 22}. It is therefore likely that, as in NSCLC, the use of FDG-PET scans will improve the coverage of the mediastinal lymph node areas in LD-SCLC, hence resulting in less geographical miss and improved local tumour control.

As FDG-PET scans may thus be more accurate than CT to stage the mediastinum, we investigated the possible role of FDG-PET scanning in the radiotherapy planning of patients with LD-SCLC. We hypothesized that (1) there would be changes in the radiotherapy fields using FDG-PET scanning compared to CT, theoretically resulting

in less geographical miss and (2) there would be differences in the radiation exposure of dose limiting normal tissues such as lungs, esophagus and spinal cord, when radiation treatment planning is performed based on FDG-PET compared to CT. We compared the radiation treatment planning of involved mediastinal lymph node areas based on FDG-PET and on CT for 21 consecutive patients with LD-SCLC. Radiotherapy was planned to the standard total radiation dose of 45 Gy delivered in 30 fractions in 3 weeks (1.5 Gy BID) either based on FDG-PET or on CT scan. DVH (dose volume histogram) parameters of the lung, the esophagus, the heart and the spinal cord were compared.

3.2 Methods and Materials

Patients

Patients diagnosed with LD-SCLC and referred for radical radiotherapy to MAASTRO clinic between January 1, 2004 and October 1, 2006 were reviewed retrospectively. Twenty-one patients, of whom either both a pre-treatment FDG-PET and a contrast-enhanced CT scan, or a combined FDG-PET-CT scan (with contrast-enhancement) was available, were eligible for this planning study.

Staging

All patients underwent bronchoscopy with biopsy, standard haematological and biochemical workup, CT of the thorax and upper abdomen, including liver and adrenal glands, and a whole body FDG-PET scan. CT or MRI of the brain was performed as part of the routine workup for all patients.

Imaging with CT and PET

For CT-based planning, a contrast-enhanced CT scan of the thorax performed for radiotherapy planning was used. For PET-based planning, a combined PET-CT scan was performed either in the diagnostic process alone or both in the diagnostic process and for radiotherapy simulation. In both cases, the PET-CT scan was made in radiotherapy position. Patients had to be fasting for at least 6 hours before the examination. The injected total activity of FDG was calculated based on the weight of the patient: $(\text{weight} \times 4 + 20)$ MBq. After a rest period of 60 minutes (time needed for uptake of FDG) PET and CT images were acquired. A CT-scan of the whole thorax was performed with intravenous contrast.

The CT-findings were interpreted by an experienced chest radiologist. Lymph nodes were considered to be pathological on CT when their axial diameter exceeded 1 cm. FDG-PET scans were visually interpreted by an experienced PET scan specialist. The involved lymph node stations were recorded according to the Mountain and Dresler classification scheme²³, both on the basis of the CT and FDG-PET scan, by the diagnostic radiologist and the nuclear medicine specialist, respectively.

Radiation treatment planning and dosimetry

Radiotherapy planning was performed with a XiO (Computerized Medical Systems (CMS) Inc.) treatment planning system, using inhomogeneity corrections based on a convolution algorithm. For all patients, a Gross Tumour Volume (GTV) and a Planning Target Volume (PTV) were defined based on CT data and PET data, respectively, for the CT- and PET-CT based plans. This was carried out in two separate sessions by the same person (JvL), in order to avoid intra-observer variability. For the primary tumour, the GTV was delineated based on CT only using the lung window settings ($W = 1700$, $L = -300$). We deliberately avoided contouring on the basis of ill-defined areas on PET scan. Instead, the sharp boundaries of the CT scan images were used. These procedures aimed at minimizing the problems of tumour size determination on PET scans in general and of a moving part of the body in particular, as no respiratory gating was used. For delineation of the lymph nodes on CT, mediastinal window setting ($W = 600$, $L = 40$) was used. The involved anatomical region as described by the radiologist or nuclear medicine specialist in the original diagnostic report (i.e. before the start of chemotherapy) was delineated²⁴. With respect to the pathological lymph nodes on PET, the involved zones were delineated based on the anatomical information of the CT scan. In this way, the whole pathological anatomical region of the mediastinum (e.g. area 7) was taken as GTV for that lymph node station. No SUV-threshold was used, as a visual scale has been shown to be at least as accurate as the use of a SUV-threshold to distinguish benign from malignant nodes^{25, 26}. CT and PET images were automatically registered based on Mutual Information and were subsequently fused using Focal (CMS Inc.). If the PET scan was negative in the mediastinum and the CT scan positive, the mediastinum was considered not to harbour cancer cells, and was hence not included in the PET-CT based GTV. The margin from the GTV to the CTV (Clinical Target Volume) was 5 mm, and from the CTV to the PTV also 5 mm, both for CT- and for PET- based treatment planning. No assessments of tumour movement, for example by slow CT scans, were performed. No elective nodal irradiation was planned.

Contouring of the lung was done automatically by the treatment planning system. For the calculation of the $V_{\text{lung}20}$ (Percentage of lung receiving more than 20 Gy), we followed the published guidelines namely: the volume of both lungs reduced by the PTV was used, whereas for the mean lung dose (MLD), the volume of both lungs

minus the GTV was considered⁸. The esophagus was delineated from just below the larynx to the gastro-esophageal junction. Neither the GTV nor the PTV was subtracted from this volume⁸. The spinal cord was drawn throughout the whole CT scan and was considered to be at the inner margin of the bony spinal canal.

The heart was contoured from its caudal part at the apex until its cranial level at the beginning of the large vessels. The latter were not included in the contour of the heart. The pericardium was a part of the contour of the heart.

A 3-dimensional conformal treatment plan was calculated on the CT-based PTV and the PET-CT-based PTV for all patients, with a prescribed dose of 45 Gy in 30 fractions delivered in 3 weeks (1.5 Gy BID) to the PTV, according to ICRU 50 guidelines²⁷. Dosimetric values were calculated on the basis of DVH's and dose distributions on each axial CT plane both for CT and PET-CT based planning.

For the tumour and pathological lymph nodes, factors analyzed were GTV and PTV volume. Because no consistent DVH parameters are known to predict early and late esophageal toxicity, the $V_{\text{eso}30}$, the $V_{\text{eso}35}$, the $V_{\text{eso}40}$, the $V_{\text{eso}45}$, the $V_{\text{eso}50}$, the maximal esophageal dose (D_{max}) and the mean esophageal dose (MED) were analyzed^{8, 28, 29}. For the lung, the $V_{\text{lung } 20}$ and the MLD were analyzed as predictors for radiation pneumonitis⁸. The maximal dose to the spinal cord was recorded, although it was not expected that in either the CT-based or in the PET-CT based plan the tolerance of the spinal cord (50 Gy) would be exceeded. The mean dose to the heart ($D_{\text{heart-mean}}$), as well as the maximal dose (D_{heartmax}), the $V_{\text{heart } 30}$, the $V_{\text{heart } 35}$, the $V_{\text{heart } 40}$, the $V_{\text{heart } 45}$, and the $V_{\text{heart } 50}$ was recorded.

Ethics

As this was a retrospective planning/modelling study, patients were diagnosed and treated previously according to standard guidelines in our institute. No approval of the Ethical Committee was required.

Statistics

On the basis of literature at the start of the project, we hypothesized that introducing PET in radiotherapy planning would change the treatment fields in 25% of the patients¹⁶. In order to detect this change with a 95% confidence interval of 5-45%, at least 19 patients should be included in this study³⁰.

Results are either expressed as mean $\pm$ standard deviation (SD) or as a proportion with 95 % confidence intervals (95% CI). Statistical differences between paired parameters from CT versus PET-CT based plans were evaluated with the Wilcoxon signed rank test. Differences were considered to be significant when the two-tailed p-value was less than 0.05.

3.3 Results

Patient characteristics and FDG-PET and CT correlations

All 21 patients had LD-SCLC, as defined by PET-CT for the detection of distant metastasis. Two patients had stage N0, while 14 patients had the same nodal areas involved on both PET and CT. Five patients had mediastinal nodal involvement on both PET and CT, but in different nodal areas (Table 3.1).

Table 3.1 Patient characteristics

Pt. No.	No. of involved lymph node stations: PET vs. CT	Primary tumour	Involved lymph node station	
			PET-scan	CT-scan
PET<CT				
2		Right upper lobe	2L,3L,4L, 2R, 3R, 4R	2L,3L,4L, 2R, 3R, 4R, 10R, 5, 7
12		Left hilus	4L, 10L, 5, 7	4L,10L, 4R, 5, 7
17		Left hilus	10L, 7	4L,10L, 7
PET>CT				
6		Right upper lobe	2R, 4R, 10R, 5, 7	2R, 4R, 10R, 7
7		Left upper lobe	2L, 4L, 10L, 5, 7	2L, 4L,10L, 5
PET=CT				
1		Right upper lobe	4L, 2R, 4R, 10R, 7	4L, 2R, 4R, 10R, 7
3		Left lower lobe	None	None
4		Left upper lobe	2L, 4L, 5, 6	2L, 4L, 5, 6
5		Right upper lobe	4R, 10R, 7	4R, 10R, 7
8		Right hilus	4R, 10R	4R, 10R
9		Left upper lobe	None	None
10		Unknown	4L, 1R, 2R, 4R, 3, 7	4L, 1R, 2R, 4R, 3, 7
11		Right upper lobe	4L, 2R, 4R, 10R, 3, 7	4L, 2R, 4R, 10R, 3, 7
13		Lingula	6	6
14		Unknown	2R, 4R, 10R, 5, 7	2R, 4R, 10R, 5, 7
15		Right upper lobe	4R, 10R, 7	4R, 10R, 7
16		Right upper lobe	10R	10R
18		Left hilus	4L, 10L, 5, 6, 7, 8	4L, 10L, 5, 6, 7, 8
19		Right upper lobe	2L, 4L, 7	2L, 4L, 7
20		Left lower lobe	10L, 10R, 5, 6, 7	10L, 10R, 5, 6, 7
21		Left hilus	2L, 4L, 10L, 2R, 5, 6, 7	2L, 4L, 10L, 2R, 5, 6, 7

Pt. No.: patient number. PET: positron emission tomography. CT: computed tomography

In three patients (14 %), there were less nodal stations involved on PET compared to CT: in the first patient, PET showed no involvement of the CT-involved stations 5, 7 and 10; in the second and third patient, there was no involvement of station 4R

(Figure 3.1) and 4L, respectively. In two patients (10%), PET identified nodal stations that were negative on CT: station 5 and 7, respectively.

Figure 3.1 Image of a patient with different nodal involvement on CT and PET (patient 12)
Station 4R is positive on CT and negative on PET

Radiotherapy (RT) plans

In 5 of 21 patients (24%, 95% CI: 5-40%), there was a change in RT plans with the incorporation of the PET-data. For two patients (10%), the radiation fields based on PET were larger than based on CT, while in 3/21 (14%) patients the CT-based radiation fields were larger.

Nodal GTV

Taken all 21 patients together, the nodal GTV was $57.9 \pm 67.0 \text{ cm}^3$ on CT and $56.8 \pm 66.5 \text{ cm}^3$ on PET ($p = 0.92$). For the three patients with a nodal GTV on PET that was smaller than on CT (Table 3.1), the nodal GTV was $81.0 \pm 50.9 \text{ cm}^3$ on CT and $61.5 \pm 29.0 \text{ cm}^3$ on PET. Two patients had a nodal GTV on PET that was larger than on CT. Their nodal GTV was $72.5 \pm 71.4 \text{ cm}^3$ on CT and $81.0 \pm 76.4 \text{ cm}^3$ on PET.

Normal tissue radiation exposure

An overview of the radiation exposure of normal tissues comparing CT- and PET-based plans is shown in Table 3.2. Incorporating the PET information in the radiation planning did not lead to a statistically significant change in any of the dosimetric factors analyzed.

For the three patients in whom the nodal GTV decreased with PET, the MED decreased from 25.0 ± 8.5 to $21.0 \pm 5.7 \text{ Gy}$ and $D_{\max}$ from 46.2 ± 0.2 to $45.5 \pm 0.7 \text{ Gy}$. The V_{20} decreased from $25.5 \pm 4.9\%$ to $22.0 \pm 7.1\%$; the MLD decreased from 13.2 ± 2.5 to $11.6 \pm 3.3 \text{ Gy}$. For the two patients in whom the nodal GTV was larger on PET, the MED increased from 23.0 ± 5.7 to $24.5 \pm 3.5 \text{ Gy}$; $D_{\max}$ remained the same with a

dose of 46.5 ± 0.7 Gy. The V_{20} increased from $16.0 \pm 2.8\%$ to $20.0 \pm 1.4\%$; the MLD increased from 9.9 ± 1.6 to 11.7 ± 1.3 Gy.

Table 3.2 Normal tissue radiation exposure

Normal tissue		CT-based plan ($\pm$ SD)	PET-based plan ($\pm$ SD)	p-value
Esophagus	MED (Gy)	24.4 ($\pm$ 8.6)	24.1 ($\pm$ 8.5)	0.50
	$D_{\max}$ (Gy)	45.8 ($\pm$ 2.9)	45.7 ($\pm$ 2.9)	0.32
Lung	V_{20} (%)	25.6 ($\pm$ 12.4)	25.6 ($\pm$ 12.3)	1.00
	MLD (Gy)	13.7 ($\pm$ 5.6)	13.7 ($\pm$ 5.6)	0.89
Heart	D_{mean} (Gy)	12.2 ($\pm$ 9.7)	12.2 ($\pm$ 9.7)	0.79
	V_{30} (%)	19.7 ($\pm$ 19.1)	19.5 ($\pm$ 19.2)	0.46
Spinal cord	$D_{\max}$ (Gy)	41.0 ($\pm$ 5.1)	40.9 ($\pm$ 5.1)	0.27

SD: standard deviation; PET: positron emission tomography; CT: computed tomography; MED: mean esophageal dose; $D_{\max}$: maximal (esophageal, respective heart) dose; MLD: mean lung dose.; D_{mean} : mean (heart) dose

3.4 Discussion

The treatment of choice for patients with LD-SCLC consists of concurrent chemoradiotherapy³¹, which is at the expense of dose-limiting toxicity, primarily of the esophagus and lung^{6, 7}. Moreover, there is still a considerable amount of local tumour failure⁷.

An obvious way of reducing radiation fields and hence toxicity is by omitting elective nodal irradiation of clinically uninvolved nodal stations. This selective nodal irradiation has been shown to be effective in NSCLC based on CT, and even further, based on FDG-PET, with an acceptable amount of isolated nodal failures^{9, 11}. In LD-SCLC however, we observed 11% of isolated nodal failures when only irradiating mediastinal nodal stations that were positive on CT¹⁵. Because literature suggests that like in NSCLC, FDG-PET has a greater accuracy than CT for staging mediastinal nodal areas in SCLC as well¹⁶⁻²⁰, we hypothesized that there would be less geographical misses by using PET for radiation treatment planning. Furthermore, the differences in the nodal PTV could also change the radiation exposure of normal tissues. Therefore, we retrospectively planned the radiation treatment for 21 consecutive patients with LD-SCLC using CT with and without PET information.

The incorporation of FDG-PET data into RT planning led to a change in the radiation fields in 24% of patients. This is in line with previous studies on FDG-PET in the staging of SCLC^{16, 32}, showing a difference in positive nodal areas between PET and CT in 25% and 21% of patients, respectively. In the present study, both increases (2/21) and decreases (3/21) in radiation fields were observed. Assuming that like in NSCLC,

PET is more accurate than CT in identifying pathologic lymph nodes in SCLC¹⁶⁻²⁰, the increase in radiation fields on the basis of PET could theoretically lead to the avoidance of geographical misses. In 10% of patients, PET-based radiotherapy planning increased the radiation fields. In those patients, irradiation based on CT could theoretically result in a geographic miss. This percentage is about the same as the amount of geographical misses we found with selective nodal irradiation based on CT only (11%)¹⁵. Theoretically, the decrease of the GTV in some patients could lead to a decreased radiation exposure of lung and esophagus and hence less toxicity^{28, 33}. However, taken all patients together, no significant changes in the GTV or in the radiation exposure of the normal organs (esophagus, lungs, heart and spinal cord) were observed. This is in contrast to the incorporation of FDG-PET in radiotherapy planning of NSCLC, where generally reductions of the radiation fields were observed¹¹⁻¹⁴.

The present study has some limitations. First, no pathologic verification of the lymph nodes was obtained. However, as FDG-PET scans are likely to be more accurate than CT to detect mediastinal nodal involvement in SCLC^{16, 20-22}, we believe that our results support the need to investigate in clinical studies the role of FDG-PET scans in radiotherapy planning of LD-SCLC. Second, no system was used to take into account respiratory movements. We therefore cannot rule out the possibility that the exact anatomical localisation of the mediastinal lymph nodes may have been blurred. However, motion artefacts are less of a problem in the mediastinum compared to the primary lung tumour³⁴. In any case, new technology, such as combined 4D-PET-CT scanners may further increase the usefulness of integrating PET scan data into PET-CT simulation^{35, 36}. Third, the fact that different individuals were involved in the identification of nodal stations could theoretically introduce interobserver variability. Regarding PET however, it has been published that in NSCLC a good interobserver agreement was found with respect to staging mediastinal lymph node stations³⁷. For contrast-enhanced CT, a good intra- and interobserver agreement to detect enlarged mediastinal lymph nodes in patients with lung cancer was described³⁸. Therefore, as only contrast-enhanced CT images were used, we believe to have minimized possible interobserver variability.

The largest potential benefit of incorporating FDG-PET scans in radiotherapy planning of LD-SCLC may be the reduction of isolated nodal failures compared to CT-based planning¹⁵. Therefore, a phase II trial, evaluating PET-scan based selective nodal irradiation in LD-SCLC, in which a larger amount of patients will be included, is ongoing in our department.

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CHAPTER 4

Selective nodal irradiation on basis of ^{18}F FDG-PET scans in limited disease small cell lung cancer: a prospective study

**Judith van Loon
Dirk De Ruyscher
Rinus Wanders
Liesbeth Boersma
Jean Simons
Michel Öllers
Anne-Marie Dingemans
Monique Hochstenbag
Gerben Bootsma
Wiel Geraedts
Cordula Pitz
Jaap Teule
Ali Rhami
Willy Thimister
Gabriel Snoep
Cary Dehing-Oberije
Philippe Lambin**

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Abstract

Background and Purpose

To evaluate the results of selective nodal irradiation (SNI) on basis of FDG-PET scans in patients with limited disease small cell lung cancer (LD-SCLC), on isolated nodal failures.

Methods and Materials

A prospective study was performed of 60 patients with LD-SCLC. Radiotherapy was given to a dose of 45 Gy in twice daily fractions of 1.5 Gy, concurrent with carboplatin and etoposide chemotherapy. Only the primary tumour and the mediastinal lymph nodes involved on the pre-treatment PET scan were irradiated. A chest CT-scan was performed 3 months after completion of radiotherapy and every six months thereafter.

Results

A difference was seen in the involved nodal stations between the pre-treatment FDG-PET and CT scans in 30% (95% CI: 20-43%) of patients. Of the 60 patients, 39 (65%, 95% CI: 52-76%) developed a recurrence. Two patients (3%, 95% CI: 1-11%) experienced an isolated regional failure. The median actuarial overall survival was 19 months (95% CI: 17-21 months). The median actuarial progression free survival was 14 months (95% CI: 12-16 months). 12% (95% CI: 6-22%) of patients experienced acute grade 3 (CTCAE v 3.0) esophagitis.

Conclusions

FDG-PET based selective nodal irradiation for LD-SCLC resulted in a low rate of isolated nodal failures (3%), with a low percentage of acute esophagitis. These findings are in contrast to those from our prospective study of CT-based selective nodal irradiation, which resulted in an unexpectedly high percentage of isolated nodal failures (11%). Because of the low rate of isolated nodal failures and toxicity, we believe that our data support the use of PET-based SNI for LD-SCLC.

4.1 Introduction

The prognosis of patients with limited disease small cell lung cancer (LD-SCLC) has improved significantly with the application of accelerated radiotherapy (RT) and concurrent chemotherapy¹, which have become the current standard treatment. Although long term survival rates of approximately 25% have been reached, more than 30% of patients will still develop local failure with this treatment¹. Improving locoregional tumour control by simply increasing the radiation dose is not straightforward, because dose limiting toxicity occurs, consisting of severe reversible esophagitis and lung damage²⁻⁴. An attractive strategy to reduce the toxicity is to diminish the radiation fields by omitting routine elective nodal irradiation (ENI) of the mediastinum. This strategy has proved its efficacy in non-small cell lung cancer (NSCLC), in which radiation fields could be safely reduced by selective nodal irradiation (SNI), using CT, and even further using ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans⁵⁻⁸. Treating only FDG-positive mediastinal areas decreased the radiation exposure of the lungs and the esophagus sufficiently as to allow for radiation dose-escalation in NSCLC^{9, 10}. Although selective irradiation of clinically involved nodes is also regularly applied in clinical practice for SCLC, no published data are available supporting this practice. A recent report from the International Atomic Energy Agency meeting emphasized the need for prospective clinical evidence regarding SNI for SCLC¹¹.

To date, only a few prospective data concerning selective nodal irradiation (SNI) for SCLC are available. In a previous phase II trial from our group, isolated nodal failures were observed outside of the clinical target volume (CTV) in 11 % of patients undergoing SNI, using CT¹². These isolated nodal failures all occurred in the ipsilateral supraclavicular fossa. Baas et al.¹⁰ and Belderbos et al.¹³ reported an isolated nodal recurrence in the ipsilateral supraclavicular fossa in 1 of 36 patients treated with concurrent chemotherapy and CT-based involved field irradiation. Although no definitive conclusions could be drawn because of the small sample size, those findings imply that the safety of SNI in NSCLC cannot be straightforwardly extrapolated to SCLC patients. The available data suggest that FDG-PET scans are more accurate than CT in the primary staging of SCLC¹⁴⁻¹⁷. In a planning study on FDG-PET based selective mediastinal node irradiation in 21 LD-SCLC patients to investigate the potential role of FDG-PET in RT planning¹⁸, we found a change in the treatment plan compared with the CT based plan in 24% of patients. Because of these results, we decided to prospectively evaluate SNI based on FDG-PET for LD-SCLC. Our primary end point was to evaluate the proportion of isolated nodal failures; secondary end points were the patterns of recurrence and esophageal and pulmonary toxicity.

4.2 Methods and Materials

Patient population

Patients diagnosed with LD-SCLC and referred for radical RT to Maastricht clinic between December 2004 and November 2006 were prospectively evaluated. The inclusion criteria were cytologically or histologically proven SCLC; limited disease, defined as International Union Against Cancer Stage I-III, with the exclusion of T4 lesions because of malignant pleural or pericardial effusion; World Health Organization (WHO) performance status 0-2; age at least 18 years; adequate pulmonary function (forced expiratory volume in 1 second >1 litre). Patients with severe recent cardiac disease (e.g., arrhythmia, congestive heart failure, infarction) were excluded. The minimal follow-up time after the start of RT was 18 months.

Staging

All patients underwent bronchoscopy with biopsy and standard haematological and biochemical workup. Brain imaging was performed with either MRI or a contrast-enhanced CT. Pre-treatment imaging of the chest consisted of either both a whole body FDG-PET scan and a contrast-enhanced CT scan of the chest, or a combined whole body FDG-PET-CT scan with contrast.

Chest imaging with FDG-PET and CT

For PET-based RT planning, a combined PET-CT scan was performed either during the diagnostic process only or during both the diagnostic process and for RT simulation. In both cases, to ensure optimal co-registration, the PET-CT scan was obtained with the patient in the RT position with both arms above the head¹⁹. Patients had to have fasted for at least 6 hours before the examination. The injected total activity of FDG was calculated from the weight of the patient: $(\text{weight} \times 4 + 20)$ MBq. After a rest period of 60 min (interval needed for FDG uptake), the PET and CT images were acquired. A CT scan of the whole thorax was performed with intravenous contrast during free-breathing.

Lymph nodes were judged positive and included in the CTV on basis of the report of the PET and CT scan. The CT and PET findings were interpreted and reported independently by an experienced chest radiologist and nuclear medicine specialist, respectively.

The CT-findings from the diagnostic CT scan were also interpreted by an experienced chest radiologist. Lymph nodes were considered to be pathologic on CT when their axial diameter was >1 cm. The lymph nodes were considered positive on the FDG-PET scan on basis of visual interpretation by an experienced PET scan specialist.

No quantitative standardized uptake value (SUV) threshold was used, as a visual scale has been shown to be at least as accurate as the use of a SUV-threshold to distinguish benign from malignant nodes^{20, 21}. The involved lymph node stations were recorded according to the Mountain and Dresler classification scheme²².

Radiotherapy

For RT planning, contrast-enhanced CT or combined FDG-PET-CT was performed that extended from the cricoid to the second lumbar vertebra, with a maximal slice thickness of 3 mm. Patients were scanned in the supine position with both arms above the head. The CT and PET images were automatically registered using a rigid registration technique based on mutual information and were subsequently fused using Focal software (Computerized Medical Systems (CMS), St Louis, MS). RT planning was performed with a XiO treatment planning system (CMS), using inhomogeneity corrections based on a convolution algorithm. For all patients, the gross tumour volume (GTV) and planning target volume (PTV) were defined on basis of the PET and CT data. In the case of induction chemotherapy, the post-chemotherapy volume was considered as the GTV of the primary tumour, whereas for the lymph nodes, only the pre-treatment extension was considered. For the primary tumour, the GTV was delineated using the CT findings only, using lung window settings (W = 1700, L = -300). We deliberately avoided contouring on the basis of ill-defined areas on the PET scan. Instead, the sharp boundaries of the CT scan images were used. For planning of the lymph nodes, the pre-treatment anatomic sites of the involved zones on the FDG-PET scan were delineated on the planning CT scan in a mediastinal window setting (W = 600, L = 40). The whole pathologic anatomic region as described by the nuclear medicine specialist in the original diagnostic report (i.e., before the start of chemotherapy) was delineated²³. If the PET scan was negative in the mediastinum and the CT scan positive, the mediastinum was not included in the GTV. The margin from the GTV to the CTV (Clinical Target Volume) was 5 mm, and from the CTV to the PTV 5 mm for the nodal areas and 10 mm for the primary lung tumour. No elective nodal irradiation was performed.

Contouring of the lung was done automatically by the treatment planning system. The mean lung dose (MLD) was analyzed as a possible predictor for radiation pneumonitis. For the calculation of the MLD, the volume of both lungs minus the GTV was considered²⁴. The dose constraint to the lungs was set at a MLD of 19 Gy. The esophagus was delineated from just below the larynx to the gastro-esophageal junction. Neither the GTV nor the PTV was subtracted from this volume. The mean esophageal dose (MED) and the maximal esophageal dose (Dmax) were analyzed as possible predictors of early and late esophageal toxicity^{24, 25}. The spinal cord was drawn throughout the whole CT scan and was considered to be at the inner margin

of the bony spinal canal. The maximum allowed dose to the spinal cord was 54 Gy, and this dose constraint was not reached in the present study.

All patients were treated with a three-dimensional conformal treatment plan using 6-10 MV photons. The prescribed dose to the PTV was 45 Gy in 30 fractions within 3 weeks (1.5 Gy twice daily, with a minimal interval between two fractions of 8 hours) according to the ICRU report 50 guidelines²⁶. During RT, patients were seen weekly by the radiation oncologist, for the evaluation of acute side effects.

Chest RT was planned to start as early as possible after the beginning of chemotherapy. After thoracic irradiation and 5 cycles of chemotherapy, re-staging was performed including a chest X-ray and contrast-enhanced CT scan or MRI of the brain. If no progression was found on the chest X-ray and no brain metastases were seen, patients were offered prophylactic cranial irradiation (PCI) to a dose of 25 Gy in 10 fractions.

Chemotherapy

Patients underwent chemotherapy according to the standard protocol in the Comprehensive Cancer Centre Limburg (the Netherlands). The standard protocol was carboplatin on day 1 and etoposide (120 mg/m²) on day 1-3. The carboplatin dose was based on the target area under the curve (5mg/ml/h) * (glomerular filtration rate + 25), with the glomerular filtration rate calculated according to the Cockcroft-Gault formula. The chemotherapy cycles were repeated every 21 days for a total of 5 cycles.

Post-treatment follow-up

The follow-up consisted of a visit 3 weeks after the end of RT for the evaluation of acute side effects. Thereafter, visits every 3 months, including history taking and physical examination, were performed, for the first 2 years. After this period, 6-month visits were performed until 5 years after treatment. CT of the thorax was performed 3 months after RT completion and every 6 months thereafter. When a patient presented with a recurrence outside of the follow-up visits, chest imaging was performed with chest X-ray and CT. After the detection of a recurrence, the follow-up visits were continued at 3 month intervals, with the type of imaging being guided by the site of progression and the presence of symptoms.

Local tumour control was evaluated according to the criteria of Green et al.²⁷. An isolated nodal recurrence was defined as a recurrence in the regional nodes outside the CTV, in the absence of in-field failure or distant metastases.

The pulmonary and esophageal toxicity were scored according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (Table 4.1)²⁸. Toxicity

was scored before the start of RT, at the weekly visits during RT, and at the follow up visits.

Table 4.1 Toxicity grading criteria according to the Common Terminology Criteria for Adverse Events, version 3.0

Adverse event	Grade				
	1	2	3	4	5
Esophagitis	Asymptomatic, pathologic, radiologic or endoscopic findings only	Symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements); IV fluids indicated < 24 hrs	Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 hrs	Life threatening consequences	Death
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic, narcotic medication indicated	Symptomatic, significantly interfering with sleep or ADL	-	-
Dyspnea	Dyspnea on exertion, but can walk 1 flight of stairs without stopping	Dyspnea on exertion, unable to walk 1 flight of stairs or 1 city block (0.1 km) without stopping	Dyspnea with ADL	Dyspnea at rest; intubation/ventilator indicated	Death

Ethics

The trial was performed in accordance with the Dutch laws and regulations. The study protocol was registered at the National Institute of Health (NIH) clinical trial database, under NCT00572923.

Statistical analysis

On basis of the planning study we had previously performed¹⁸, we hypothesized that introducing PET into the RT planning would change the treatment fields in 25% of the patients compared with CT-based planning²⁹. From the results of PET based SNI for NSCLC, we expected the percentage of isolated nodal failures to not exceed 5%. As the upper bound of the 95% confidence interval (CI), we used the observed 11% of isolated nodal failures with CT-based SNI¹². To detect this rate of failures, at least 50 patients were needed for the present study³⁰

The results are expressed as the mean $\pm$ standard deviation (SD) or as a proportion, with the 95 % CI's. The estimates of overall survival (OS) and progression free survival (PFS) rates were calculated with the Kaplan Meier method, on an intent to treat basis, starting from the first day of RT. Correlations between the dose volume parameters and toxicity were calculated using a two-sided Spearman's test or a chi-square test in the case of nominal variables.

4.3 Results

Patient and treatment characteristics

A total of 60 patients with LD-SCLC, referred to our institution between December 2004 and November 2006 were included. The baseline patient characteristics are summarized in Table 4.2. Most patients were male (67%). All patients received chemotherapy, which in 97% consisted of carboplatin-etoposide. One patient received carboplatin-paclitaxel because she was diagnosed with ovarian cancer during the diagnostic workup. A total of 59 patients (98%) received a dose of 45 Gy. Five patients were treated with sequential chemoradiotherapy instead of concurrent chemoradiotherapy. The reasons for this protocol violation were either a too high MLD owing to the size of the primary tumour, or a delay in patient referral. One patient was not considered fit enough to undergo accelerated RT with concomitant chemotherapy and was therefore treated with 5 cycles of induction chemotherapy, followed by RT to a dose of 54 Gy in 30 once-daily fractions.

The median interval between the first day of chemotherapy and the start of chest RT for patients treated with concurrent chemo-radiotherapy was 18.0 ± 11.1 days (range: -13 to 49 days). The overall treatment time of RT was 21 ± 3.7 days (range 17-41). The median interval between the start of chemotherapy and the end of RT (SER) was 39 ± 34.0 days (range: 7-176). The median SER for patients treated with concurrent chemoradiotherapy was 38 ± 11.6 days (range: 7-71 days). Of the 60 patients, 50 (83%, 95% CI: 72-91%) received PCI.

A difference in mediastinal staging according to CT and PET was observed in 30% (95% CI: 20-43%) of the patients (Figure 4.1). In 15% (95% CI: 8-26%), more nodal stations were involved on PET than on CT, and in 13% of patients (95% CI: 7-24%) fewer nodal stations were involved on PET than on CT. In 1 patient, nodal stations were involved on PET that were not involved on CT and vice versa. In 3 patients (5%, 95% CI 2-14%) supraclavicular nodal stations were found to be involved on PET, but the CT scan was negative for these stations.

Table 4.2 Baseline patient and treatment characteristics

Characteristic	Value $\pm$ SD (%)
<i>Age (years)</i>	
Median	66.0 $\pm$ 8.9
Range	48-85
<i>Gender</i>	
Male	40 (66.7)
Female	20 (33.3)
<i>WHO performance status</i>	
0	13 (21.7)
1	39 (65.0)
2	8 (13.3)
<i>Lung function (Median FEV1, %)</i>	70.0 $\pm$ 20.2
<i>Tumour location</i>	
Right upper lobe	17 (28.3)
Right middle lobe	5 (8.3)
Right lower lobe	4 (6.7)
Left upper lobe	11 (18.3)
Left lower lobe	6 (10.0)
Right hilus	7 (11.7)
Left hilus	8 (13.3)
Unknown	2 (3.3)
<i>Chemotherapy</i>	
Carboplatin-Etoposide	58 (96.7)
Carboplatin-Paclitaxel	1 (1.7)
Unknown	1 (1.7)
<i>Interval between CTx-RT (days)</i>	
Mean	27.8
Range	13-158
<i>Dose (Gy)</i>	
45	59 (98.0)
54	1 (2.0)
<i>OTT of RT (days)</i>	
Median	21.0 $\pm$ 3.7
Range	17-41
<i>SER (days)</i>	
Median	39.0
Range	7-176

WHO: world health organization; FEV1: forced expiratory volume in 1 second; CTx: Chemotherapy; RT: radiotherapy; OTT: overall treatment time; SER: interval between the start of CTx and the end of RT

Figure 4.1 Difference in involved nodal stations between PET and CT
a) Representative image of a patient with a positive nodal station 7 on PET, while CT is negative
b) Representative image of a patient with a positive nodal station 4L on CT, while PET is negative

Patterns of failure

An overview of the frequency and site of relapses is listed in Table 4.3.

Table 4.3 Frequency and location of recurrences as assessed by CT	
Recurrence	Number of patients (%)
<i>None</i>	21 (35)
<i>Local</i>	9 (15)
In field	3 (5.0)
Out of field	4 (6.7)
Both in field and out of field	2 (3.3)
Isolated local	2 (3.3)
Local and distant/nodal	7 (11.7)
<i>Nodal</i>	20 (33.3)
In field	8 (13.3)
Out of field	7 (11.7)
Both in field and out of field	5 (8.0)
Isolated nodal	2 (3.3)
Nodal and distant/local	18 (30.0)
<i>Distant</i>	34 (56.7)
Isolated distant	19 (31.7)
Distant and local/nodal	15 (25.0)
Isolated brain	9 (15.0)

The minimal follow up of all surviving patients was 18 months. The median follow-up for all patients was 18.5 ± 10.3 months (range: 3-52 months). Of the 60 patients, 39 (65%, 95% CI: 52-76%) developed a recurrence. Two patients (3%, 95% CI: 1-11%) experienced an isolated nodal recurrence. Both recurrences were treated with concurrent chemoradiotherapy. The first patient, whose primary tumour was located in the left lower lobe, developed a nodal recurrence in station 4R at 15 months after treatment. Different nodal stations had been involved before treatment on PET (stations 5 and 10L) and CT (station 10L), but station 4R was not involved before treatment on PET or CT. The second patient, with the primary tumour located in the lingula of the left lung, developed nodal recurrence in station 2L and the left supra-clavicular region, also 15 months after treatment. Those stations were not involved before treatment on the basis of PET or CT (only station 6 involved).

In 87% (95% CI: 73-94%), distant metastases (either isolated or combined with local or nodal recurrence) were present at recurrence. Nine patients (15%, 95% CI: 8-26%) were diagnosed with isolated brain metastases, of whom 6 had previously received PCI. A nodal recurrence outside the treatment field combined with recurrence inside the treatment field occurred in 5 (8%, 95% CI: 4-18%) patients. In one of them, the nodal recurrence occurred in a nodal station that was positive on CT, but negative on PET, and hence had not been included in the treatment field.

Survival

The median actuarial overall survival (OS) time for all patients was 19 months (95% CI: 17-21 months) (Figure 4.2), with a 2 year OS rate of 35%. The median OS for patients treated with concurrent chemoradiotherapy was also 19 months (95% CI: 16-22 months). The median actuarial progression free survival (PFS) was 14 months (95% CI: 12-16 months) (Figure 4.3), the 2 year PFS rate was 26%.

Figure 4.2 Actuarial overall survival

Figure 4.3 Actuarial progression free survival

Toxicity

An overview of the dose-volume-histogram (DVH) parameters according to the toxicity grade is presented in Table 4.4. The mean DVH parameters were as follows: mean MLD 12.9 ± 4.2 Gy; mean MED: 22.1 ± 8.6 Gy; mean Dmax: 44.5 ± 8.6 Gy. Treatment related toxicity to the lungs was relatively mild, with grade 3 cough in 1 patient and grade 3 dyspnea in 2 patients. However, 62% of patients experienced acute esophagitis of grade 2 or more, with 12% (95% CI: 6-22%) experiencing grade 3 esophagitis. The frequency of grade 3 esophagitis in patients treated with concurrent chemoradiotherapy was 13% (95% CI: 7-25%). No grade 4 or 5 toxicity was observed. The esophagitis resolved within 4 weeks after RT in all patients. No significant correlation was found between the toxicity grade and the radiation parameters, neither for lung, nor for esophageal toxicity.

Table 4.4 Dose Volume Histogram (DVH) parameters according to the toxicity grade*

Toxicity	N of patients (%)	Parameter	
Lung Toxicity			
Cough		MLD ± SD (Gy)	
G0	11 (18.3)	12.0 ± 4.1	
G1	34 (56.7)	13.8 ± 4.)	
G2	14 (23.3)	13.5 ± 3.3	
G3	1 (1.7)	6.9 ± 0.0	
Dyspnea		MLD ± SD (Gy)	
G0	22 (36.7)	11.8 ± 3.7	
G1	27 (45.0)	13.5 ± 3.9	
G2	9 (15.0)	15.2 ± 4.1	
G3	2 (3.3)	16.5 ± 3.4	
Esophageal toxicity			
Esophagitis		MED ± SD (Gy)	Dmax ± SD (Gy)
G0	9 (15.0)	14.6 ± 9.7	41.0 ± 10.2
G1	14 (23.3)	23.4 ± 9.3	44.1 ± 9.7
G2	30 (50.0)	22.9 ± 7.8	44.9 ± 3.4
G3	7 (11.7)	24.0 ± 6.8	47.0 ± 0.9

G: Grade; MLD: Mean Lung dose; MED: Mean esophageal dose; Dmax: maximal esophageal dose

* Common Terminology Criteria for Adverse Events, version 3.0

4.4 Discussion

This is the first prospective study evaluating selective nodal irradiation based on FDG-PET scans in LD-SCLC patients.

In the absence of clinical evidence regarding the safety of SNI, radiation oncologists are confronted with the choice between a possible reduction in treatment related toxicity and the possibility of increasing the risk of locoregional failure¹¹. A phase II trial by our group evaluating the safety of CT-based SNI resulted in an unacceptably

high percentage of isolated regional failures (11%, 95% CI: 2-29%). In contrast, in the present study with SNI based on PET, isolated nodal recurrences occurred in 3% of patients (95% CI: 1-11%). This proportion is comparable to that found with SNI in NSCLC, in which about 2% experienced an isolated nodal recurrence with SNI on basis of FDG-PET scans^{5,6}.

The remarkable difference between the value of SNI based on CT vs. PET in LD-SCLC, may be explained by the discrepancy in the involved nodal stations on the PET and CT scans. Indeed, we observed different lymph node stations involved on PET compared with those on CT in 30% of our LD-SCLC patients. The proportion of patients in whom more nodal stations were involved on PET than on CT was similar to the percentage in whom fewer nodal stations were involved on PET than on CT. These data correspond to those found in the planning study we performed, in which a difference in involved nodal stations in 24% of patients was observed. In our prospective study concerning CT-based SNI for SCLC, all isolated nodal failures occurred in the ipsilateral supraclavicular area¹². The present study showed involvement of the ipsilateral supraclavicular nodes on PET in 5% of patients whose CT scan was negative for this region. This confirms that PET scanning can result in the upfront detection of supraclavicular lymph node metastases, thereby reducing the risk of an isolated nodal recurrence in this area.

Patients with an isolated nodal failure could theoretically have been cured if elective nodal irradiation had been performed instead of SNI. However, aside from the nodal recurrences, both local and distant recurrences still occurred in most patients, emphasizing the need for better treatment strategies for this disease.

The median OS in our study of 19 months (2 year OS rate: 35%) was lower than that reported in the trial by Turrisi et al.¹, in which LD-SCLC patients were treated with concurrent chemoradiotherapy with elective nodal irradiation (median OS of 23 months and 2 year OS rate of 47%). A possible explanation for this difference in survival is the relatively long SER in our study (39 days, range: 20-176). Moreover, the standard chemotherapy regimen in our region consisted of carboplatin-etoposide, not cisplatin-etoposide chemotherapy as in the trial by Turrisi et al.¹. Although one randomized prospective trial showed equal efficacy for both treatment regimens in the treatment of SCLC³¹, no definitive conclusions could be drawn regarding the outcomes with concurrent chemoradiotherapy for LD-SCLC. Finally, in the trial by Turrisi et al.¹, patients with contralateral hilar or supraclavicular involvement were excluded, whereas they were included in our study.

Lung toxicity was generally mild and rare, with only 5% of patients experiencing grade 3 toxicity (cough or dyspnea according to the CTCAE 3.0 criteria). A remarkably low percentage of severe acute esophagitis was found, with only 12% (95% CI: 6-

22%) of patients experiencing grade 3 esophagitis. In patients who have undergone elective nodal irradiation, or CT based SNI, grade 3 esophagitis usually occurs in about 30% of patients^{1,6}. This cannot be straightforwardly explained by a reduction of radiation fields, because both our previous planning study and the present trial showed an equal percentage of increases and decreases in radiation fields when using PET instead of CT. Possible hypotheses include the relatively long SER in the present study³², a lower than average neutropenia level³³, which was not investigated in the present study, or simply an observation due to chance. If the current finding of lower esophageal toxicity holds true, PET based SNI could provide opportunities for dose escalation and hence, improvement of locoregional tumour control. Therefore, more studies are warranted to investigate this finding.

The use of FDG-PET-CT is likely to be the most accurate non-invasive staging method for the mediastinum in SCLC^{15, 29, 34}. However, the most reliable method to detect mediastinal nodal involvement remains pathological verification. The available studies have indicated that CT underestimates mediastinal nodal involvement³⁵⁻³⁷. No prospective data exist concerning correlation of the pathologic findings with PET findings in SCLC. Because of the low rate of isolated nodal failures found in the present study and the morbidity associated with invasive staging, we believe that our data support the use of PET-based SNI for LD-SCLC.

4.5 Conclusion

This prospective study shows that PET-based SNI in LD-SCLC is safe and is associated with low toxicity.

4.6 References

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Part

II

**The value of FDG-PET-CT in the follow-up
of locally advanced NSCLC patients**

CHAPTER 5

**Follow-up with ^{18}F FDG-PET-CT after
radical radiotherapy with or without
chemotherapy allows the detection of
potentially curable progressive disease in
non-small cell lung cancer patients:
a prospective study**

**Judith van Loon
Janneke Grutters
Rinus Wanders
Liesbeth Boersma
Michel Öllers
Anne-Marie Dingemans
Gerben Bootsma
Wiel Geraedts
Cordula Pitz
Jean Simons
Sakar Abdul Fatah
Gabriel Snoep
Monique Hochstenbag
Philippe Lambin
Dirk De Ruyscher**

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Abstract

Background and purpose

Follow-up of patients treated with curative intent for non-small cell lung cancer (NSCLC) with X-ray or CT-scans is of unproven value. Furthermore, most patients with progressive disease present with symptoms outside of follow-up visits. Because the accuracy of ^{18}F FDG-PET-CT is superior to CT, we hypothesized that FDG-PET-CT scans 3 months post-treatment could lead to early detection of progressive disease (PD) amenable for radical treatment.

Methods and Materials

Hundred patients with NSCLC, treated with curative intent with (chemo) radiation, were prospectively evaluated. All patients underwent a planned FDG-PET-CT scan three months after the start of radiotherapy.

Results

Twenty-four patients had PD 3 months post-treatment. 16/24 patients were symptomatic. No curative treatment could be offered to any of these patients. In 3/8 asymptomatic patients progression, potentially amenable for radical therapy was found, which were all detected with PET, not with CT only.

Conclusions

PET scanning after curative treatment for NSCLC led to the detection of progression potentially amenable for radical treatment in a small proportion (3%) of patients. Selectively offering a PET-CT scan to the patient group without symptoms could possibly lead to an effective follow-up method.

5.1 Introduction

Lung cancer is the leading cause of cancer death, with an estimated 161.000 patients dying of this disease in the United States in 2008 ¹. The survival of non-metastatic non small cell lung cancer (NSCLC) patients remains poor, with 5-year survival rates of about 50 % in stages I-II and 20 % in stage III disease ^{2,3}. This poor survival is due to a high amount of both locoregional and distant progression ⁴. Theoretically, early detection of progressive disease (PD) at a time when radical therapy is an option, could improve the survival. In NSCLC however, there are at present no convincing data supporting that early detection of progression improves survival ⁵⁻⁸. Moreover, most patients who have PD present with symptoms outside of planned follow-up visits ^{5,9}. A recent study showed no significant improvement of survival with intensive follow-up by repeated CT-imaging compared to less intensive radiologic follow-up ⁵. A major restriction of both conventional chest X-ray and CT after curative treatment for NSCLC is the poor discriminating capacity between residual or recurrent tumour and post-treatment changes ^{7,10}. Therefore, repeated imaging is often needed to confirm PD. This delay could lead to missing the chance for salvage treatment.

¹⁸F-fluorodeoxyglucose positron emission tomography (¹⁸FDG-PET) scanning, which allows imaging of glucose uptake of tissues, has shown to be superior to CT in the evaluation of lung lesions and mediastinal lymph nodes ¹¹⁻¹³, as well as in the detection of distant metastases in the primary staging of NSCLC ¹⁴. Furthermore, FDG-uptake of the primary tumour before and during therapy, as well as 3 months after treatment is prognostic for outcome ¹⁵⁻²². Finally, PET is more accurate than CT in the distinction of tumour from post-radiotherapy (RT) effects ^{18, 23, 24}. Based on these data, we hypothesized that the use of PET-CT in the follow-up of patients with NSCLC treated with curative intent would be superior to CT alone. The aim of our study was to evaluate the detection rate of PD amenable for salvage treatment using routine PET-CT in the follow-up of NSCLC patients treated with curative intent with (chemo) radiation. Therefore, we prospectively investigated the impact of follow-up with PET-CT 3 months after therapy on the outcome in 100 consecutive patients with NSCLC, who were treated with curative intent.

5.2 Methods and Materials

Patient population and study design

Patients with stages I-III NSCLC, who were treated with curative intent with (chemo) radiotherapy at our institute from February 2005 until August 2007, consenting to

an additional PET-CT in the follow-up, were prospectively evaluated. Patients with stage IV disease on the basis of a solitary brain metastasis, treated with curative intent, were also included. As part of the primary staging, all patients underwent an FDG-PET-CT and imaging of the brain (either MRI or CT) before the start of treatment. The follow-up consisted of a visit 3 weeks after the end of treatment for the evaluation of acute side effects. Thereafter, 3-monthly visits, comprising history taking and physical examination, were performed alternately by the pulmonologist and radiation oncologist, for the first 2 years. Thereafter, 6-monthly visits were performed until 5 years post-treatment. AN FDG-PET-CT scan was planned irrespective of the presence of symptoms at 3 months after the start of radiotherapy, with a minimum interval of 2 months (60 days) to account for persistent increased FDG-uptake immediately after therapy. Within 1 week following the PET-CT scan, a follow-up visit was planned. Request of other diagnostic imaging procedures was left at the decision of the physician, as indicated by the presence of symptoms.

Treatment characteristics

Patients were treated with radical radiotherapy (RT), either alone (medically inoperable stage I-II disease) or in combination with concurrent or sequential chemotherapy in stage III disease. For stages I and II NSCLC, radical RT was given in fractions of 1.8 Gy, twice daily, to a mean lung dose (MLD) of 19 Gy (maximal total tumour dose: 79.2 Gy)²⁵. Patients with stage III disease received induction chemotherapy with one cycle of carboplatin-gemcitabine (carboplatin (total dose: target AUC*(GFR+25) on day 1 - gemcitabine 1250 mg/m² on days 1 and 8). This was followed by concurrent chemoradiotherapy. RT was given to a dose of 45 Gy in twice daily fractions of 1.5 Gy, followed by 2 Gy daily fractions to a MLD of 19 Gy (maximal total tumour dose: 69 Gy), concurrent with cisplatin 50 mg/m² and vinorelbine 20 mg/m² on days 1 and 8. Patients with stage III disease who were considered unable to undergo concurrent chemo-radiotherapy were treated either with radical RT alone, or with sequential chemo-radiotherapy, consisting of three cycles of induction chemotherapy (carboplatin-gemcitabine) followed by RT as described for stages I/II.

PET-CT imaging

A combined whole-body PET-CT scan was performed about 3 months (but at least 2 months) after the start of radiotherapy. Patients had to be fasting for at least 6 hours before the examination. The injected total activity of FDG was calculated based on the weight of the patient: (weight * 4) + 20 MBq. After a rest period of 60 minutes (time needed for uptake of FDG), PET and CT images were acquired. A whole-body CT-scan was performed with intravenous contrast. The CT- and FDG-

PET findings were first interpreted and reported independently by an experienced chest radiologist and nuclear medicine specialist, respectively. Tumour progression was defined according to the EORTC criteria for PET²⁶ and to the RECIST criteria for CT²⁷. Thereafter, both specialists jointly evaluated the combined PET-CT images, from which a distinct report was written.

Data acquisition

For each patient, the following data were collected: patient demographics; initial tumour characteristics (stage according to the TNM-classification (UICC, 6th edition), location and histology); and treatment characteristics (dose, overall treatment time (OTT) of radiotherapy and treatment modality).

Results of the PET-CT scan were recorded as described in the diagnostic report of the radiologist and nuclear medicine specialist. Progressive disease was defined as locoregional when situated at or around the original tumour site or regional lymph nodes and further specified as within or outside the RT field. Progression was defined as distant when situated either in a different lobe as the primary tumour, or outside of the thorax. The site of distant relapse was recorded as well. If both locoregional and distant progression was detected, both were recorded. PD was judged as either diagnosed on basis of CT alone when it was described in the distinct report of the CT (PD according to the RECIST criteria), or as diagnosed with PET when it was only described in the distinct report of the PET (PD according to the EORTC criteria) and/or the report of the combined PET-CT, with the report of the CT being either negative or inconclusive.

PD was defined as amenable for salvage treatment when it was either locoregional, or in case of oligometastasis, defined as 1 or 2 metastases, amenable for radical local treatment by either radiotherapy or surgery²⁸. The distinction between locoregional progression and post-RT changes was recorded on the basis of the diagnostic report and was made on visual interpretation by the nuclear medicine physician. Because these radiation-induced changes can normally be readily distinguished from persistent or recurrent tumour by their FDG-uptake distribution, no quantitative threshold was used^{24, 29}.

The absence or presence of symptoms at time of the PET-CT was noted. Furthermore, it was judged whether at least one of the symptoms was corresponding to the site (or one of the sites) of progression found on PET-CT. This was based on the following assumptions: pain was defined as corresponding to the site of progression when it was localized at the dermatome corresponding to the site. Pulmonary symptoms (cough, dyspnoea) were defined as corresponding when progression was either locoregional or metastases in the lung, and symptoms had increased over time after RT. Neurological symptoms were judged corresponding when either brain

metastases were diagnosed, or symptoms were consistent with the site of metastasis in the central or peripheral nervous system.

No distinction was made between the detection of a second primary or PD. Because of the short interval between the primary treatment and the PET-CT scan 3 months after therapy, a second tumour in the same lobe was considered as PD, while a second tumour in another lobe was considered a distant relapse rather than a second primary. Survival data were obtained by consultation of the Dutch Communal Data (GBA) register. Follow-up time was defined as the time from the end of radiotherapy until death or the last time of follow-up. At the time of analysis, 51 patients had died. For three patients, survival data could not be retrieved.

Statistical analysis

We estimated that 25% of the patients would have detectable PD at the time of the post-treatment FDG-PET-CT scan^{30, 31}, with an estimated 25% of them being eligible for salvage treatment. In order to detect this proportion (6%) with a 95% confidence interval (CI) of 1-11%, at least 85 patients evaluable 3 months post-treatment would be needed. To account for possible dropouts, 100 patients were included.

Statistical calculations were performed using SPSS (Version 15.0 for Windows). Results were described as either median or mean $\pm$ one standard deviation (SD) when the results were normally distributed. When there was no normal distribution, results were described as either median or mean with the range. For the calculation of 95% confidence intervals (95% CI) for proportions, the Wilson score interval was used³². P-values were calculated with the Chi-square test for proportions.

Ethics

The trial was performed according to the required Dutch laws and regulations. All patients gave informed consent for the study, which was part of two study protocols, NCT00573040 and NCT00572325.

5.3 Results

Patient and treatment characteristics

From February 2005 until August 2007, 100 NSCLC patients, stages I-III, treated with curative intent, were included. Patient, tumour and treatment characteristics are listed in Table 5.1. The mean follow-up of all patients was 55.9 ± 29.2 weeks, ranging from 13 to 182 weeks. Seventy males and 30 females were included, with a mean age of 66.0 ± 9.7 years (range: 44-86).

Table 5.1 Patient, tumour and treatment characteristics

	N ± SD (%)
<i>Age</i>	
Mean (years)	66.0 ± 9.7
Range	44-86
<i>Gender</i>	
Male	70 (70)
Female	30 (30)
<i>Stage</i>	
IA	4 (4)
IB	6 (6)
IIA	0 (0)
IIB	3 (3)
IIIA	25 (25)
IIIB	61 (61)
IV	1 (1)
<i>Histology</i>	
Adenocarcinoma	15 (15)
Large cell carcinoma	30 (30)
Squamous cell carcinoma	18 (18)
Bronchioloalveolar cell carcinoma	1 (1)
NSCLC, NOS	36 (36)
<i>Treatment</i>	
Radical RT only	16 (16)
Sequential Chemo-RT	65 (65)
Concurrent Chemo-RT	19 (19)
<i>Dose (Gy)</i>	
Median	63.5
Range	50.4-79.2
<i>Time interval*</i>	
Median	16 ± 3.1
Range	9-27
<i>Follow-up**</i>	
Mean	55.9 ± 29.2
Range	13-182

N= number of patients; SD= standard deviation; NOS: not otherwise specified

*Weeks from the start of radiotherapy to the date of PET-CT

**Weeks from the end of radiotherapy until death or lost to follow-up

The median radiation dose delivered was 63.5 Gy, ranging from 50.4 to 79.2 Gy. Most (86/100) patients had stage III disease at time of presentation. 84% of patients received chemotherapy, either sequential to or concurrent with radiotherapy. One patient had stage IV disease. This patient had a solitary brain metastasis, which was treated with stereotactic radiotherapy before radical treatment of the lung tumour.

Results of PET-CT scanning 3 months after treatment

The mean time interval from start of RT until planned surveillance PET-CT scan was 16 ± 3.1 weeks (range: 9-27 weeks). All patients underwent the scan more than 2 months after the start of RT, and 75% underwent the scan within 4 months after start of RT. Twenty-four patients had PD, of which 7 had locoregional progression only, 7 distant only and 10 had both locoregional and distant progression. The primary stage and treatment of the patients with progression are described in Table 5.2. Of the 24 patients with progression, 17 (71%, 95% CI: 51-85%) were detected with CT only, while for 7 patients, the PET scan was necessary for the detection of the progression, with CT being either negative or inconclusive (Figure 5.1). Of the 8 patients who were symptomatic at the time of progression, PET was required for the detection in 4/8 patients (50%, 95% CI: 22-78%), while for the symptomatic patients, PET was required in 3/16 patients (19%, 95% CI: 6-43%). In 36 patients (36%, 95% CI: 27-46%), the PET-scan showed findings that were defined in the diagnostic report as post-RT effects. In all patients, these findings could easily be distinguished from PD on the basis of the combined PET-CT images.

Table 5.2 Characteristics of progressive disease	
	N (%)
<i>Primary stage</i>	
I	2 (8)
II	0 (0)
III	21 (88)
IV	1 (4)
<i>Primary treatment</i>	
Radical RT	2 (8)
Sequential Chemo-RT	16 (67)
Concurrent Chemo-RT	6 (25)
<i>Site of progression</i>	
<i>Locoregional</i>	17
Inside RT-field	10 (59)
Outside RT-field	6 (35)
Both Inside and Outside	1 (6)
<i>Distant</i>	17
Bone	9 (38)
Brain	4 (17)
Liver	2 (8)
Muscle	1 (4)
Adrenal gland	4 (17)
Lung	4 (17)
Axilla	1 (4)
N: number of patients

Figure 5.1 Disease progression: detection modality and treatment intent according to presence of symptoms

Sites of progression

An overview of the sites of progression at the time of the PET-CT scan is shown in Table 5.2. Seventeen patients had locoregional PD. In 10 patients, the progression was located inside the RT-field, in 6 patients outside the RT-field and in one patient both inside and outside the RT field. Six of 17 patients with distant metastases had metastases at more than one site.

Correlation of PET-CT findings with symptoms

The presence and distribution of symptoms are described in Table 5.3. Forty five patients (45%, 95% CI: 36-55%) had symptoms at the time of the PET-CT scan. Sixteen of them (36%, 95% CI: 23-50%) had PD on PET-CT. The sensitivity and specificity of symptoms for the presence of progression was 67% (95% CI: 47-82%) and 62% (95% CI: 51-72%), respectively. In 13/16 (81%, 95% CI: 57-93%) patients, the symptoms were in agreement with the site of progression. In the whole group, cough was the most common symptom, followed by pain. In the subgroup of patients with progression, pain was by far the most common symptom.

Table 5.3 Type and frequency of symptoms according to the presence or absence of progression				
Symptoms	All patients (%)	Pts without progression (%)	Pts with progression (%)	p-value
Cough	18	20	13	0.42
Pain	15	5	46	<0.001
Dyspnea	14	15	13	0.81
Neurological	6	3	17	0.01
Dysphagia	3	3	4	0.70
Malaise	2	1	4	0.38
Palpable mass	1	0	4	0.07
Fatigue	1	1	0	0.57

Treatment at the time of progression

The type of treatment of the patients after detection of PD is described in Figure 5.1. Of the 24 patients, 18 (75%, 95 CI: 55-88%) underwent treatment directly after the detection of PD.

PD amenable for salvage treatment was detected in 3/100 (3%, 95% CI: 1-8%) patients (Table 5.4), of which two eventually received a radical treatment.

Table 5.4 Patients with progressive disease amenable for radical treatment							
Case	Primary stage	Follow up*	Interval*	Results PET	Results CT	Therapy	Outcome**
1	T4N0M0	22	12	Partial remission of primary tumour Hotspot left-adrenal gland	Volume reduction of primary tumour Nodus 1.8 cm left adrenal gland	Proposed for pneumonectomy and resection of adrenal metastasis No candidate for pneumonectomy → second line CTx	10 wks: alive
2	T1N0M0	70	18	Hotspot left hilar node	Negative	Radical RT	52 wks: alive; NED
3	T2N3M0	89	13	Pathological uptake in both adrenal glands	Slight increase in volume of both adrenal glands	Bilateral extirpation of adrenal glands	76 wks: alive; NED

CTx: chemotherapy; RT: Radiotherapy; NED: no evidence of disease.
*Weeks from start of radiotherapy
**Weeks from diagnosis of progressive disease

All 3 were detected by PET, and none of the 3 patients had symptoms at the time of detection of PD. The first patient finally underwent palliative chemotherapy because her lung function did not allow a pneumonectomy. The second patient had

regional progression in the left hilus, which was treated with radical RT, and was alive without evidence of disease 1 year after the diagnosis of PD. The third patient was diagnosed with bilateral adrenal metastases (Figure 5.2), for which he underwent a bilateral extirpation of the adrenal glands. Pathological examination confirmed the presence of adrenal metastases. He was alive without evidence of disease 1.5 years after diagnosis of the distant metastases.

Figure 5.2 Case 3. Bilateral adrenal metastases

5.4 Discussion

At present, no data from randomized trials are available concerning the optimal follow-up in NSCLC, while other available data show inconsistent results³³. Guidelines from different cancer associations differ widely in their recommendations concerning chest imaging, from either no routine imaging to surveillance chest CT-scanning. No evidence exists that extensive follow-up with surveillance chest CT-imaging is superior to routine follow-up with physical examination and a chest X-ray. A major disadvantage of CT-scanning is the poor sensitivity and specificity for distinguishing post treatment changes from progressive disease, which is reflected in a high negative predictive value (99%) and a low positive predictive value (53%)^{7, 10}. The accuracy of PET after treatment is assumed to be lower than that at initial staging because of inflammatory and perfusion changes due to therapy¹². Nevertheless, PET has still shown to have a high accuracy in detecting recurrent lung cancer, with a sensitivity up to 98% and a specificity of 62-92%^{9, 12, 34}. In this study, by using combined PET-CT scans, post-RT changes could be distinguished from PD in all patients.

Early detection of isolated locoregional progression or oligometastasis could allow a radical treatment, with long term survival rates up to 30% and 22%, respectively^{28, 35-37}. In the present trial, PET-CT scanning 3 months after curative treatment for NSCLC led to the detection of PD potentially amenable for radical treatment in 3/100 (3%, 95 % CI 1-8 %) patients. These 3 patients were all asymptomatic and progression was only detected with PET, not with CT alone. The most important question is whether an earlier detection of progression results in a longer overall survival. The improved overall survival reported in some retrospective studies, could be attributable to lead time bias^{5, 8, 38}. In the present study, we showed that none of the symptomatic patients with PD were amenable for radical treatment. Furthermore, none of the patients in whom progression was detected with CT only were amenable for radical treatment, while 3 out of 8 patients with progression (all detected with PET) in asymptomatic patients were potentially amenable for radical treatment. The detection of PD with PET-CT in the 2 patients who finally received a radical treatment, being alive without evidence of disease 52 and 76 weeks after salvage therapy, has almost certainly led to a longer overall survival compared to a policy in which diagnostics were only performed at the time when symptoms developed. Of the 3 patients with PD potentially amenable for radical treatment, two had (either uni- or bilateral) adrenal metastases. Because radical treatment by adrenalectomy may result in long term survival rates of 25%³⁹, we believe that there are good arguments to treat this patient group with radical intent.

No pathological confirmation was obtained in the patient with regional progression in the left hilus and in one of the patients with adrenal metastases on PET. As reported earlier, the accuracy of FDG-PET-scanning for the detection of a recurrence is high, with a specificity of 84%⁹. The accuracy of FDG-PET for the diagnosis of adrenal metastasis is reported to be 92-100%⁴⁰⁻⁴².

Another important aspect is the timing of the PET-CT. It is recommended to perform a PET-CT scan not earlier than 3 to 6 months after treatment to avoid false positive results due to post-radiotherapy changes^{12, 43}. Hicks and colleagues found no confounding of the evaluation of tumour response by the presence of post radiotherapy inflammatory changes in 73 patients who underwent a PET-CT scan 70 days after radical radiotherapy⁴⁴. Our data support those findings, as post-radiotherapy changes, being present in 36% of patients, did not influence the response evaluation. Furthermore, uptake associated with post radiotherapy pneumonitis can last for 15 months after the end of radiotherapy⁴⁵. Theoretically, performing a PET-CT scan earlier after therapy could result in the detection of more cases with potentially curable disease.

A potential drawback of PET-CT is that it is rather costly. An important topic for further research is therefore whether the effects of PET-CT are worth the extra

costs and for which patient groups routine PET-CT would be deemed cost-effective. As PD amenable for salvage treatment was only detected in asymptomatic patients, the added value of routine PET-CT imaging seems to be confined to this group (55% of the patients). In patients with symptoms three months after treatment, the type of symptoms could guide the choice for an additional investigation, and routine PET-CT imaging could possibly be reserved for the selection of patients without symptoms. Hereby, a potentially cost-effective follow-up method could be developed. The cost-effectiveness of PET-CT imaging in the follow-up will be examined in a separate study.

5.5 Conclusion

For all patients, PET-CT scanning after curative treatment for NSCLC led to the detection of progression amenable for salvage treatment in a small proportion, which is of questionable clinical value. The possible advantage seems to be confined to the patient group without symptoms. Selectively offering a PET-CT scan to this patient group could lead to an effective follow-up method. Further research is needed in this field.

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CHAPTER 6

¹⁸FDG-PET-CT in the follow-up of non-small cell lung cancer patients after radical radiotherapy with or without chemotherapy: an economic evaluation

**Judith van Loon
Janneke Grutters
Rinus Wanders
Liesbeth Boersma
Anne-Marie Dingemans
Gerben Bootsma
Wiel Geraedts
Cordula Pitz
Jean Simons
Boudewijn Brans
Gabriel Snoep
Monique Hochstenbag
Philippe Lambin
Dirk De Ruyscher**

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Abstract

Background and purpose

The optimal follow-up strategy of non-small cell lung cancer (NSCLC) patients after curative intent therapy is still not established. In a recent prospective study with 100 patients, we showed that an FDG-PET-CT 3 months after radiotherapy could identify progression amenable for curative treatment in 2% (95% CI: 1-7%) of patients, who were all asymptomatic. Here, we report on the economic evaluation of this study.

Methods and Materials

A decision-analytic Markov model was developed in which the long-term cost-effectiveness of 3 follow-up strategies was modelled with different imaging methods 3 months after therapy: a PET-CT scan; a chest CT scan; and conventional follow-up with a chest X-ray. A probabilistic sensitivity analysis was performed to account for uncertainty. Because the results of the prospective study indicated that the advantage seems to be confined to asymptomatic patients, we additionally examined a strategy where a PET-CT was applied only in the subgroup of asymptomatic patients. Cost-effectiveness of the different follow-up strategies was expressed in incremental cost-effectiveness ratios (ICERs), calculating the incremental costs per quality adjusted life year (QALY) gained.

Results

Both PET-CT and CT based follow-up were more costly but also more effective than conventional follow-up. CT-based follow-up was only slightly more effective than conventional follow-up, resulting in an incremental cost-effectiveness ratio (ICER) of € 264.033 per QALY gained. For PET-CT based follow-up, the ICER was € 69.086 per QALY gained compared to conventional follow-up. The strategy in which a PET-CT was only performed in the asymptomatic subgroup resulted in an ICER of € 42.265 per QALY gained as opposed to conventional follow-up. With this strategy, given a ceiling ratio of € 80.000, PET-CT based follow-up had the highest probability of being cost-effective (73%).

Conclusions

This economic evaluation shows that a PET-CT scan 3 months after (chemo)-radiotherapy with curative intent is a potentially cost-effective follow-up method, and is more cost-effective than CT alone. Applying a PET-CT scan only in asymptomatic patients is probably as effective and more cost-effective. It is worthwhile to perform additional research to reduce uncertainty regarding the decision concerning imaging in the follow-up of NSCLC.

6.1 Introduction

The most effective follow-up strategy for non-small cell lung cancer (NSCLC) patients treated with curative intent with radiotherapy (RT) with or without chemotherapy is still not established. This uncertainty is reflected in the large heterogeneity in recommendations from the different cancer societies, diverging from no imaging at all to repeated imaging with chest CT scans¹. The added value of chest X-rays and/or chest CT has not been confirmed in any prospective study. A major reason for this lack of efficacy is the poor discriminating capacity of both imaging modalities. Here, ¹⁸FDG-PET-CT could have additional benefit, which has shown to be more accurate than CT in the evaluation of response to treatment as well as in outcome prediction²⁻⁴. We recently reported the results of a prospective study in 100 patients treated with chemo-radiotherapy or RT alone with curative intent, which showed that indeed, an FDG-PET-CT 3 months after therapy can detect progression amenable for treatment with curative intent, and hereby, possibly lead to an increase in survival⁵. Progressive disease (PD) amenable for curative treatment, however, was only found in 2% (95% confidence interval (CI): 1-7%) of patients. The study showed that the advantage seemed to be confined to the patient group that did not have symptoms at the time that the PET-CT scan was performed. In this patient group, 5% (95% CI: 2-15%) had progression, potentially amenable for curative therapy, which were all detected with FDG-PET, not with CT alone. In contrast, none of the symptomatic patients were diagnosed with progression with curative treatment options.

While a PET-CT scan 3 months post-treatment thus seems to be potentially beneficial, at least in a subset of patients, it is also more costly. This raises the question regarding the cost-effectiveness of a PET-CT-based follow-up method compared to usual follow-up with either repeated chest X-rays or CT scans, or imaging on the basis of symptoms. In order to make an evidence-based decision regarding which follow-up strategy to prefer, the costs of each strategy are essential to take into account. Information regarding cost-effectiveness can be obtained through an economic evaluation, in which a comparative analysis is performed of alternative courses of action in terms of both their costs and consequences⁶, on the basis of the currently available evidence.

To be able to add this information to the decision making process, we performed the current economic evaluation to evaluate the cost-effectiveness of PET-CT based follow-up as opposed to conventional follow-up in NSCLC patients treated with curative (chemo)RT.

6.2 Methods and Materials

Three follow-up strategies were compared with different imaging methods 3 months after therapy: the “usual” or conventional follow-up (anamnesis, physical examination and a chest X-ray), the PET-CT based follow-up (anamnesis, physical examination and a PET-CT scan) and the CT based follow-up (anamnesis, physical examination and a chest CT scan). After the 3 months post-treatment time-point, the follow-up was the same for the different strategies. Details regarding these follow-up policies are provided in Table 6.1. Because the results of the prospective study implied that the advantage of the PET-CT seems to be confined to the patient group without symptoms at the time of the PET-CT scan (55% of patients) ⁵, we additionally examined a strategy where a PET-CT was applied only in the asymptomatic subgroup. Within this strategy, symptomatic patients did not receive a standard PET-CT scan, but underwent imaging on the basis of the location of symptoms (conform Table 6.1).

Table 6.1 Alternative follow-up strategies				
Follow-up strategy	Imaging 3 months after RT	Imaging at follow-up visits after 3 months		
		No recurrence	PD, treated	PD, not treated
Usual	CXR + on basis of symptoms*	CXR	Chest CT	none
CT based	Chest CT + on basis of symptoms*	CXR	Chest CT	none
PET-CT based	PET-CT	CXR	Chest CT	none
*Imaging on basis of symptoms				
Symptoms	Diagnostics			
Pain				
Localized	Conventional radiography of involved region			
Diffuse	Bone scintigraphy			
Dyspnea	CXR			
Cough	CXR			
Dysphagia	Chest CT			
Malaise	CXR + screening blood sample			
Neurological	CT brain			
Palpable mass	CT of involved region			
Fatigue	Screening blood sample			
CXR: Chest radiography; PD: progressive disease				

Model structure

A Markov transition model was constructed with mutually exclusive health states to compare long-term costs and effects of the different follow-up strategies (Figure 6.1) ⁷. The model simulated the course of events in a hypothetical cohort of NSCLC

patients treated with curative RT with or without chemotherapy. Health states in the model were based on the absence or presence of progression and on the treatment of progression. Patients without progression were in the health state “no evidence of disease”. Patients with progression were subdivided according to their treatment: progression without treatment, progression with palliative treatment or progression with curative treatment. Patients in the CT based or usual follow up strategy, who had progression 3 months after treatment that was only detected with PET-CT and not with CT alone, were assigned the health state “progression not detected”. The final health state was “death”.

Figure 6.1 Markov Model

A hypothetical cohort of patients enters the model after the follow-up visit 3 months after radical (chemo-)RT. Patients are divided over the different health states according to the results of the prospective study

The start of the model was set after the first follow-up visit 3 months after radical therapy. At this time point, patients were divided between the different health states on the basis of the results of our prospective study⁵. In the model, patients moved between health states according to a set of transition probabilities. The cycle length of the model was 6 months, with a time horizon of 5 years.

Data sources

Input parameters were derived from the prospective study performed at our institute, published literature, the Dutch Health Insurance Board, and, if no other source was available, expert opinion. Details of the prospective study are published else-

where ⁵. In short, 100 patients with NSCLC, treated with curative intent with (chemo)radiation, were prospectively evaluated. All patients underwent a planned FDG-PET-CT scan 3 months after the start of radiotherapy, regardless of the presence of symptoms. Patients were judged symptomatic when any symptom was either new or had increased over time from the end of RT. Twenty-four percent (95% CI: 17-33%) of patients had progression 3 months post-treatment. No curative treatment could be offered to any of the patients who were symptomatic at the time of progression. In 2 of the 55 asymptomatic patients (4%, 95% CI: 1-12%), tumour progression, amenable for curative therapy, was found, which was detected with PET, not with CT only. The first patient was treated with re-irradiation for a locoregional recurrence, the 2nd patient was treated with adrenal resection for bilateral adrenal metastases.

Probabilities

All probabilities are listed in Table 6.2. As the cycle length was 6 months, probabilities of moving from one health state to another were calculated as 6 monthly transition probabilities. The median age of patients assumed to enter the model was 62 years, based on the patient characteristics of the prospective study ⁵. The extra mortality risk for surviving lung cancer patients as opposed to the general population was 1.4 ^{8, 9}. Age-specific mortality rates were used for 5 year age groups (Central Bureau for Statistics, 2007). The probability of progression after 3 months was calculated on basis of a prospective study of Mac Manus and colleagues (1-, 2-, 3- and 4 year progression free survival rates of 62%, 44%, 26% and 20% respectively) ³. Patients with progression that was not treated were assumed to have a 1-year overall survival (OS) for an OS of 19% ⁸; patients who were palliatively treated for progression were assumed to have a 1 year OS of 30% ⁹. The 1 year OS for patients who were treated with curative intent was assumed to be 45 %, based on published results with re-irradiation and adrenal resection ^{10, 11}. Percentages of patients receiving 2nd and 3rd line chemotherapy were based on a retrospective chart review of 417 patients with advanced NSCLC ¹².

Costs

An overview of the costs associated with the follow-up procedures, treatment, and terminal care is outlined in Table 6.2. All costs are reported in Euros and converted to the year 2008. Future costs and effects were discounted to their present value by a rate of 4% and 1.5%, respectively ¹³. Costs of diagnostic procedures and treatment were derived from the Dutch Health Insurance Board, adjusted to the 2007 price level (Central Bureau for Statistics 2007). The costs for first line chemotherapy were based on 4 cycles of docetaxel 75 mg/m². Costs of second line chemotherapy were

based on treatment with erlotinib during 125 days. Costs associated with side effects were based on calculations from the National Institute for Clinical Excellence¹⁴. The costs associated with dying were based on a report of Kommer and Polder¹⁵, in which costs associated with cancer death are described separately from costs associated with dying from other causes.

Effects

Global health-related quality of life (QOL) data were expressed in utility scores, varying from zero (death) to one (perfect health). The use of utility scores allows the calculation of Quality Adjusted Life Years (QALYs) and cost per QALY ratios. Utility scores were derived from a cross-sectional study performed by Trippoli and colleagues¹⁶. Based on this study, patients with progression had a utility score of 0.53, while patients without progression had a utility score of 0.68. Patients with progression that was curatively treated were assumed to have the same utility score as patients without progression, based on expert opinion (DDR). Furthermore, patients that were treated with palliative intent for PD were assumed to have the same utility as patients who received no treatment, on the basis of literature showing no significant difference in QOL with the administration of docetaxel 75 mg/m² as second line chemotherapy¹⁷. All utility scores are listed in Table 6.2.

Table 6.2 Inputs

	Estimated value	SE	Distribution	Source
Transition probabilities				
First 3 months				
<i>Strategy independent probabilities</i>				
PD	0.24	0.04	beta	[1]
Symptoms with PD	0.68	0.09	beta	[1]
Symptoms without PD	0.38	0.06	beta	[1]
<i>Strategy dependent probabilities</i>				
<i>PET-CT</i>				
Detection of symptomatic PD	1	fixed		EO
Detection of asymptomatic PD	1	fixed		EO
Treatment of asymptomatic PD	0.63	0.16	beta	[1]
Treatment of symptomatic PD	0.81	0.095	beta	[1]
Radical treatment of asymptomatic PD	0.4	0.2	beta	[1]
Radical treatment of symptomatic PD	0	fixed		[1]
<i>CT</i>				
Detection of symptomatic PD	1	fixed		
Detection of asymptomatic PD	0.5	0.17	beta	[1]
Treatment of asymptomatic PD	0.63	0.16	beta	[1]
Treatment of symptomatic PD	0.81	0.095	beta	[1]
Radical treatment of asymptomatic PD	0	fixed		[1]
Radical treatment of symptomatic PD	0	fixed		[1]
<i>Usual</i>				
Detection of symptomatic PD	1	fixed		EO
Detection of asymptomatic PD	0	fixed		EO
Treatment of asymptomatic PD	0	fixed		[1]
Treatment of symptomatic PD	0.81	0.095	beta	[1]
Radical treatment of asymptomatic PD	0	fixed		[1]
Radical treatment of symptomatic PD	0	fixed		[1]
After 3 months				
<i>Progression</i>				
Detection of undetected PD	0.8	fixed		EO
PD, 1 st year	0.21	0.036	beta	[2]
PD, 2 nd year	0.16	0.036	beta	[2]
PD, 3 rd year	0.23	0.036	beta	[2]
PD, 4 th year	0.12	0.036	beta	[2]

Table 6.2 Inputs

	Estimated value	SE	Distribution	Source
<i>Treatment</i>				
Radical	0.01	0.02	dirichlet	EO
Palliative	0.56	0.02	dirichlet	[3]
No treatment	0.43	0.02	dirichlet	[3]
<i>Death</i>				
Death with PD, no treatment	0.56	0.025	beta	[4]
Death with PD, palliative treatment	0.46	0.025	beta	[5]
Death with PD, radical treatment				
1 st year	0.33	0.019	beta	[6, 7]
2 nd year	0.18	0.019	beta	
3 rd year	0.02	0.019	beta	
Death with undetected PD	0.54	0.025	beta	EO ¹
Utility scores				
No PD	0.68	0.1	beta	[8]
PD, not treated	0.53	0.1	beta	[8]
PD, palliatively treated	0.53	0.1	beta	EO
PD, radically treated	0.68	0.1	beta	EO
PD, undetected	0.53	0.1	beta	[8]
Costs				
Diagnostics				
<i>First 3 months</i>				
PET-CT whole body	1364	fixed		[9]
Chest-CT	206	fixed		[9]
CXR	39	fixed		[9]
Follow-up visit	59	fixed		[9]
<i>After 3 months²</i>				
<i>Follow-up, No PD³</i>				
1 st year	196	fixed		[9]
2 nd year	98			
3 rd year	49			
<i>Follow-up, PD</i>				
Treated ⁴	529	fixed		[9]
Untreated ⁵	118	fixed		[9]
Treatment				
Probability of 2 nd line chemotherapy	0.47			[3]
Probability of palliative RT	0.18	0.018	beta	[10]

Table 6.2 Inputs

	Estimated value	SE	Distribution	Source
Unit costs				
<i>Radical</i> ⁶	5746	fixed		[1, 9]
<i>Palliative chemotherapy</i>				
1 st line ⁷				
No of cycles	4			[5]
Costs/cycle	1302			[9]
Side effects	349			[11]
Total costs	5557	fixed		
2 nd line ⁸				
Mean treatment time (days)	125			[9]
Costs/treatment	9100			[9]
Side effects	120			[11]
Total costs	9220	fixed		
<i>Palliative RT</i>	1017	fixed		[9]
Dying				
Dying of cancer, terminal care ⁹	11602	800	gamma	[12]
Dying of other causes	15448	800	gamma	[12]

EO: expert opinion; CXR: Chest X-ray; RT: radiotherapy; DHIB: Dutch Health Insurance Board

¹ Calculated from the probability of dying with a recurrence without treatment and with palliative treatment

² Costs per 6 monthly cycle

³ Based on follow-up visit with CXR, 4 times in 1st year, twice in 2nd year and once a year thereafter

⁴ Based on follow-up visit with chest-CT, 4 times/year

⁵ Based on follow-up visit without imaging, 4 times/year

⁶ Based on type of radical treatment in prospective study, being adrenal resection and radical radiotherapy

⁷ Docetaxel, 3-weekly cycles

⁸ Erlotinib

⁹ The costs of dying from cancer described in Kommer et al. were discounted by the costs of palliative treatment calculated in the current study

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Cost-effectiveness analysis

The analysis was performed from a health care perspective. The cost-effectiveness of the different follow-up strategies was compared using incremental cost-effectiveness ratios (ICERs), calculating the incremental costs per QALY gained. Whether a follow-up strategy is deemed cost-effective depends on how much the society is willing to pay for a gain in effect, which is referred to as the ceiling ratio. The Dutch Health Council advises an informal ceiling ratio of € 80.000¹⁸.

The input parameters of the model are inevitably associated with uncertainty. Probabilistic modelling is used to reflect this uncertainty in the parameters and to describe the effects on uncertainty over the outputs of interest¹⁹. Distributions to the model parameters, based on their mean value and standard error, were assigned to reflect the uncertainty in the estimation of that parameter (Table 6.2)²⁰. A probabilistic sensitivity analysis was performed using Monte Carlo simulation with 5,000 random iterations from the assigned distributions. To illustrate the results of the simulation, cost-effectiveness acceptability curves (CEACs) were calculated to characterize the likelihood that a certain follow-up strategy would be deemed cost-effective at different ceiling ratios^{19, 21}, representing the uncertainty surrounding the cost-effectiveness for this range of thresholds.

Expected Value of Perfect Information

As uncertainty exists, there is always a chance that the “wrong” decision will be made^{19, 22}. In this case, society would suffer a loss as a consequence. The decision to reduce the chance of a wrong decision by performing additional research involves balancing between the costs of acquiring more information with the value associated with it. The EVPI (expected value of perfect information) is the expected value of obtaining perfect knowledge of the “true” values of all parameters. We calculated the total EVPI by subtracting the net monetary benefit of the follow-up

strategy we would choose under conditions of uncertainty, from the net monetary benefit of the optimal decision we would make if we knew the “true” parameter values. The population EVPI was then calculated by multiplying the EVPI per patient by the number of patients that could potentially benefit from additional research. In the present study, this is the total number of patients with inoperable NSCLC treated with curative intent with (chemo)RT. We estimated that of the 1.35 million lung cancer patients per year, of whom 80% have NSCLC, 30% are amenable for curative (chemo)RT, being a total of 1,5 million patients worldwide in the next 5 years.

6.3 Results

Cost effectiveness of different follow-up strategies

Results of the analysis regarding the cost-effectiveness of the different follow-up strategies are presented in Table 6.3A. With regard to PET-CT based follow-up, the additional costs per extra curatively treated patient were € 64.096 compared to conventional follow-up. The ICER (incremental cost-effectiveness ratio) for PET-CT based follow-up was € 69.086 per QALY gained compared to conventional follow-up. Although CT-based follow-up was less costly, it was also less effective than PET-CT based follow-up, resulting in an ICER of € 264.033 per QALY gained.

Figure 6.2 shows cost-effectiveness acceptability curves for the 3 follow-up strategies. The figure shows that there is considerable uncertainty regarding which follow-up strategy is deemed cost-effective around the informal threshold of the Dutch Health Council. Given this ceiling ratio of € 80.000¹⁸, PET-CT based follow-up and conventional follow-up had a similar probability of being cost-effective (48% and 47%, respectively), while the probability of CT-based follow-up being cost-effective was only 5% (Figure 6.2).

Cost-effectiveness of a follow-up strategy with a PET-CT in the asymptomatic subgroup

The same analysis was performed, but a PET-CT scan was now only performed in patients who were asymptomatic 3 months after treatment (55% of patients) (Table 6.3B). Symptomatic patients received imaging on the basis of the location of symptoms. The usual follow-up strategy and CT-based follow-up strategy remained the same. Performing PET-CT based follow-up only in the asymptomatic subgroup had no influence on the effects, but reduced the costs per patient from €15.265 to €14.767. Hence, this strategy resulted in a lower ICER of € 42.265 per QALY gained as opposed to conventional follow-up. With this strategy, PET-CT based follow-up had the highest probability of being cost-effective (73%) compared to conventional follow-up (27%) at a ceiling ratio of € 80.000 (Figure 6.3).

Table 6.3 Cost-effectiveness of different follow-up strategies

Follow-up strategy	Expected costs/patient in € (95%CI [*])	Expected survival in months (95%CI)	Expected QALYs (95%CI)	ICER ^{**}
<i>A) Whole group</i>				
Conventional	13.983 (12.783-15.156)	24 (22-27)	1.28 (0.98-1.58)	
CT-based follow-up	14.269 (13.076-15.441)	24 (22-27)	1.28 (0.99-1.59)	264.033
PET-CT-based follow-up	15.266 (14.072-16.440)	25 (22-28)	1.30 (1.00-1.61)	69.086
<i>B) Asymptomatic patients only</i>				
Conventional	13.983 (12.805-15.162)	24 (22-27)	1.28 (0.98-1.58)	
CT-based follow-up	14.269 (13.101-15.444)	24 (22-27)	1.28 (0.99-1.59)	264.033
PET-CT-based follow-up	14.768 (13.584-15.952)	25 (22-28)	1.30 (1.00-1.61)	42.265

QALY: Quality Adjusted Life Year; ICER: Incremental Cost Effectiveness Ratio

*95% Confidence Intervals (CI) based on probabilistic analysis

**Expressed in €/QALY gained compared to conventional follow-up

Figure 6.2 Cost-effectiveness acceptability curve (CEAC) for the strategy in which a PET-CT is performed in all patients

The probability of cost-effectiveness of a certain follow-up strategy is plotted against the willingness to pay per quality adjusted life year (QALY) gained

Figure 6.3 Cost-effectiveness acceptability curve (CEAC) for the strategy in which a PET-CT is performed in asymptomatic patients only

The probability of cost-effectiveness of a certain follow-up strategy is plotted against the willingness to pay per quality adjusted life year (QALY) gained

Expected value of perfect information

In the current analysis, the uncertainty surrounding the decision whether or not to implement PET-CT based follow-up resulted in an EVPI of € 282 per person, given a ceiling ratio of € 80.000. Implementing PET-CT based follow-up affects all patients with locally advanced NSCLC, treated with curative (chemo)RT, involving a total of 1,5 million patients worldwide in the next 5 years. This makes the population EVPI $(1.5 \cdot 10^6) \cdot 290 = € 423$ million, meaning that perfect information on this topic is worth € 423 million.

The EVPI for the implementation of PET-CT based follow-up only in the subgroup of asymptomatic patients was € 83 per person, given a ceiling ratio of € 80.000. The population EVPI for this strategy was € 125 million. The population EVPI for different ceiling ratios, both for the total group and for the asymptomatic subgroup, is presented in Figure 6.4.

Figure 6.4 Expected Value of Perfect Information (EVPI)

The expected value of perfect information at different ceiling ratios.

Total group: EVPI for the strategy in which a PET-CT is performed in all patients.

No symptoms: EVPI for the strategy in which a PET-CT is performed in asymptomatic patients only

6.4 Discussion

Until now, no imaging procedure has become standard in the follow-up of NSCLC, mainly because of the fact that progression or recurrence is mostly detected at a stage that no curative treatment is possible, and hence, no survival benefit can be expected²³. Our recent prospective study on a single ¹⁸F-DG-PETscan 3 months post-therapy confirmed the hypothesis that this imaging modality, in contrast to CT alone, is able to detect progression amenable for curative treatment in a small percentage of patients. The question remained, however, whether this potential benefit for the individual patient outweighs the increased costs²⁴.

The current economic evaluation shows that performing a PET-CT scan 3 months after curative (chemo-)RT is a potentially cost-effective follow-up method, and is more cost-effective than CT alone. Performing a PET-CT scan only in the subgroup of asymptomatic patients is probably as effective and more cost-effective.

Inherently to the design of the study, there are some limitations that need to be addressed. Firstly, the current results are surrounded by considerable uncertainty, caused by uncertainty in the input parameters of the model. One important cause is the relatively small patient population (N=100) in the prospective study, from which the extent of the potential benefit of PET-CT was derived⁵. This economic evaluation aimed however, to base the decision regarding which follow-up strategy is to be preferred on the currently available evidence. Decisions will have to be made anyway, so it is better to support the decision with the available evidence including its uncertainties than doing something without any evidence at all²⁵. Using decision-analytic modelling we were able to incorporate this uncertainty in the model by assigning distributions to the model parameters. The incorporation of uncertainty also makes results easier to interpret by decision makers, as one can calculate which strategy has the highest probability of being cost-effective at different ceiling ratios (Figure 6.2 and Figure 6.3). The EVPI analysis shows us to what extent reduction of uncertainty by performing additional research is worthwhile. The value of totally eliminating uncertainty of the input parameters of the model was € 435 million, for a ceiling ratio of € 80.000, implying that additional research on this subject is of great value and outweighs the associated costs.

Secondly, the threshold (also referred to as the ceiling ratio) below which a certain strategy is considered cost-effective is arbitrary and differs between countries. In the current analysis, a threshold of € 80.000 (informal ceiling ratio of the Dutch Health Council) was used. Thresholds reported in literature range from € 35.000 (\$ 50.000) to € 210.000 (\$ 300.000)^{24, 26, 27}. With a higher ceiling ratio, the probability that the PET-CT based follow-up strategy is cost-effective becomes higher, while the usual follow-up strategy has the highest probability of being cost-effective at lower ceiling ratios. Hence, whether a strategy is deemed cost-effective depends on how much the society is willing and able to pay for a gain in effect.

Thirdly, the use of a model to estimate costs and effects is always associated with a simplification of reality²⁵. In the current analysis, we have chosen to compare the PET-CT based follow-up method with two follow-up strategies most commonly used according to the guidelines of the different institutions¹. Furthermore, in the model, the difference between the 3 strategies was based upon different imaging only at one time point during follow-up, i.e. 3 months after curative treatment. This time point was chosen based on the prospective study which showed a possible advantage of PET over CT in detecting potentially curable progression at 3 months after treatment and because a PET scan performed at this interval has shown to be prognostic of outcome^{2, 4}. In none of the patients in the prospective study, additional investigations were requested to confirm the findings of the PET-CT scan. Hence, in the current economic evaluation, no costs were calculated to take into account false positive findings in the PET-CT strategy. No costs were calculated for false positive findings in the usual and CT-based follow-up strategy either, minimiz-

ing the chance of overestimating the cost-effectiveness of PET-CT. Another drawback of the limitation to one time-point is that the potential gain of repeated imaging with e.g. chest CT scans cannot be derived from this study. The available literature however, does not confirm a benefit of repeated CT-scanning in the follow-up²⁸. A definitive answer regarding the value of CT based follow-up can be expected from a multicentre phase III trial which is currently ongoing in France, in which conventional follow-up with chest X-rays is compared with an intensive follow-up strategy with repeated chest CT scans in NSCLC patients after curative resection²⁹.

The performed economic evaluation is aimed to guide decision making regarding which strategy to choose, and is not intended to reveal scientific truth²⁰. On the basis of the currently available evidence, however, the following conclusions can be drawn: Firstly, performing a chest CT scan in the follow-up is less cost-effective than performing a PET-CT scan 3 months after treatment. Hence, if any imaging is wished to be performed for treatment evaluation, one would prefer to perform a PET-CT scan 3 months after therapy above CT alone. Secondly, irrespective of the question whether certain imaging is cost-effective, the final decision to perform the test depends on what the society can afford²⁴. Finally, the results show that it is worthwhile to perform additional research to reduce the uncertainty surrounding the decision whether to implement PET-CT in the follow-up, including questions regarding the time-point and frequency and what the additional financial burden is.

6.5 References

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Part

III

**Development of novel PET tracers for the
non invasive imaging of specific
tumour characteristics**

CHAPTER 7

PET imaging of hypoxia using [^{18}F]HX4: A phase I trial

**Judith van Loon
Marco Janssen
Michel Öllers
Hugo Aerts
Ludwig Dubois
Monique Hochstenbag
Anne-Marie Dingemans
Roy Lalisang
Boudewijn Brans
Bert Windhorst
Guus van Dongen
Hartmuth Kolb
James Zhang
Dirk De Ruyscher
Philippe Lambin**

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Abstract

Background and purpose

Non-invasive PET imaging of tumour hypoxia could help in the selection of patients who could benefit from chemotherapy or radiation with specific anti-hypoxic treatments such as bioreductive drugs or hypoxic radio-sensitizers. In this phase I trial, we aimed to determine the toxicity of [^{18}F]HX4, a member of the 2-nitroimidazole family, at different dose levels. The secondary aim was to analyze image quality related to the HX4 dose and the timing of imaging.

Methods and Materials

Patients with a histologically proven solid cancer without curative treatment options were eligible for this study. A study design with two dose-steps was used in which a single dose of a maximum of 222 MBq (step 1) or 444 MBq (step 2) [^{18}F]HX4 was injected. Toxicity was scored on day 0 and on days 3 and 7 after injection, according to the CTCAE 3.0 scoring system. PET-CT images of the largest tumour site were acquired 30, 60 and 120 minutes after injection.

Results

Six patients with stage IV carcinomas were included: four with non-small cell lung carcinoma, one with thymus carcinoma and one with colon carcinoma. No toxicity was observed in any of the patients at either dose level. The median tumour to muscle ratio 120 minutes after injection was 1.40 (range: 0.63-1.98).

Conclusions

The findings of this study show that [^{18}F]HX4 PET imaging for the detection of hypoxia is not associated with any toxicity. Imaging was successful; however, future trials are needed to determine the optimal image parameters.

7.1 Introduction

Tumour hypoxia is an important marker of cancer prognosis, being associated with aggressive growth, metastasis, and resistance to anticancer therapy ¹. Non-invasive PET imaging with hypoxia-specific 2-nitro-imidazoles has the ability to quantify tumour hypoxia and could help in the selection of those patients who could benefit from chemotherapy or radiation with specific anti-hypoxic treatments such as bio-reductive drugs or hypoxic radio-sensitizers ². Furthermore, in contrast to invasive electrode measurements, PET imaging provides the opportunity to display the spatial distribution of hypoxia, which is essential for its integration with radiation dose distribution. [^{18}F]Fluoromisonidazole ([^{18}F]FMISO) is the first radiolabelled 2-nitroimidazole derivative proposed for hypoxia imaging with PET ^{3,4}. The relatively low uptake of [^{18}F]FMISO observed in hypoxic lesions coupled with its slow clearance from normoxic tissue however, limits the clinical potential of this agent ⁵. A number of other ^{18}F -labelled nitroimidazole derivatives have been identified, investigated and reported to overcome these problems ^{6,7}.

The 2-nitroimidazole nucleoside analogue, 3-[^{18}F]fluoro-2-(4-((2-nitro-1H-imidazol-1-yl)methyl)-1H-1,2,3-triazol-1-yl)propan-1-ol ([^{18}F]HX4), was developed as a potential marker and radio-sensitizer for hypoxic tumour cells. Because of better water solubility and faster clearance, we expect that [^{18}F]HX4 has better pharmacokinetic properties than currently used nitroimidazole hypoxia markers such as [^{18}F]FMISO. In this phase I trial, we aimed to determine the toxicity of [^{18}F]HX4 at different dose levels, with the secondary aim of analyzing image quality in relation to the HX4 dose and timing of imaging.

7.2 Methods and Materials

Patient inclusion

Patients with a histologically or cytologically confirmed stage IV solid cancer at any site, primary or secondary, without curative treatment options, were eligible. Patients were required to have a WHO performance status of 0 to 1, normal white blood cell count and differential, normal platelet count and no anaemia requiring blood transfusion or erythropoietin. Additional eligibility criteria were adequate hepatic function; adequate renal function (calculated creatinine clearance at least 60 ml/min); no administration of ^{18}F in the previous 24 hours; and a minimum age of 18 years. Patients with a recent (< 3 months) myocardial infarction, uncontrolled infectious disease, pregnancy, or concurrent treatment with anti-cancer agents or radiotherapy were excluded.

Approval for the study protocol (NCT00690053) was obtained from the medical ethics committee and the radiation safety committee. All patients gave written informed consent.

Study design

A study design with two dose steps was used (Figure 7.1). In step 1, a single dose of up to 222 MBq [^{18}F]HX4 was injected, and in step 2 a single dose of up to 444 MBq was injected. Six patients were included, three in each dose step. If in any patient a toxicity of grade 2 or more was observed, three more patients were included in this dose step. If another toxicity of grade 2 or more occurred in one or more of these three patients, the study would be stopped. If no more than one of six patients experienced grade 2 toxicity, the step was considered safe.

Figure 7.1 Flowchart of the study

* If toxicity of grade 2 or more was observed in none of these patients, the step was considered safe. If toxicity of grade 2 or more was observed in one or more patients, the study was stopped

Synthesis of [^{18}F]HX4

[^{18}F]HX4 was synthesized from the HX4 precursor in a two-step process (Figure 7.2). The product obtained was purified and formulated into a sterile and pyrogen-free solution, suitable for use in humans. The radiochemical purity was required to be

higher than 95% in every batch. The specific radioactivity of [^{18}F]HX4 exceeded 14.8 MBq/ μmol . The radiopharmaceutical was produced at the government-licensed GMP-compliant (EMA Eudralex 4) radiopharmaceutical production facility of the Department of Nuclear Medicine and PET Research of the VU University Medical Centre (license number 108897F).

Figure 7.2. Synthesis of [^{18}F]HX4

The precursor was supplied by Siemens Molecular Imaging (Erlangen, Germany). The first step incorporates a nucleophilic substitution of radioactive fluorine (in the form of ^{18}F) onto the precursor material, yielding the fluorinated intermediate which is then hydrolyzed to obtain the active drug product

PET-CT imaging

PET-CT images of the largest tumour site were acquired 30, 60 and 120 minutes after injection. Imaging at later time-points after injection was deliberately avoided to minimize the burden of the study in these patients with advanced stage disease. Images were acquired with the patient in the supine position. CT and PET images were automatically registered based on mutual information and were subsequently fused using dedicated software (TrueD, version VC50; Siemens Medical, Erlangen, Germany).

The tumour was delineated on the CT scan by the same observer (JvL). The location of the [^{18}F]HX4 uptake and the SUV_{max} (maximal standardized uptake value) were determined within the delineated tumour using a gradient-based method which was implemented in the software. Tumour to muscle ratios (TMR) for [^{18}F]HX4 uptake were calculated at all time-points by dividing the tumour SUV_{max} by the skeletal muscle SUV_{max} . The skeletal muscle SUV_{max} was determined by calculating the average SUV_{max} in two circular regions of interest drawn in the paraspinal muscles.

In patients in whom an [^{18}F]FDG-PET scan was performed for diagnostic purposes during the week before or after the [^{18}F]HX4 scan, uptake of [^{18}F]FDG and [^{18}F]HX4 was compared. The location of the [^{18}F]FDG uptake was determined using automated SUV-thresholding with the threshold depending on the tumour-to-background signal ratio (SBR-method)⁸.

Toxicity scoring

Toxicity was scored on day 0 and days 3 and 7 after injection, according to the CTCAE (Common Terminology Criteria for Adverse Events) version 3.0 scoring system. Blood was sampled before injection and at each control point, and tests included haematology and kidney and liver function. Due to the relatively short physical half-life of ¹⁸F (110 min) and biological half-life of HX4 (less than 3 hours), after 1 day the radio-activity of both the drug and its metabolites have disappeared and no additional toxicity from the radiation is expected.

The timeline for each patient entering the study is illustrated in Figure 7.3.

Figure 7.3 Time line of the study
CTCAE 3.0: Common Terminology Criteria for Adverse Events, version 3.0

7.3 Results

Patient characteristics

Six patients, with a median age of 63 years (range: 54-68), were included. The patient characteristics are shown in Table 7.1.

	Age	Sex	Length	Weight	WHO*	Site	Primary tumour Histology	Prior therapy
1	67	f	1.58	58	1	Lung	Adenocarcinoma	Chemotherapy, radiotherapy brain
2	54	f	1.76	64	0	Lung	Adenocarcinoma	Chemotherapy
3	58	m	1.79	82	0	Thymus	Carcinoid	Surgery, radiotherapy
4	62	m	1.90	80	1	Lung	Adenocarcinoma	Surgery, chemotherapy, radiotherapy
5	63	f	1.70	70	1	Lung	Squamous cell carcinoma	Surgery, chemotherapy
6	68	m	1.68	80	0	Colon	Adenocarcinoma	Surgery, chemotherapy

*World Health Organisation performance status

All patients had a stage IV carcinoma: four had a non-small cell lung carcinoma, one had a thymus carcinoma and one patient a colon carcinoma. Three patients had stage IV disease at primary diagnosis, while the other had developed metastases after therapy with curative intent. All patients had previously undergone anti-cancer therapy. Two patients were unable to undergo the last scan at 120 minutes after injection due to pain (not drug-related).

Toxicity

Results of the toxicity scoring are shown in Table 7.2. No toxicity according to the CTCAE 3.0 criteria was observed at any time-point in the first three patients included in dose step 1. Hence, it was considered safe to continue with dose step 2. Again, no toxicity was observed in any of the three patients. One patient reported mild transient headache (grade 1) the day after the [^{18}F]HX4 injection, which was considered unlikely to be related to the injection.

Table 7.2 Toxicity scoring							
Pt	Injected activity (MBq)	Vital signs*	Toxicity scoring**				Medication*
			Haematology	Liver function	Renal function	Symptoms	
1	222	0	0	0	0	0	0
2	222	0	0	0	0	0	0
3	222	0	0	0	0	0	0
4	444	0	0	0	0	1***	0
5	444	0	0	0	0	0	0
6	444	0	0	0	0	0	0

Toxicity was scored before study entry (baseline) and on days 0, 3, and 7 of the study. The blood test results were compared with those at baseline and evaluated by the physician

*Every change in vital signs or medication compared to the baseline values was scored, with “0” indicating no change

**Grade according to the CTCAE version 3.0

***Mild headache, not related to the ¹⁸F[HX4] administration

Image analysis

Images of two patients at 120 minutes after injection are presented in Figure 7.4. They show a heterogeneous uptake of [¹⁸F]HX4 throughout the tumour. The median TMR at 30, 60 and 120 minutes after injection was 1.17 (range: 0.20-1.83), 1.25 (range: 0.25-1.67) and 1.40 (range: 0.63-1.98). In two of four patients in whom images were available at 120 minutes after injection a considerable increase was seen in the TMR compared to 60 minutes after injection.

In three patients an [¹⁸F]FDG-PET scan performed during the week before or after the [¹⁸F]HX4-PET scan was available. In these three patients, there was a good correlation between the uptake of FDG and [¹⁸F]HX4, as shown in Figure 7.5.

Figure 7.4 $[^{18}\text{F}]\text{HX4}$ images of 2 patients

a), b) Patient 4, TMR=1.35; a) coronal, b) transversal images
c), d) Patient 5, TMR=1.98; c) coronal, d) transversal images

Figure 7.5 Correlation between the uptake of [^{18}F]HX4 and ^{18}F FDG (patient 5)

FDG-uptake in the tumour was delineated using automated SUV-thresholding depending on the tumour-to-background signal ratio. The HX4 positive regions in the tumour were delineated using gradient-based image analysis

- a) ^{18}F FDG -PET-CT images, axial view; b) ^{18}F FDG -PET-CT images, coronal view
c) [^{18}F]HX4-PET-CT images, axial view; d) [^{18}F]HX4-PET-CT images, coronal view

7.4 Discussion

Preclinical experience gained with [^{18}F]HX4 and unlabelled HX4 did not indicate any adverse events at the dose levels used in these exploratory trials. The current phase I trial confirmed these preclinical data, with no toxicity according to the CTCAE 3.0 criteria observed in any of the patients. The time curves of the TMR showed a large divergence between the patients. In two patients, a substantial increase in the TMR was seen in the second hour after injection, indicating that the optimal TMR for imaging may be at later time points. In the three patients in whom an ^{18}F FDG-PET scan was available, a good correlation was found between the hypoxic areas imaged with HX4 and the areas of high FDG uptake. This is consistent with the often observed relationship between tumour hypoxia and FDG uptake^{9,10}.

From the imaging perspective, there were some limitations inherent in the study design. Firstly, the imaging was limited to 120 minutes after injection. This time horizon was chosen to limit the burden on the patients, who were all suffering from

end-stage disease. Future studies, with the final aim of adapting treatment according to hypoxia, will be performed in patients with earlier stage disease, in whom imaging at later time points would be acceptable. Secondly, only static PET imaging was performed. Hence, no correction could be made for heterogeneity in tumour perfusion. With kinetic imaging, tumour perfusion can be measured, thereby offering the opportunity to differentiate between differences in delivery of [^{18}F]HX4 and differences in pO_2 within the same tumour⁴. Finally, in order to allow radiotherapy dose distribution within the tumour on the basis of hypoxia, the stability of hypoxic regions within the tumour before and at different time-points during chemo- and radiotherapy should be assessed.

7.5 Conclusion

The results presented show that [^{18}F]HX4 PET imaging is not associated with any toxicity. Future trials are needed to determine optimal imaging conditions, with the final aim of developing adaptive treatment strategies based on [^{18}F]HX4-imaged hypoxia.

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CHAPTER 8

PET imaging of Cetuximab-Zirconium-89 uptake: a phase I trial

**Judith van Loon
Hugo Aerts
Marco Janssen
Michel Öllers
Ludwig Dubois
Anne-Marie Dingemans
Arne van Belle
Monique Hochstenbag
Roy Lalisang
Erik Vegt
Boudewijn Brans
Pascal Kempers
Ronald Boellaard
Danielle Vugts
Guus van Dongen
Dirk De Ruyscher
Philippe Lambin**

Manuscript in preparation

Abstract

Background and Purpose

Non invasive PET imaging of cetuximab uptake could help to select patients with the highest chance of benefit from this treatment. Cetuximab labelled with Zirconium-89 is a promising new conjugate to determine tumour uptake of cetuximab, which has been tested in pre-clinical animal models with excellent results (Aerts et al, J Nucl Med 2009).

In this trial (NCT00691548), we aimed to determine the toxicity of ^{89}Zr -cetuximab in incurable cancer patients, with tumour visualization as a secondary aim.

Methods and Materials

The safety of two different dose schedules was tested. In step 1, the toxicity of two consecutive low radioactivity doses of ^{89}Zr -cetuximab (60 MBq) was investigated. In step 2, the toxicity of a single larger dose (120 MBq) was investigated. Labelled cetuximab administration was preceded by a standard loading dose of unlabelled cetuximab. Toxicity was scored twice weekly up to 14 days after injection, according to the CTCAE 3.0 scoring system and with blood tests for haematological and liver/kidney function. Total body PET-CT scans were acquired on day 4, 5 and 6 (step 1) and 5, 6, 7 (step 2) post injection. Images were analyzed using dedicated software.

Results

Seven patients with a histologically proven solid tumour without curative treatment options were included. One patient was excluded before administration of the studied drug because of hypertension during the administration of unlabelled cetuximab. Six patients had NSCLC, whereas 1 patient had a tonsillar carcinoma. Five of six patients who completed the study experienced skin toxicity. No additional toxicity was associated with the administration of ^{89}Zr -cetuximab. The maximal tumour to blood ratio (TBR) observed was 1.6. In general, the most optimal TBR was found at later imaging time points (day 6 and day 7).

Conclusions

No additional toxicity was observed for ^{89}Zr -cetuximab administration. ^{89}Zr -cetuximab is thus safe to be implemented in immuno-PET studies guiding cetuximab therapy.

8.1 Introduction

Monoclonal antibodies are increasingly used in oncology as a mean to specifically target receptors at the surface of tumour cells that are associated with tumour aggressiveness, such as proliferation, hypoxia and angiogenesis. Cetuximab is a monoclonal antibody that blocks the Epidermal Growth Factor Receptor (EGFR). The EGFR is a transmembrane glycoprotein which is commonly expressed in many normal human tissues. It is a member of the tyrosine kinase family of growth factor receptors and is overexpressed in many human malignancies^{1, 2}. EGFR is activated upon ligand binding to the extracellular domain, which results in the induction of a signal transduction pathway that cascades many cellular operations concerning cell growth and division. EGFR activation and overexpression appear to be important tumour cell mechanisms in the development of resistance to radiation and chemotherapy in epithelial cancers, with decreased rates of local tumour control and survival³⁻⁷.

Cetuximab specifically binds to the EGFR with high affinity, internalising the receptor and thus effectively blocking ligand-induced EGFR phosphorylation. It is a very promising drug to combine with radiotherapy alone or with concurrent chemoradiation, as it has shown to improve local tumour control without enhancing the toxicity of radiotherapy or chemotherapy^{8, 9}. It plays currently a role as part of the standard treatment for a variety of cancers, including colorectal cancer and squamous cell carcinoma of the head and neck. The selection of patients with the highest chance of benefit from cetuximab treatment is of obvious relevance, also in view of its high costs. As no direct relationship has been observed between EGFR expression determined with immunohistochemistry and response to cetuximab treatment, EGFR status of the primary tumour cannot be used as a selection criterion. As the expression of EGFR can be induced by radiation and chemotherapy, it is possible that an initially EGFR-negative tumour may become positive early during therapy, thereby still benefiting from cetuximab treatment¹⁰⁻¹². On the other hand, EGFR expressing tumours will not respond to cetuximab when cetuximab does not reach therapeutic concentrations in the tumour because of e.g. interstitial pressure and vascular perfusion changes in the micro-environment of the tumour or the surrounding tissues. In this regard, non-invasive visualization and quantification of tumour uptake of cetuximab with positron emission tomography (PET) before and during therapy could contribute significantly to patient selection and determination of the needed dosage¹³.

As the biologic half-life of cetuximab in the blood is 70-100 hours, a positron emitter with a long half-life is needed to visualize its uptake. Zirconium-89 (⁸⁹Zr), a positron emitter with a half life of approximately 78 hours, can successfully be coupled to

cetuximab and has shown excellent results in preclinical animal models¹⁴. In the preclinical study, tumour cell lines with varying EGFR expression levels were used for in vivo imaging experiments. PET with ⁸⁹Zr-labeled cetuximab was performed on tumour-bearing NMRI-nu mice at several time points after injection and uptake was quantified within regions of interest on selected tissues. Uptake of ⁸⁹Zr-labeled cetuximab was demonstrated in the EGFR-positive tumours. Furthermore, it was shown that indeed, levels of EGFR expression did not correlate with ⁸⁹Zr-cetuximab uptake, implying that pharmacokinetic and -dynamic factors influence the cetuximab distribution in the tumour¹⁴.

Here, we report the results of a phase I study to determine toxicity of Zirconium-89 labelled cetuximab in incurable cancer patients, with tumour visualisation as a secondary end point.

8.2 Methods and Materials

Patient selection

Patients with a histologically or cytologically confirmed solid cancer at any site without curative treatment options were eligible. Inclusion criteria were as follows: WHO performance status 0 to 2; adequate bone marrow, hepatic and renal function (calculated creatinine clearance at least 60 ml/min); life expectancy > 3 months and written informed consent to the study. Patients with a recent (< 3 months) myocardial infarction, uncontrolled infectious disease, pregnancy, previous administration of cetuximab or concurrent treatment with anti-cancer agents or radiotherapy were excluded. EGFR expression and mutation status as well as k-ras mutation were assessed for the primary tumour.

The study protocol (NCT00691548) was approved by the medical ethical committee and the radiation safety committee (MECazM 083039.7 and 2008-8, respectively).

Study design

A two dose-step study design was used, graphically represented in Figure 8.1. The study design anticipated on the future aim, which is to determine the tumour uptake of ⁸⁹Zr-cetuximab before and during therapy. Therefore, in step 1, the toxicity of two consecutive low doses of ⁸⁹Zr-cetuximab was investigated. A standard loading dose of 400 mg/m² of cetuximab was administered, followed by administration of the cetuximab labelled with ⁸⁹Zr (60 MBq) on day 0. The second injection on day 14 consisted of a dose of 250 mg/m² of cetuximab, followed by cetuximab labelled with 60 MBq ⁸⁹Zr.

As a larger radioactivity dose of ^{89}Zr is possibly needed to obtain the best image quality, the toxicity of a single larger dose of ^{89}Zr -cetuximab was investigated in step 2. A loading dose of 400 mg/m^2 of cetuximab was administered in 3 patients, followed by administration of the cetuximab labelled with $120 \text{ MBq } ^{89}\text{Zr}$.

Step 1

Step 2

* days of scanning in step 2 depend on imaging results in step 1

Figure 8.1 Timeline of the study

A two dose-step study design was used. In step 1, the toxicity of two low doses of ^{89}Zr -cetuximab was investigated. In step 2, the toxicity of a single larger dose of cetuximab was tested. PET-CT imaging was performed at three consecutive days after administration, starting at day 4 in dose step 1

* In step 2, PET-CT scans on day 3 and 7 after injection were optional and depended on the imaging results in step 1: If in step 1 two or more patients had a higher tumour to blood ratio (TBR) on day 4 then on day 5, an additional scan on day 3 would be performed. If in step 1 two or more patients had a higher TBR on day 6 then on day 5, an additional scan on day 7 would be performed

In both steps, the ^{89}Zr -labelled cetuximab was administered within one hour after the administration of the loading dose. Six patients were included, three in each dose step. If grade 2 or higher toxicity was observed related to the administration of the studied drug (^{89}Zr -labelled cetuximab) in any patient, 3 more patients had to be included in this dose step. When at maximum 1/6 patients experienced grade 2 toxicity, the step was considered safe.

Toxicity scoring

Toxicity was assessed during treatment, and twice weekly thereafter until 14 days after the last injection, according to the CTCAE 3.0 scoring system. At baseline and on days 7 and 14 after injection, blood testing was performed for haematology (haemoglobin, hematocrite, mean cell volume, reticulocytes, white blood cell count and differentiation, platelets), kidney function (creatinine) and liver function (aspar-

tate aminotransferase, alanine aminotransferase, alkalic phosphatase, γ -GT, bilirubin).

The most common side effect of cetuximab administration that was anticipated for was skin toxicity (acne-form rash). The classification of the degree of skin toxicity according to the CTCAE is provided in Table 8.1¹⁵.

Table 8.1 Grading of toxicity related to cetuximab administration	
Toxicity grade	Clinical presentation
1	Follicular localized pustules Asymptomatic
2	Follicular localized pustules < 50% of body surface Itchy
3	Follicular localized pustules > 50% of body surface Itchy
4	Exfoliative or ulcerative erythroderma

Synthesis of ⁸⁹Zr labelled cetuximab

⁸⁹Zr was produced by a (p,n) reaction on natural ⁸⁹Y as described by Verel et al.¹⁶. Subsequently, labelling of ⁸⁹Zr to the mAb cetuximab was performed as previously reported¹⁷. In short, desferrioxamine B was succinylated (N-sucDf), temporarily filled with iron (Fe³⁺), and coupled to cetuximab using a tetrafluorophenol-N-sucDf ester. The premodified mAb was purified on a PD10 column after removal of Fe³⁺ by transchelation to ethylenediaminetetraacetic acid (EDTA). Approximately 1 N-sucDf moiety was coupled per cetuximab molecule, assessed by using ⁵⁹Fe. Next, N-sucDf-cetuximab was labelled with ⁸⁹Zr in 0.5 M N-(2-hydroxyethyl)piperazine-N9-(2-ethanesulfonic acid) (HEPES) buffer at pH 7.0 and again purified on a PD10 column to remove unbound ⁸⁹Zr. ⁸⁹Zr-cetuximab preparations contained 10 mg ⁸⁹Zr-cetuximab in 5 mg/ml gentisic acid in 0.9% NaCl, containing 60 or 120 MBq ⁸⁹Zr. ⁸⁹Zr-cetuximab release criteria were: radiochemical purity > 90%; immunoreactivity > 70%; pH = 4.7 – 5.3; sterile and free of endotoxins (European Pharmacopeia).

PET-CT imaging

Whole body immuno-PET-CT imaging was performed at day 4, 5 and 6 after injection in dose step 1. Imaging time points in step 2 were adapted based on the tumour to blood ratios at subsequent days in step 1. A list mode acquisition of the largest tumour site was carried out in addition to the whole body PET-CT. Furthermore, an optional ¹⁸F-fluorodeoxyglucose (FDG)-PET scan was performed within the study period, at least 24 hours before or 10 days after the ⁸⁹Zr-cetuximab administration.

Images were acquired with the patient in supine position. CT and PET images were automatically registered based on mutual information and fused using dedicated software (TrueD, version VC50, Siemens Medical, Erlangen, Germany).

The tumour was delineated on the CT scan by the same observer (JvL). If available, FDG-PET information was used in addition to the CT. The maximum standardized uptake value (SUV_{max}) and the location of the ^{89}Zr -cetuximab uptake within the delineated tumour were determined using dedicated software (TrueD VC50, Siemens Medical, Erlangen, Germany). Maximal tumour to blood ratios (TBRs) for ^{89}Zr -cetuximab uptake were calculated at all time points by dividing the tumour SUV_{max} by the SUV_{max} in the aortic arch.

For patients in whom an ^{18}F -FDG-PET scan was performed within one week before or after the ^{89}Zr -cetuximab scan, the ^{18}F FDG and ^{89}Zr -cetuximab uptake was visually compared. The location of the ^{18}F FDG uptake was determined using automated SUV-thresholding with the threshold depending on the tumour-to-background signal ratio (SBR-method)^{18, 19}.

8.3 Results

Patient characteristics

Seven patients, with a median age of 63 years (range: 53-75), were included. The third patient was excluded from the study before injection of the ^{89}Zr -labelled cetuximab, because of malignant hypertension during the administration of the unlabelled cetuximab. The tension normalized within two hours of observation without further sequelae. Patient and tumour characteristics are shown in Table 8.2.

Six patients had a non-small cell lung carcinoma (NSCLC) and 1 had a tonsillar carcinoma. All patients had previously undergone anti-cancer therapy. In one patient, EGFR expression and mutation and k-ras mutation status of the primary tumour could not be assessed due to insufficient quantity of histological material. In the other patients, none of the primary tumours showed overexpression of EGFR or a mutation in exons 18-21 of the EGFR gene. In one patient, the primary tumour showed a mutation in the k-ras gene.

Each patient received ^{89}Zr -labelled cetuximab administration as planned. In two patients (patient 2 and 4) enrolled in the first dose step, however, the second series of PET-CT scans could not be completed due to pain and dyspnea attributable to disease progression.

Table 8.2 Patient characteristics

	Age	Sex	Length	Weight	WHO PS	Primary tumour				Prior therapy
						Site	Histology	Mutation [*]	Overexpression	
1	72	m	1.85	75	0	Lung	SCC	NA	NA	CTx
2	61	m	1.76	82	1	Lung	LCC	k-ras: + EGFR: -	No	CTx, RT
3**	55	f	1.56	61	0	Lung	LCC	-	-	CTx
4	75	m	1.79	74	2	Lung	AC	k-ras: - EGFR: -	No	CTx
5	53	m	1.80	91	1	Lung	SCC	k-ras: - EGFR: -	No	CTx
6	63	m	1.78	86	0	Lung	AC	k-ras: - EGFR: -	No	CTx
7	63	m	1.86	95	1	Tonsil	SCC	k-ras: - EGFR: -	No	RT, CTx

*k-ras: codons 12 and 13; EGFR: exons 18-21

**Excluded patient: 55 year old female, NSCLC

WHO PS: World Health Organisation performance status; m: male; f: female; SCC: squamous cell carcinoma; LCC: large cell carcinoma; AC: adenocarcinoma; NA: not assessable due to insufficient quantity of histological material; CTx: Chemotherapy; RT: Radiotherapy

Toxicity

An overview of the toxicity per patient is presented in Table 8.3.

Table 8.3. Toxicity scoring

Pt	Injected activity (MBq)	Vital signs [*]	Toxicity scoring [*]					Medication [*]
			Haematology	Liver function	Renal function	Skin	Symptoms	
1	2x60	0	0	0	0	2	0	1**
2	2x60	0	0	0	0	1	0	0
3	none	NA	NA	NA	NA	NA	NA	NA
4	2x60	0	0	0	0	0	0	0
5	120	0	0	0	0	2	0	1**
6	120	0	0	0	0	2	0	1**
7	120	0	0	0	0	1	0	0

Toxicity was scored before study entry (baseline) and at days 7 and 14 after cetuximab administration
NA: not assessed because of premature exclusion from the study

*Every change in vital signs or medication compared to the baseline values was scored, with "0" indicating no change.

**Doxycycline 100 mg, Hydroxyzine 25 mg, Metronidazolcream 10 mg/g

Image analysis

Images of ^{89}Zr -cetuximab uptake in the tumour of 2 patients are presented in Figure 8.2. For these patients, an ^{18}F -FDG-PET scan was performed 1 week after the ^{89}Zr -cetuximab scan. A heterogeneous uptake of ^{89}Zr -cetuximab was observed throughout the tumour and the rest of the body. In patient 1, a remarkable mismatch was observed between FDG- and ^{89}Zr -cetuximab uptake (Figure 8.3).

For the patients in dose step 1, the average maximum TBR at day 4, 5 and 6 after injection was 0.89 (range: 0.83-0.94), 0.98 (range: 0.88-1.05) and 1.09 (range: 0.76-1.60), respectively. As the most optimal TBR was found at day 6 after injection, imaging in dose step 2 was performed at days 5, 6 and 7. For patients in dose step 2, the average maximum TBR at day 5, 6 and 7 after injection was 0.88 (range: 0.57-1.05), 0.86 (range: 0.54-1.02) and 0.91 (range: 0.42-1.20). Three patients had a maximum TBR of ≥ 1 at any of the imaging time points: patient 4 had a maximum TBR of 1.60, patient 6 had a maximum TBR of 1.20 and the maximum TBR of patient 7 was 1.11.

Figure 8.2. ^{89}Zr -cetuximab and ^{18}F -FDG images of 2 patients

^{89}Zr -cetuximab images at day 7 after injection are shown. ^{18}F -FDG images were acquired at day 14 after ^{89}Zr -cetuximab administration.

a), b) Patient 6, max TBR=1.20; a) FDG-PET-CT, b) ^{89}Zr -cetuximab-PET
c), d) Patient 7, max TBR=1.11; c) FDG-PET-CT, d) ^{89}Zr -cetuximab-PET

Figure 8.3. Correlation between ^{89}Zr -cetuximab and ^{18}F FDG uptake in patient 1

a) FDG-PET-CT (day 12 after ^{89}Zr -cetuximab administration)

b) ^{89}Zr -cetuximab-PET-CT (day 6 after injection)

8.4 Discussion

Although zirconium-89 labelled with other monoclonal antibodies has been evaluated in patients before without additional toxicity²⁰, the current phase I trial is the first study in humans evaluating ^{89}Zr labelled with cetuximab. No additional toxicity was associated with the ^{89}Zr administration. Acne-form eruption was observed in 83% of patients, a rate comparable to that found with the therapeutic administration of cetuximab^{8, 15, 21}. One patient developed malignant hypertension during the administration of unlabelled cetuximab. Although rare, this side-effect has been described previously²².

Many preclinical data show additive anti-tumour effects for cetuximab with radiotherapy and chemo-radiotherapy in experimental models^{9, 23, 24}. The mechanisms underlying clinical response or resistance to treatment against EGFR with cetuximab are unknown. Until now, the only factors found to be associated with tumour-response to cetuximab are wild-type K-RAS and an increased EGFR gene copy number. EGFR status was not associated with significant differences in response rates or survival. Also, time-frames of EGFR-expression during the course of (chemo)-radiation are largely unknown. EGFR tyrosine kinase activity can be initiated by a single dose of radiation in experimental tumour models²⁵. Repeated doses of daily radiation, similar to standard clinical therapy, stimulate increased EGFR expression in experimental models²⁶. Visualization and quantification of cetuximab uptake in the tumour with PET before and during (chemo)-radiotherapy would have major benefit in the appropriate selection of patients for cetuximab treatment¹³.

The maximal TBR of ^{89}Zr -cetuximab uptake in the patients included in this phase I study was 1.6. Correlation of the ^{89}Zr -cetuximab and FDG uptake showed a remarkable mismatch between the two tracers in one patient. Although a large divergence was observed between patients in the time curves of the TBR, overall, the most optimal TBR was observed at the latest time point of imaging, being day 6 for dose

step 1 and day 7 for dose step 2. Therefore, we would suggest the time point of 6 to 7 days after administration to perform Zr-cetuximab imaging.

Several possibilities may explain the low TBRs observed in this study. First, the results may represent true negative findings in this selected patient group. Biopsies taken prior to any treatment of the primary tumours of the patients enrolled in this study did not show overexpression of EGFR or a mutation in the EGFR gene. All patients, however, had undergone extensive treatment with chemotherapy or radiotherapy, of which the long term effect on EGFR expression is largely unknown. Five of the 6 included patients had NSCLC. Although 40-80% of NSCLC tumours show EGFR expression¹, response rates to cetuximab monotherapy in pre-treated patients with EGFR expressing primary tumours of only 5% are reported²¹. Second, the loading dose administered in this study (400 mg/m²), which is the standard in therapeutic regimens might be either too low or too high to enable adequate tumour visualization. The rationale of the loading dose of cetuximab is that cetuximab first binds irreversibly to EGFR expressing liver cells, and that tumour cells are only targeted after the liver has been saturated²⁷. This rationale is supported by animal studies as well as by the positive relation between skin toxicity and tumour response to cetuximab, implying that skin saturation only occurs after the liver has been saturated²⁸⁻³⁰. On the other hand, it cannot be excluded that the unlabelled cetuximab is already sufficient to saturate the EGF receptors on the tumour cells. Future studies should address these critical questions. Finally, it is possible that cetuximab might not reach its target receptor at tumour cells due to limited blood supply and interstitial pressure of the tumour³¹. Hereby, a disparity could result between the in vivo EGFR expression and the uptake of cetuximab, a finding that has been confirmed in our preclinical study with ⁸⁹Zr-cetuximab¹⁴.

Future studies are planned addressing the role of each of these contributing factors. Patients will be studied at primary diagnosis before the start of any antitumour therapy, to allow correlation of EGFR expression at histology with imaging results. As radiotherapy induces upregulation of EGFR expression, visualization of ⁸⁹Zr-cetuximab uptake before and after a single fraction of RT will be evaluated. ⁸⁹Zr-cetuximab administration with different loading doses of unlabelled cetuximab will be evaluated to address its influence on tumour visualization. Finally, kinetic imaging enables the measurement of tumour perfusion, and this should thus be incorporated in future clinical trials.

8.5 Conclusion

The administration of ^{89}Zr labelled cetuximab to image EGFR expression in vivo is not associated with any additional toxicity. Based on the tumour to background ratios, a time delay of 6-7 days after injection is advised for further research.

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Part

IV

Discussion

CHAPTER 9

Therapeutic implications of molecular imaging with PET in the combined modality treatment of lung cancer

**Judith van Loon
Dirk De Ruyscher
Angela van Baardwijk
Liesbeth Boersma
Michel Öllers
Philippe Lambin**

Submitted

Abstract

With the introduction of targeted chemotherapy and radiotherapy techniques, accurate definition of the tumour volume becomes increasingly important. Molecular imaging with PET, and certainly integrated PET-CT, combining functional and anatomical imaging, has many potential advantages over anatomical imaging alone in the combined modality treatment of lung cancer. The aim of the current article is to review the available evidence regarding PET with FDG and other tracers in the combined modality treatment of locally advanced lung cancer. The following topics are addressed: tumour volume definition, outcome prediction and the added value of PET after therapy, and finally its clinical implications and future perspectives.

The additional value of FDG-PET in defining the primary tumour volume has been established, mainly in regions with atelectasis or post-treatment effects. Selective nodal irradiation (SNI) of FDG-PET positive nodal stations is the preferred treatment in NSCLC, being safe and leading to decreased normal tissue exposure, providing opportunities for dose escalation. First results in SCLC show similar results. FDG-uptake on the pre-treatment PET scan is of prognostic value. Data on the value of pre-treatment FDG-uptake to predict response to combined modality treatment are conflicting, but the limited data regarding early metabolic response assessment during treatment do show predictive value. FDG response after radical treatment is of prognostic significance. An FDG-PET scan in the follow-up has potential benefit in NSCLC, while data in SCLC are lacking. Radiotherapy boosting of radioresistant areas identified with FDG-PET is subject of current research.

Tracers other than ^{18}F FDG are promising for treatment response assessment and the visualization of intra-tumour heterogeneity, but more research is needed before they can be clinically implemented.

9.1 Background

Lung cancer accounts for 219,000 new cancer cases and 159,000 deaths a year in the United States, representing 15% of cancer cases and 28% of cancer deaths in 2009¹. As patients often present with primary irresectable disease, the majority of patients with localized disease is currently treated with multimodality treatment using a combination of surgery, chemotherapy (CTx), radiotherapy (RT) and targeted agents. Although survival has significantly improved with combined modality treatment, still, about one third of locally advanced lung cancer patients experience local failure as their first site of relapse. Furthermore, these combined treatment strategies are often associated with dose limiting toxicity, prohibiting further intensification of treatment. This could potentially be overcome by targeted antitumour therapy with more conformal RT techniques and targeted agents. This provides opportunities to increase locoregional control without increasing toxicity. Furthermore, progress is made in strategies directed at an early adaptation of therapy dependent on the treatment response, which may lead to optimization of the therapeutic ratio in each individual. After completion of curative treatment, improvement of outcome could be accomplished by an early detection of local progression, increasing the possibility for those patients to be offered salvage therapy.

The introduction of these techniques makes accurate definition of the tumour volume to be treated increasingly important. This emphasizes the need for imaging techniques enabling accurate definition of the presence and extent of tumour before, during and after curative treatment in cancers of the respiratory tract. While CT and MRI are the most accurate imaging modalities with respect to anatomical information, they often lack the potential to distinguish between vital tumour and non-malignant tissue. Here, molecular imaging with positron emission tomography (PET), providing metabolic information, has additional value. Different radiopharmaceuticals have been evaluated for the imaging of malignant tumours, of which ¹⁸F-fluorodeoxyglucose (¹⁸FDG) is by far most commonly used. FDG-PET scanning utilizes the difference in accumulation of FDG between normal and cancerous tissues, based on an enhanced glucose metabolism in cancer cells. Other PET tracers, visualizing specific molecular pathways in tumours such as proliferation (e.g., ¹¹C-methionine, ¹¹C-choline, ¹⁸F-fluorothymidine) hypoxia (e.g., ¹⁸F-FMISO) or expression of certain receptors (Her2Neu, EGFR) are increasingly being used in the evaluation of malignancies.

Thus, metabolic imaging with PET, and certainly integrated PET-CT, combining functional and anatomical imaging, has many potential advantages over anatomical imaging alone in the combined modality treatment of lung cancer. PET using FDG is

at present most widely applied in the clinical practice of non-small cell lung cancer (NSCLC). Its use in small cell lung cancer (SCLC) is rapidly emerging.

The aim of the current article is to review the available evidence on the use of PET in the combined modality treatment of locally advanced lung cancer. For NSCLC and SCLC separately, the role of PET imaging will be addressed with respect to the following topics:

- Definition of the tumour volume to be treated, both with respect to the primary tumour and the locoregional lymph nodes
- Outcome prediction on basis of PET before or early after the start of treatment, and the added value of PET after therapy

With regard to both these topics, the clinical implications of the use of PET are addressed, and future perspectives are provided.

Because ^{18}F FDG is by far most commonly applied in clinical practice, the majority of evidence comes from this tracer. Therefore, where “PET” is used in this article, this refers to “ ^{18}F FDG-PET”, unless otherwise stated. Wherever other tracers have shown additional value, or are regarded as promising in the near future, they will be discussed.

9.2 Search strategy

A comprehensive literature search was conducted using the “Pubmed” database. Included search terms were: “Non small cell lung cancer”, “Small cell lung cancer”, “NSCLC”, “SCLC”, “Target volume definition”, “Delineation”, “Gross tumour volume (GTV)”, “Clinical target volume (CTV)”, “Tumour heterogeneity”, “Selective nodal irradiation”, “Prognostic value”, “Outcome prediction”, “Follow-up”, “Combined modality treatment”, “Chemotherapy”, “Radiotherapy” or “Radiation” in combination with “PET”, “Positron emission tomography” or “Molecular imaging”.

Reference lists of relevant articles were searched for further studies. Only publications in the English language and published online before February 1, 2010 were included.

9.3 Non-small cell lung cancer (NSCLC)

NSCLC represents more than 80% of lung cancer cases ². Combined chemoradiotherapy is the standard treatment for locally advanced (stage III), inoperable NSCLC.

NSCLC is the tumour type in which the role of ^{18}F FDG-PET imaging has been investigated most extensively.

The added value of PET to select patients for combined modality treatment has been studied extensively ³⁻⁵, and it was shown that PET staging results in superior outcome due to stage migration: up to 30% of stage III patients are diagnosed with distant metastases ^{6, 7}. This clearly affects patient outcome as it withholds toxic therapy in individuals who will not benefit from it.

Below, we will discuss the role of PET in the radiation treatment planning and evaluation of combined chemoradiotherapy for stage III NSCLC.

9.3.1 Definition of the tumour volume to be treated

Primary tumour

Although FDG-PET has a high sensitivity for the detection of the primary tumour, an important drawback is its lack of anatomic detail, which limits its ability to define the exact tumour boundaries. The spatial resolution of current PET scanners is limited to 4-6 mm ⁸, which is far lower than that of modern CT scanners, with a resolution down to 1 mm. There are cases, however, where anatomic imaging modalities such as CT and MRI are compromised in their ability to define the exact tumour border, such as in patients with atelectasis or tumours near the thoracic wall ⁹. Multiple studies have shown a large interobserver variation in delineation of the tumour on CT ^{9, 10}. This interobserver variation is significantly diminished by using the information of an FDG-PET scan, co-registered with CT ¹¹⁻¹⁴. Overall, volumes delineated using PET-CT are smaller ¹². Differences between PET and CT were mainly found in the regions with atelectasis ^{12, 15, 16}.

Various quantitative methods have been developed for automatic tumour delineation using PET instead of visual interpretation of the PET signal. The most straightforward method uses an absolute threshold of the standardized uptake value (SUV). The SUV_{max} threshold of 2.5 is often used for this purpose ¹⁷. An absolute threshold should be used with caution, however, as the SUV is associated with considerable variety due to both technical and biological factors ¹⁸. An alternative method is the use of a relative threshold, e.g. a certain percentage of the SUV_{max} . Recently, more complex methods have been developed, including the application of an individualized threshold based on the source-to-background ratio (SBR) or the watershed clustering method ¹⁹⁻²¹. An example of the difference in interobserver variation between manual and autocontour based delineation is provided in Figure 9.1. Nestle et al. compared absolute ($\text{SUV}_{\text{max}} \geq 2.5$), relative (40% SUV_{max}) and individual (SBR algorithm) quantitative methods and a visual interpretation method with CT-volumes ²². There were large differences in the resulting volumes, particularly in patients with a heterogeneous pattern of FDG-uptake.

Figure 9.1 Example of a manual (a) and autocontour based (b) delineation of the primary tumour

For autocontouring, the SBR based method was used

Arrows indicate changes in interobserver variation in delineation between the two methods

Ideally, validation of the delineated tumour volume should be obtained by correlating it with the tumour volume at pathologic examination, being the gold standard. The currently available data are based on two-dimensional correlations in early stage disease²³⁻²⁵. With the use of a relative threshold, a better correlation was found for CT than for PET (correlation coefficient 0.87 versus 0.77)²³. Yu et al. found the best correlation with integrated PET-CT based on an absolute threshold ($SUV_{max} \geq 2.5$)²⁴. A correlation coefficient of 0.90 was found between the maximal tumour diameter obtained with SBR-based autodelineation and pathology²⁵. Promising attempts are made to develop a three-dimensional model (Figure 9.2), but results in large patient cohorts are to be awaited²⁶⁻²⁸.

The methods described above are aimed at an accurate definition of the gross tumour volume (GTV) in order to ensure that this region is adequately covered by the RT treatment fields. Characteristics associated with radioresistance, such as hypoxia, cell density and proliferation, however, are known to be heterogeneous across the tumour²⁹⁻³¹. FDG-PET scans may allow the identification of therapy-resistant areas within the tumour. It would be logical to selectively boost the radio-resistant areas, whilst decreasing the dose to the less resistant zones, resulting in higher tumour control with similar side effects³²⁻³⁵. It has been demonstrated that regions with high FDG uptake prior to radiotherapy correspond well with the location of recurrent/persistent tumour after sequential chemo-radiotherapy or RT alone (Figure 9.3)^{36, 37}. Furthermore, those regions remain stable during a course of RT (Figure 9.4)³⁸. Thus, selective boosting of areas of assumed radioresistance identified with FDG-PET before the start of RT appears to have a good rationale.

Figure 9.2 Example of the procedure to correlate imaging with pathology in three dimensions: Estimation of the orientation of the CT with respect to the macroscopic slices

In (A), the volumes of interest (lobe, GTV-CT, bronchus entrance) are delineated in the CT slices. In (B) a 3D representation of the CT volumes is depicted. In (C) the inflated specimen after surgery is photographed. The slice direction is indicated by the dashed lines. In (D) the 3D CT volumes are rotated in such a way that the orientation corresponds to the macroscopic specimen

In (E) the CT data are resliced accordingly and for each macroscopic slice the corresponding CT slice can be found. After this procedure, X corresponds approximately to the medio-lateral direction, Y to antero-posterior, and Z to cranio-caudal

Figure 9.3 Correlation between pre-treatment high FDG-uptake areas and location of residual disease
Representative FDG-PET-CT images of three patients pre- and post-radiotherapy.

The light grey lines indicate the 50%SUVmax FDG high-uptake area pre-radiotherapy. The dark lines indicate the residual metabolic-active areas post-radiotherapy, also transposed on the pre-radiotherapy scan. Visual evaluation shows a large correspondence between the residual areas post-radiotherapy with the high FDG uptake areas pre-radiotherapy

Figure 9.4 Stability of high FDG-uptake areas during a course of RT

PET-CT images of 3 patients before treatment (Day 0) and during treatment (Days 7 and 14). Lines indicate 60% of maximal standardized uptake value (SUVmax) threshold. Visual inspection showed that location of the hotspot remained at the same location during treatment; however, the volume of the hotspot changed

The additional value of FDG-PET scanning in defining the primary tumour volume is thus beyond doubt. However, the drawbacks of FDG-PET should be kept in mind. Due to the poor resolution, blurring does occur, particularly at the tumour edges¹⁸. Those blurring effects at the tumour boundary are even more pronounced by motion artefacts. Although the long acquisition time of PET is disadvantageous with respect to defining an absolute tumour edge and quantifying metabolic activity, it may have additional value in determining the extent of tumour motion. The acquisition time of several minutes results in a tumour volume incorporating the averaged position of the tumour over multiple respiratory and cardiac cycles. In a phantom study, PET-based treatment volumes resulted in an adequate coverage of the tumour, while CT-based volumes harboured the risk of a geographical miss³⁹. Respiratory gating or 4D imaging techniques allow the incorporation of the extent of tumour movement, while optimizing image quality and quantification as the blurring effect is reduced⁴⁰. Those techniques are presently being evaluated in clinical studies^{40,41}.

Microscopic disease extension

The poor spatial resolution of PET precludes a direct evaluation of the presence and extent of microscopic disease around the macroscopic tumour border. Definition of the area of potential microscopic spread in patients treated with chemoradiotherapy is important as this region should be covered in the radiation field. The only way to quantify microscopic spread beyond the tumour border visible on imaging is by correlating imaging with the findings at pathologic examination. Until now, this correlation has only been performed between CT and pathology⁴²⁻⁴⁴. Furthermore, no correction was applied for deformation of the lung lobe after surgery. Methods for the correlation of both PET and CT with pathology, which do take into account deformation, are under development^{26, 27}. First results indicate an average microscopic spread in vivo of 9 mm²⁷, suggesting that currently applied margins might be too small to cover microscopic disease.

Lymph nodes

Accurate identification of nodal metastases has become of particular importance since routine elective nodal irradiation, i.e. the prophylactic irradiation of clinically uninvolved lymph nodes, is no longer recommended in NSCLC^{45, 46}. FDG-PET has a higher sensitivity and specificity for the detection of lymph node involvement in NSCLC than CT (sensitivity: 83% vs. 62%; specificity: 97% vs. 91%, respectively)⁴⁷. Both PET- and CT-based selective irradiation of involved lymph nodes has proven its safety in NSCLC, with the occurrence of isolated nodal failures (INF) in less than 5% of patients⁴⁸⁻⁵¹. One study found INF in up to 15% with PET-based SNI⁵². However, the accuracy of the identification of lymph nodes in this study was questionable, as only visual interpretation of non-coregistered PET images was used. In general, the

PET-based treatment volumes are smaller than CT-based volumes^{53, 54}. Selective nodal irradiation (SNI) has shown not only to be safe, but also to result in a reduction of radiation fields based on CT, and even further based on PET⁵⁰. A modelling study showed that treating only FDG-positive mediastinal areas decreases radiation exposure of the lungs and the esophagus sufficiently as to allow for radiation dose-escalation^{50, 54}. An example of the difference resulting from RT planning with PET-CT compared to CT alone is illustrated in Figure 9.5.

Figure 9.5 Example of the effects of RT planning with PET-CT compared to CT alone

Projection of the planning target volume (PTV) of a 66-yearold female with a large cell carcinoma of the right lower lobe with pathological lymph nodes on CT scan in areas 4R and 3R and on FDG-PET scan in area 7. Although the lung exposure was lower with PET-CT than with CT (V20 25 vs. 30% and MLD 15.4 vs. 19.3 Gy, respectively), the oesophageal exposure was higher with PET-CT because of the involvement of level 7 (MED 16.9 vs. 14.1 Gy, V55 18 vs. 4%, Dmax 60.1 vs. 58.6 Gy, respectively, for PET-CT and CT)

Although PET-defined SNI appears to be safe, ideally, pathological confirmation of PET-positive mediastinal nodes should be obtained. Pathological validation of the CT-and PET-based nodal treatment volumes was performed in 998 lymph nodal stations from 105 patients⁵⁵. The coverage of all pathologic lymph nodes was 89% with PET-based treatment volumes compared to 75% with CT ($p=0.005$). Nevertheless, a false negative rate with PET up to 14% has been reported in operable patients⁵⁶. A possible explanation for the low amount of isolated nodal failures is the incidental irradiation of clinically negative lymph node stations through coverage by the beam penumbra of conventional RT fields. The Michigan group showed that risk factors of nodal metastases, such as a large tumour size and central location, were associated with a considerable dose to the high-risk nodal regions⁵⁷, indicating that incidental nodal irradiation might play an important role. Therefore, caution is warranted with the application of new RT technologies, such as stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT) and particle therapy, as

they are associated with a more conformal dose distribution and altered penumbra characteristics.

Different methods can be used for delineation of the involved lymph nodes on PET. Nestle et al. compared the nodal volumes resulting from visual delineation and absolute ($\text{SUV}_{\text{max}} \geq 2.5$), relative (40% SUV_{max}) and individual (SBR-based) thresholds⁵⁸. There were no clinically relevant differences in resulting volumes. SBR-based contouring of lymph nodes generally showed a good correlation with pathology²⁵. Regardless of the delineation method, the question remains how to incorporate the lymph nodes in the treatment volume. There are no data available on the microscopic extension of disease outside lymph nodes. This residual uncertainty can be overcome by encompassing the whole anatomical mediastinal region in the treatment volume, as was done in the Maastricht studies described above^{50, 53, 54}.

As for the primary tumour, the exact anatomical localization of the mediastinal lymph nodes may be blurred because of respiratory motion. Ideally, individually determined margins should be applied to cover the lymph nodes in all respiratory phases, as there is a large intra- and inter-individual variation in lymph node motion, not related to the motion of the primary tumour⁵⁹⁻⁶¹.

Clinical implications and future perspectives

The incorporation of PET in RT planning has shown the potential for dose escalation through a reduction of the radiation fields, mainly because of avoidance of irradiating PET negative lymph nodes^{53, 54, 62}. With individualized radiation dose escalation based on normal tissue constraints, patients treated with sequential chemo-radiation had survival rates comparable to results with concurrent chemo-radiation schedules while less toxicity was observed⁶³. These results imply that PET-based RT planning might ultimately lead to higher cure rates, and randomized prospective studies are warranted to investigate this further.

Further optimization of the radiotherapy treatment volume could be obtained by an accurate definition of the appropriate margin around the delineated tumour to cover microscopic disease. This information should become available from studies correlating PET-CT findings with pathology.

Recently, an increasing tendency has emerged to move away from the concept of homogeneous irradiation. Studies have been performed to investigate the feasibility of selectively boosting areas with residual FDG-uptake after 40-60 Gy, with diverging results^{64, 65}. Prospective trials are awaited to investigate whether radiation dose redistribution leads to better treatment outcome, for which preparations are currently being performed^{33, 66}. In the studies mentioned before, ^{18}F FDG was used as a tracer for radioresistant areas. Other tracers, e.g. for hypoxia (^{18}F -FMISO, ^{18}F -HX4)

or proliferation (^{18}F -FLT) could be used complimentary to or instead of FDG ⁶⁷⁻⁷¹. These tracers deserve further investigation for this purpose.

Conclusion

FDG-PET has an important additional role to anatomic imaging in defining the primary tumour volume. Automatic delineation with adaptive techniques, such as SBR-based methods is to be preferred above absolute thresholding. Models are under development that correlate imaging findings with pathology in three dimensions. These could finally allow validation of different thresholds for SUV-based contouring and evaluation of microscopic spread and intra-tumour heterogeneity. Selective boosting of radioresistant areas identified with FDG-PET is subject of current research.

Selective irradiation of FDG-PET positive nodal stations is safe and leads to decreased normal tissue exposure, providing opportunities for dose escalation. With the increased use of more conformal radiation techniques, the safety of PET-based SNI should be re-evaluated. Disparities in treatment volumes resulting from different contouring methods are smaller than for the primary tumour.

9.3.2 Outcome prediction on basis of PET before or early after the start of treatment, and the added value of PET after therapy

Despite the improved outcome of inoperable stage III NSCLC achieved with combined chemoradiotherapy, the majority of patients still show disease progression after treatment, with 23-43% having an isolated local recurrence as their first site of progression ⁷²⁻⁷⁶. As the treatment is associated with considerable toxicity, it would be of great value to be able to select patients before or early during treatment, with the highest probability to benefit from treatment.

Early response assessment with conventional chest X-ray and CT is limited by their poor discriminating capacity between residual tumour and treatment induced changes ^{77, 78}. PET scanning allows for the assessment of changes in glucose consumption of the tumour during chemo- and radiotherapy. Several studies have shown a correlation between the SUV and tumour cell proliferation ⁷⁹⁻⁸¹, supporting the hypothesis that an early change in FDG uptake has predictive value.

Prognostic value of pre-treatment PET

Most evidence regarding the prognostic value of pre-treatment PET comes from studies in heterogeneous patient populations with both early and late stage disease, treated with different modalities. A meta-analysis was performed within the IASLC lung cancer staging project. 11/13 eligible studies in stage I-IV NSCLC identified a high SUV as a poor prognostic factor for survival, with a combined HR for survival of 2.27 (95% CI: 1.43-3.04) for low versus high SUV ⁸². The threshold was variable be-

tween the studies, ranging from 5 to 20. Those differences are due to both technical and patient related factors, such as different scanners, time intervals between injection and scanning and fasting times. Furthermore, the relationship between SUV and prognosis is rather gradual than fixed at a single cut-off point.

Regarding the ability of PET to predict response to combined modality treatment, the first study in patients with advanced disease treated with (chemo-)radiotherapy showed a positive correlation between the tumour to muscle ratio (TMR) and response, but no significant correlation with outcome⁸³. Two later studies revealed SUV_{mean} and SUV_{max} to be significantly associated with overall survival^{84, 85}. In the first population, both tumour grade and UICC stage showed a stronger correlation with survival than the SUV⁸⁴, while in the second study, SUV_{max} was the strongest predictor⁸⁵. In contrast, the most recent study in the largest cohort of stage III and IV NSCLC patients thus far (n=214), did not show a significant relationship with survival⁸⁶. This study was not included in the mentioned IASLC meta-analysis.

Outcome prediction on basis of early PET response during combined modality treatment

Because FDG is preferentially accumulated in viable tumour cells^{87, 88}, FDG-PET imaging is an attractive method to visualize early treatment response, as the change in SUV should reflect the rate of tumour cell killing. In advanced NSCLC, the predictive value of an early metabolic response to palliative chemotherapy, as well as to radical treatment with (chemo)radiotherapy has been evaluated. Prospective observational studies have consistently shown that in advanced NSCLC treated with palliative chemotherapy, the metabolic response after 1-3 cycles of chemotherapy is strongly correlated with final outcome⁸⁹⁻⁹².

With respect to radical treatment, metabolic response to induction chemotherapy prior to radiotherapy or surgery in locally advanced NSCLC patients has been shown to correlate with outcome in multiple studies as well^{90, 93, 95, 96}. One study, however, did not show predictive value⁹⁸.

While the evidence regarding the predictive value of a metabolic response to induction chemotherapy is abundant, far less is known about its value early during the course of radical treatment itself. One study investigated the predictive value of response assessment during concurrent chemoradiotherapy⁹⁹. A significant difference in long-term survival was found between patients with and without a metabolic response after 3 weeks of concurrent chemoradiotherapy. A study evaluating response during radical RT revealed a large intra-patient heterogeneity in the evolution of SUV_{max} during and after radical RT¹⁰⁰. Different time patterns were seen for responders and non-responders, but due to the limited patient numbers, the predictive value of the SUV_{max} changes could not be assessed.

To make FDG response assessment a valuable tool in routine clinical practice, a clear definition of response should be prescribed, as the intra-patient variability of repeated tumour SUV-measurements is in the range of 10-15%¹⁰¹⁻¹⁰³. Furthermore, early response should be assessed at a fixed time interval. Ideally, the interval should be short enough to switch to a potentially more successful treatment as early as possible. This should be balanced, however, with a time interval sufficient to allow for a reliable response assessment. In 1999, the EORTC published consensus guidelines on which cut-off points should be used to define response at different time intervals¹⁰⁴, which are still widely applied in clinical practice. Weber et al. defined a metabolic response after the first cycle of chemotherapy as a decrease in FDG uptake of more than twice the standard deviation, calculated to be 20%. This definition correlated with final response according to RECIST, as well as with time to progression and overall survival⁹¹. In 2009, the PET Response Criteria in Solid Tumours (PERCIST, version 1) have been proposed resulting from a review of qualitative and quantitative methods of metabolic response assessment⁹⁷. PERCIST recommends to correct SUV for lean body mass (SUL) as this accounts for variations due to differences in body composition. A comparison between the EORTC criteria and PERCIST is provided in Table 9.1. Overall and most importantly, the same definition of response criteria should be used by different groups to be able to compare metabolic response studies across different centres.

Concerning the type of measurement, semiquantitative methods, such as the relative change in SUV, appear to perform equally well as more complex quantitative methods such as change in the net-influx constants (Ki) or metabolic rate of glucose (MRglu)⁹⁰⁻⁹². This facilitates the use of early PET response for outcome prediction in daily clinical practice.

Table 9.1 Criteria of metabolic response according to EORTC and PERCIST

	EORTC	PERCIST
Progressive Metabolic Disease (PMD)	<ul style="list-style-type: none"> • > 25% increase in SUV of tumour defined on pretreatment scan, or • > 20% increase in the longest dimension of FDG-uptake, or • Appearance of new FDG-uptake in metastatic lesions 	<ul style="list-style-type: none"> • > 30% increase in SUL peak and absolute increase of SUL units $\geq$ 0.8 from baseline scan in pattern typical of tumour and not of infection /treatment effect, or • Visible increase in extent of FDG-uptake (> 75% increase in total lesion glycolysis), or • Appearance of new FDG-avid lesions typical of cancer and not related to infection /treatment effect
Stable Metabolic Disease (SMD)	<ul style="list-style-type: none"> • < 25% increase or < 15% decrease in SUV of tumour defined on pretreatment scan, and • < 20% increase in the longest dimension of FDG-uptake 	<ul style="list-style-type: none"> • No CMR, PMR or PMD
Partial Metabolic Response (PMR)	<ul style="list-style-type: none"> • > 15% decrease in SUV of tumour defined on pretreatment scan (after 1 cycle) • > 25% decrease in SUV of tumour defined on pretreatment scan (after > 1 cycle) 	<ul style="list-style-type: none"> • > 30% decrease in SUL peak and absolute drop in SUL units $\geq$ 0.8 of the most intense lesion before and after treatment (not necessarily the same lesion) • No new FDG-avid lesions typical of cancer
Complete Metabolic Response (CMR)	<ul style="list-style-type: none"> • Complete resolution of FDG-uptake within tumour defined on pretreatment scan, not distinguishable from surrounding normal tissue 	<ul style="list-style-type: none"> • Complete resolution of FDG-uptake within measurable target lesion, less than mean liver activity and indistinguishable from surrounding background blood-pool levels • Disappearance of all other lesions to background blood-pool levels • No new FDG-avid lesions typical of cancer

SUL: Standardized uptake value corrected for lean body mass

Added value of PET after combined modality treatment

The accuracy of PET after treatment is assumed to be lower than at initial staging because of therapy induced inflammatory and perfusion changes¹⁰⁵. Nevertheless, PET still has a high accuracy in detecting recurrent lung cancer, with a sensitivity up to 98% and a specificity of 62-92%¹⁰⁵⁻¹⁰⁷, and is more accurate than CT in the distinction of tumour from post-RT effects¹⁰⁸⁻¹¹⁰. Here, the added value of a post-

treatment PET is addressed with regard to the prognostic value of a PET early after treatment as well as the role of PET in the follow-up after combined modality therapy.

We identified four studies addressing the prognostic value of PET after radical treatment in locally advanced NSCLC patients, consisting of (chemo-)RT^{74, 83, 100, 112}. Four studies evaluated the predictive value of PET after induction chemoRT before surgery^{94, 96, 111, 113}. The studies were unambiguous in their conclusion that the FDG response after chemoradiotherapy has prognostic and predictive value, respectively. Mac Manus proved the superiority of PET response above CT. Response on PET and CT were identical in only 40% of patients. In multivariate analysis, only the PET response was significantly associated with survival¹⁰⁹.

Clear cut-offs should be prescribed to define the different prognostic subgroups. In the aforementioned studies, however, there is a large heterogeneity in the way FDG-uptake after therapy was measured. Some studies reported an absolute threshold post-treatment^{83, 96, 111, 113}, while others stratified patients according to the relative change in SUV^{74, 94, 100, 109, 112}. In none of the studies a direct comparison was made between the different methods. Until more data are available we recommend the use of the EORTC criteria for PET response¹⁰⁴ for prognostic stratification, as the results of the larger studies are mainly based on these criteria.

Another important aspect is the timing of the PET-CT. The median time interval in the studies described above was 14 to 70 days. It is recommended to perform a PET-CT scan not earlier than 3 to 6 months after treatment to avoid false positive results due to post-therapy inflammatory changes^{105, 114}. The time interval should not be excessive either, as the final aim is to select patients for further therapy. Hicks et al. observed no confounding effect through post-RT inflammatory changes for response assessment with a PET-CT scan performed 70 days after radical RT¹¹⁵. As different time-points have not been compared directly, we recommend the use of the time point 70 days post-treatment.

It should be noted that the results described above only apply for patients treated with conventional or hyperfractionated RT with or without chemotherapy. In hypofractionated SBRT, where 3 to 5 large fractions are applied, persistently elevated SUV_{max} of > 3.5 have been described up to one year post treatment^{116, 117}. These different findings may be explained by localized normal tissue changes induced by SBRT, such as segmental atelectasis or focal fibrosis, that are not distinguishable from persistent or recurrent tumour.

PET in the follow-up of NSCLC could improve outcome when progressive disease can be detected early enough to allow radical retreatment. There are no convincing data supporting that early detection of progression with chest X-ray or CT scan im-

proves survival^{77, 118-120}. This might be different for FDG-PET scanning, as PET is more accurate than CT in the distinction of tumour from post-RT effects^{108, 109, 121}, and is known to be prognostic for outcome^{82, 88, 122-124}. A prospective study was performed to evaluate whether PET-CT 3 months after therapy can detect potentially curable progression in locally advanced NSCLC¹²⁵, which was the case in a small proportion (3%) of patients, who were all asymptomatic. An economic evaluation based on these results showed that a PET-CT scan 3 months after (chemo-)radiotherapy is potentially cost-effective, and is more cost-effective than CT alone¹²⁶. As the advantage was confined to the asymptomatic patients, a PET-CT scan in this group only is probably as effective and more cost-effective.

Other tracers

As response assessment early during and after therapy is complicated by the limited ability of FDG to discriminate between inflammation and tumour activity, it is worthwhile to investigate alternative tracers, corresponding more specifically with tumour proliferative activity.

The uptake of ¹⁸F-fluorothymidine (¹⁸F-FLT), a marker of DNA synthesis, has been correlated with tumour proliferative activity in various tumour sites including NSCLC¹²⁷⁻¹³². Recent (pre)clinical studies have demonstrated that FLT can detect changes in proliferation during and after irradiation in colorectal tumours and breast cancer cell lines¹³³⁻¹³⁵. One pilot study in NSCLC has shown the feasibility of FLT to image proliferation during chemo-radiotherapy⁷¹.

Amino-acid tracers theoretically have an advantage over FDG in that it more specifically accumulates in viable cancer cells¹³⁶. However, data on its usefulness in evaluating treatment response are scarce. One study compared ¹⁸F-FDG and the amino-acid tracer ¹¹C-methionine (¹¹C-Met) for evaluation of treatment response in lung cancer, but this study focussed on early stage patients treated with stereotactic RT¹¹⁷. In this study, FDG and Met showed an equal accumulation in inflammatory tissue, a finding that is supported by the results of other research groups¹³⁷⁻¹³⁹. Another amino-acid tracer has recently been put forward for monitoring treatment response, being ¹⁸F-fluoromethyltyrosine (¹⁸F-FMT). Two animal studies showed a rapid response to antitumour therapy, and less accumulation in inflammatory cells^{140, 141}.

Clinical implications and future perspectives

The clinical impact of patient selection before or early during treatment is beyond doubt, as it avoids ineffective treatment with the associated side-effects and enables alternative therapy in case of an inadequate early response. Before this principle can be implemented in clinical practice, additional research is needed to define

clear cut-off points for FDG uptake to stratify patients into different treatment modalities. With regard to early response assessment, attention should be paid to other tracers, in particular proliferation markers, as they are less susceptible to uptake in inflammatory tissue⁷¹.

A final option for improvement in outcome is the use of PET in the follow-up. Currently available data do show a potential benefit of PET in the follow-up compared to CT. Ideally, different follow-up strategies, including PET-CT based follow-up, should be compared in a randomized controlled trial to provide a definitive insight in the added value of PET in the follow-up of NSCLC patients after combined modality therapy.

Conclusion

In the overall NSCLC patient group, pre-treatment FDG-uptake is of prognostic value. Results on its ability to predict response to combined modality therapy in advanced stage NSCLC are conflicting. The most recent study in the largest patient cohort did not show a significant correlation with survival.

The predictive value of an early metabolic (FDG) response during induction chemotherapy has been established. Less is known about the predictive value of a metabolic response during radical (chemo-)RT, but the limited available data show a correlation with survival. The FDG response after radical treatment is of proven prognostic significance. A time interval of 70 days after the end of treatment is recommended for metabolic response assessment on basis of the EORTC criteria.

An FDG-PET scan in the follow-up after combined modality therapy can detect progression amenable for radical retreatment in a limited number of patients.

Tracers other than FDG are promising for treatment response assessment, but more research is needed before they can be clinically implemented.

9.4 Small cell lung cancer (SCLC)

SCLC is a tumour with a poor prognosis, characterized by a rapid growth rate. Traditionally, staging of those patients has been limited to the distinction between limited (LD) and extensive disease (ED)¹⁴². Approximately 25% of patients present with limited-disease (LD), defined as disease confined to one hemithorax, including the mediastinum and bilateral supraclavicular fossae¹⁴³⁻¹⁴⁵. Even in this patient group, surgery is rarely an option because of the advanced stage of locoregional disease. Concurrent chemo-radiation is currently the first choice treatment. Literature is sparse on the role of PET in LD-SCLC. The available literature suggests that FDG-PET has additional value above standard staging procedures in SCLC¹⁴⁶⁻¹⁵³, with a reported sensitivity and specificity up to 100% and 95%¹⁵⁴. Staging with PET can positively influence the outcome of chemoradiotherapy for LD-SCLC patients by means

of stage migration. Upstaging from LD to ED by FDG-PET scanning occurs in 6-33%^{146-148, 155-158} and downstaging in 3-40%^{147, 148, 155, 157} of patients.

9.4.1 Definition of the tumour volume to be treated

Primary tumour

In order to define the tumour volume, PET should be assessed for its ability to distinguish malignant from surrounding normal tissue. Studies addressing this issue are focussed on NSCLC¹¹⁻¹⁴. The same holds true for correlation studies with pathology^{24, 26, 27, 43, 44}. Therefore, we can only assume that similar caveats apply as described above for NSCLC. In short, a major limitation of PET is the low spatial resolution. Hence, the major gain is to be expected in regions where anatomical imaging techniques lack the capacity to discriminate malignant from normal tissue, e.g. in areas with atelectasis. Another question refers to which method should be applied for PET-based tumour delineation. Again, comparison and validation of different methods has exclusively been performed in NSCLC^{22, 25}. No conclusions can be drawn regarding which method is to be preferred, except that adaptive techniques are likely to be more accurate than the use of an absolute or relative SUV-based threshold^{20, 21}. Obviously, blurring effects due to motion do hinder exact tumour delineation. Respiration correlated imaging techniques have the potential to include individual tumour motion in the treatment volume, in conjunction with optimal image quality, as blurring effects are significantly reduced^{40, 41}.

Microscopic disease extension

As described previously, the only way to define microscopic disease extension beyond the tumour border visible on imaging is to correlate imaging with pathology. There are no data on image correlation with pathology available for SCLC.

Lymph nodes

The available data suggest that an FDG-PET scan can identify metastases to regional lymph nodes in 14-25% of patients whose mediastinal CT scan is negative^{146, 150, 157}. With the high sensitivity and specificity of PET in SCLC, it is likely that the use of PET scans improves the coverage of mediastinal lymph node areas in LD-SCLC. Until recently, only few prospective data concerning selective nodal irradiation (SNI) in SCLC were available. A report from the International Atomic Energy Agency (IAEA) meeting emphasized the need for prospective clinical evidence regarding SNI in SCLC¹⁵⁹. CT-based SNI resulted in an unacceptable amount (11%) of isolated nodal failures outside the treatment volume¹⁶⁰. These findings imply that results on the safety of SNI in NSCLC cannot straightforwardly be extrapolated to SCLC.

Since the publication of the IASLC report, two studies have become available evaluating FDG-PET based SNI in SCLC. In a planning study, a difference in the treatment plan resulting from PET- and CT-based SNI was found in 24% of patients¹⁶¹. Radiation fields increased in 10% and decreased in 14% of patients, respectively. No significant changes in the radiation exposure of the normal tissue were observed. In the subsequent prospective study, 3% of the patients experienced an isolated nodal failure after a minimal follow-up of 18 months, comparable to results in NSCLC. A remarkably low percentage (12%) of grade III esophagitis was found, while this occurs in about 30% of patients receiving elective nodal irradiation or CT based SNI^{160, 162}. This finding deserves further investigation. The low rate of isolated nodal failures and toxicity thus supports the use of PET-based SNI in LD-SCLC.

A few points of caution should be taken into consideration. First, incidental irradiation of surrounding nodal stations might partially explain the low rates of isolated nodal failures with SNI. Therefore, results should be re-evaluated with the application of more conformal techniques (SBRT, IMRT, particle therapy). A second point of attention consists of the methods for target volume definition. In the available study, the mediastinal nodal regions involved on PET were included in the treatment field¹⁶³. As our literature search did not yield any study evaluating autocontouring methods for lymph node delineation in SCLC, we recommend SNI of the whole mediastinal nodal station involved on PET.

Clinical implications and future perspectives

As in most cases, the bulk of disease in SCLC is located in the hilar and mediastinal regions, reduction of the treatment volume can mainly be reached by omitting elective nodal irradiation. As mentioned above, the first study with PET-based SNI showed a remarkably low rate of oesophageal toxicity¹⁶³. If this finding holds true, PET based SNI indeed provides opportunities for treatment intensification. With regard to RT planning, another point of consideration is the concept of subboosting areas of supposed radioresistance. FDG-PET, as well as PET with other tracers, could help to identify those regions within the tumour. Although this concept is readily evolving in NSCLC, no such trend is observed until now in SCLC. Although it is reasonable to assume that characteristics associated with radioresistance are also heterogeneous in SCLC²⁹⁻³¹, the disease load in NSCLC is different from SCLC, as most of the tumour load is accounted for by nodal stations. Studies on the evolution and stability of regions with high FDG-uptake in NSCLC are entirely focussed on the primary tumour, and no such information is available with respect to lymph nodes. These issues should be addressed when heterogeneous dose escalation is taken into consideration in SCLC.

Conclusion

There are no data available on the role of FDG-PET in defining the borders of the primary tumour. In contrast with CT-based SNI, first results indicate that selective irradiation of FDG-PET positive nodal stations appears to be safe and results in remarkably limited toxicity. With the increased use of more conformal radiation techniques, the safety of PET-based SNI should be re-evaluated. It is recommended to encompass the whole anatomical mediastinal region containing FDG-positive nodes in the treatment volume.

9.4.2 Outcome prediction on basis of PET before or early after the start of treatment, and the prognostic value of PET after therapy

The majority of SCLC patients still shows disease progression short after the completion of chemoradiotherapy, with over 30% having an isolated local recurrence as their first site of progression¹⁶². Furthermore, the treatment is associated with considerable toxicity, with grade 3 esophagitis in up to 27% of patients^{111, 164-166}. Therefore, the ability to predict the benefit from treatment would be of great clinical value, hereby avoiding ineffective treatment in the patient group in which benefit is less likely. Recent data have made clear that the traditional staging system with two categories (limited and extensive disease) is on its own not an adequate predictor of survival and is not sufficient to stratify patients for the most optimal therapy^{167, 168}. Since recently, it is recommended to use the TNM staging for SCLC, as it has proven to result in a better stratification of patients in prognostic subgroups^{169, 170}. FDG uptake on PET before, during or after therapy could have a role as additional prognostic and predictive marker in SCLC.

Prognostic value of pre-treatment PET

Evidence concerning the prognostic value of FDG-uptake before treatment in SCLC is scarce. One study was identified that addressed this subject¹⁷¹. The majority of patients had LD and were treated with concurrent chemoradiotherapy. Overall, as well as for the subgroup with LD, patients with a high SUV_{max} (i.e., higher than the median) had a significantly worse overall survival than patients with a low SUV_{max} (LD: 20.1 vs. 35.3 months). Three prognostic subgroups could be defined on basis of FDG-uptake and disease stage. Those results imply that different treatment strategies are required for LD with low and high SUV_{max}. Randomized clinical studies are warranted to answer whether FDG-uptake in combination with anatomical staging is predictive of outcome and can be used to select the appropriate therapy for each patient group.

Outcome prediction on basis of early PET response during combined modality treatment

The predictive ability of an FDG response early after the start of chemotherapy has been evaluated in 2 studies, both after one cycle of chemotherapy^{172, 173}. However, patients with both LD and ED were investigated. Therefore, the results reflect the predictive value of an FDG response early during palliative chemotherapy or radical chemoradiotherapy. Furthermore, both studies used CT response after completion of therapy as a reference, and not survival. Both studies concluded that the metabolic response was correlated with the response according to RECIST.

A couple of important questions need to be addressed in future studies to make early response assessment with PET during treatment a valuable clinical tool. Those questions include the type of measurement, the definition for response, and the most optimal time interval for the measurement of early response. Regarding response criteria, the use of the EORTC recommendations¹⁰⁴, a 20% threshold, as well as the criteria for visual response assessment by MacManus are valid¹⁰⁹: Fischer et al. compared the visual method with the EORTC criteria in SCLC response evaluation after one cycle of chemotherapy and found no significant difference¹⁷². Regarding the type of measurement and the time interval, no separate data on SCLC are available. As long as no such data are available, the most practical alternative is to adhere to the NSCLC recommendations. Those are the use of relatively simple semi-quantitative measurements such as SUV_{max} ⁹⁰⁻⁹², and a time interval of 1 to 3 cycles of chemotherapy⁹⁰⁻⁹².

Caution is warranted, however, when projecting results obtained in NSCLC at SCLC. As mentioned before, those are two distinct types of disease with different clinical behaviour. SCLC is characterized by a rapid response to chemo- and radiotherapy. Therefore, a response to therapy could be more rapidly visible on CT than it is in NSCLC, which might restrict the beneficial effect of PET. This hypothesis is supported by the study of Fischer et al., who found that early response assessment after one cycle of chemotherapy with CT and PET showed a comparable correlation with the final evaluation on basis of RECIST¹⁷².

Added value of PET after combined modality treatment

Two retrospective studies evaluated the prognostic value of PET after treatment in SCLC patients^{151, 174}, with one specifically aimed at LD¹⁷⁴. The first study included both LD and ED, and both treated and untreated patients, with treated LD patients representing 50% of the study population. It is hard to draw separate conclusions on this group, but overall, there was a significant negative correlation between PET positivity or SUV_{max} and overall survival¹⁵¹.

The study evaluating exclusively LD patients has some limitations: only 73% was treated with chemoradiotherapy, the remaining patients with palliative chemotherapy¹⁷⁴. Furthermore, the time interval between the end of treatment and PET-scanning was variable (3-125 days). Finally, the definition of PET positivity was rather broad. With those limitations in mind, the study showed a significant difference in progression free survival between PET positive and -negative patients, with a trend for overall survival.

A prerequisite for PET in the follow-up to have a positive impact on the final outcome is that progression should be detected at a time that radical retreatment is still an option. The rapid growth rate and early dissemination make it less likely for progression to be detected in a “curable” stage in SCLC than in NSCLC. Although no studies have addressed the role of FDG-PET in the follow-up of SCLC, it can therefore be questioned whether PET scanning is advantageous with respect to outcome.

Clinical implications and future perspectives

It is obvious that the currently available data are insufficient to modify or adapt treatment on basis of pre-treatment FDG uptake or an early metabolic response in SCLC patients. Research in the field of early response assessment is of particular importance to define the additional benefit of PET above CT given the rapid response of SCLC to chemo- and radiotherapy.

Finally, the role of PET after combined modality therapy of LD-SCLC should be addressed. Given the early dissemination of SCLC, most benefit is to be expected with a tracer that allows response evaluation early after treatment. Given the high uptake in inflammatory regions, FDG might not be ideal for this purpose. Therefore, other tracers should be evaluated.

Conclusion

Studies evaluating the prognostic value of PET, its ability to predict response to combined modality treatment and the added value of PET after treatment in SCLC are scarce. Available results mainly come from studies in patients with both limited and extensive disease. Overall, results do show some predictive value of an FDG response before and during therapy, as well as prognostic value of FDG uptake after treatment. No studies have evaluated the impact of PET in the follow-up of SCLC.

9.5 General conclusions

Molecular imaging with PET, using different tracers, has the potential to distinguish between vital tumour and non-malignant tissue and to identify intra-tumour characteristics. The additional value of FDG-PET in defining the primary tumour volume has been established, mainly in regions with atelectasis or post-treatment effects.

Three dimensional models that correlate imaging findings with pathology are being developed for NSCLC, which could allow validation of different thresholds for SUV-based contouring, evaluation of microscopic spread and intra-tumour heterogeneity. FDG-PET has the ability to identify regions within the tumour that are associated with radioresistance, and for NSCLC, it has been proved that these regions remain stable during a radiotherapy course. Therefore, boosting of radioresistant areas identified with FDG-PET appears to be feasible and is subject of current research. Selective irradiation of FDG-PET positive nodal stations in NSCLC is safe and leads to decreased normal tissue exposure, providing opportunities for dose escalation. For this reason, it is the preferred treatment in NSCLC. First results in SCLC suggest that the same holds true for SCLC. Data on the predictive value of pre-treatment FDG-uptake and an early metabolic response during combined modality treatment are conflicting and limited, respectively. The FDG response after radical treatment is of prognostic significance. A time interval of 70 days between end of treatment and PET scanning is recommended for response evaluation in NSCLC. A PET scan in the follow-up of NSCLC potentially improves survival through the detection of progression with radical treatment options. Data on its value in the follow-up of SCLC are lacking.

Tracers other than ^{18}F FDG are promising for treatment response assessment and the visualization of intra-tumour heterogeneity, but more research is needed before they can be clinically implemented.

9.6 References

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CHAPTER 10

General Discussion and Future Perspectives

Combined modality treatment with chemotherapy and radiotherapy (RT) is the treatment of choice for the approximately one third of lung cancer patients presenting with locally advanced disease. Although survival has improved significantly with combined modality therapy, the prognosis remains very poor. The objective of this thesis was to address the potential of molecular imaging with PET to optimize combined modality treatment in lung cancer. In this chapter, the main findings are summarized and discussed in view of the currently available evidence. Future perspectives to further improve outcome in locally advanced lung cancer are provided.

10.1 FDG-PET-CT based target volume definition to optimize radiotherapy for locally advanced lung cancer

Microscopic disease extension

In RT planning, a margin of surrounding tissue is added to the gross tumour volume (GTV) to ensure coverage of potential microscopic spread, resulting in the clinical target volume (CTV) ¹.

Microscopic spread beyond the tumour border visible on imaging can only be quantified by correlating imaging with the findings at pathologic examination. Population statistics in NSCLC report an average distance of microscopic spread ranging from 1.5 mm to 8 mm ²⁻⁵. These ranges are probably underestimated as tissue deformations occur between in-vivo imaging and ex-vivo pathology. This underestimation may arise up to a factor of 2 ^{6,7}, suggesting that currently applied margins, usually around 5 mm, are probably too small to allow delivery of the full radiotherapy dose to areas with microscopic disease. The dose required to eradicate microscopic disease, however, is expected to be lower than the dose for macroscopic tumour ^{8,9}. Furthermore, not all lung tumours do show microscopic disease spread ^{3,7}. In this thesis, a prediction model for the presence of microscopic spread in NSCLC was developed on the basis of risk factors on pre-treatment PET-CT (Chapter 2). Mean tumour density on CT and tumour volume on CT were predictive for the presence of microscopic disease. After validation in an independent patient cohort, finally, these factors could allow an individual adaptation of the dose to the tissue surrounding the GTV according to subgroups of patients, thus optimizing the balance between local control and toxicity in the individual patient.

FDG-PET based selective nodal irradiation

Routine elective nodal irradiation is no longer recommended in NSCLC ^{10,11}. FDG-PET scan is more accurate for the detection of lymph node involvement than CT in both NSCLC and SCLC ¹²⁻¹⁶. In NSCLC, the sensitivity and specificity of PET compared

to CT are 83% vs. 56% and 89% vs. 81%, respectively. Although in SCLC, no clinical trials are available that directly assess the diagnostic performance for lymph node staging, the available data report a sensitivity and specificity of 89-100% and 78-95% in the overall staging of SCLC. This suggests that the diagnostic accuracy for lymph node staging of PET is higher than CT in SCLC as well ¹⁶.

Both PET- and CT-based selective nodal irradiation (SNI) of involved lymph nodes has proven its safety in NSCLC, with an isolated nodal failure rate of less than 5% ¹⁷⁻²⁰. In NSCLC, SNI is not only safe, but also results in a reduction of radiation fields based on CT, and even further based on FDG-PET ²¹, providing opportunities for radiation dose-escalation through decreased radiation exposure of the lungs and the esophagus ^{21, 22}.

In SCLC, data on the applicability of SNI are scarce ²³. CT-based SNI cannot be considered safe, as it resulted in an amount of 11% of isolated nodal failures ²⁴. We confirmed in a planning study that differences in the treatment plan resulting from PET- and CT-based SNI occur, which was the case in 24% of patients (Chapter 3). The subsequent prospective study indicated that FDG-PET-based SNI is safe, with 3% of the patients experiencing an isolated nodal failure (Chapter 4). The treatment resulted in a remarkably low percentage (12%) of grade III esophagitis. Anticipating that further intensification of the combined modality treatment regimen results in improved outcome in SCLC patients as well ²⁵, two intensified RT schedules are currently compared to the standard treatment schedule (45 Gy twice daily) in a randomized phase III trial ²⁶. The low rate of isolated nodal failures and toxicity supports the use of PET-based SNI in future intensified treatment schedules for stage I-III SCLC.

Caution is warranted with the application of more conformal RT technologies, such as stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT) and particle therapy, as they are associated with altered penumbra characteristics.

10.2 Value of FDG-PET-CT in the follow-up of locally advanced lung cancer

The most effective follow-up strategy for lung cancer patients treated with curative intent therapy is still not established. This uncertainty is reflected in the large heterogeneity in recommendations from the different cancer societies, diverging from no imaging at all to repeated imaging with chest CT scans ²⁷. The added value of chest X-rays and/or chest CT has not been confirmed in any prospective study. The most recent study comparing intensive follow-up with repeated CT-imaging to less

intensive radiologic follow-up showed no significant improvement of survival²⁸. A main reason for this is the fact that progression or recurrence is mostly detected at a stage that no more radical treatment options exist, and hence, no survival benefit can be expected²⁹. The poor discriminating capacity of CT and chest X-ray between residual tumour and post-treatment changes^{30, 31} causes a delay as progression is often only confirmed after repeated imaging.

FDG-PET-CT is more accurate than CT in the evaluation of response to treatment as well as in outcome prediction³²⁻⁴⁰. This formed the rationale for the hypothesis that PET-CT may have additional benefit. We report in this thesis the results of a prospective study in 100 NSCLC patients treated with chemo-radiotherapy or RT alone with curative intent. This study confirms that an FDG-PET-CT 3 months after therapy can detect progression amenable for treatment with curative intent, and hereby, possibly lead to an increase in survival. This was, however, only the case in a small proportion of patients (2%), and only in the subgroup that was asymptomatic at the time of scanning (Chapter 5). Based on these results, an economic evaluation was subsequently performed comparing PET-CT based follow-up with usual follow-up with either a CT scan or repeated chest X-rays. A PET-CT scan 3 months after (chemo-)radiotherapy turned out to be potentially cost-effective, and was more cost-effective than CT alone. As the advantage was confined to the asymptomatic patients, representing 55% of the total population, performing a PET-CT in this group only is probably as effective and more cost-effective (Chapter 6).

Hence, we suggest that on basis of the currently available evidence, if any imaging is wished to be performed for treatment evaluation in NSCLC, an FDG- PET-CT scan 3 months after therapy is to be preferred above CT alone. The uncertainty surrounding the decision whether to implement PET-CT in the follow-up makes it worthwhile to perform additional research. This uncertainty is caused for a major part by the relatively small patient population in the prospective study. In this respect, a direct comparison between conventional, CT based and PET-CT based follow-up in a randomized trial, including a prospective evaluation of the associated costs, would add significantly to the final decision regarding which strategy to implement in routine clinical practice.

A multicentre phase III trial in NSCLC patients after curative resection is currently ongoing in France which should give a definitive answer regarding the value of CT based follow-up⁴¹. Unfortunately, however, PET-CT scans are not included in this trial.

No studies have addressed the role of FDG-PET in the follow-up of SCLC. Because of the rapid growth rate and early dissemination of SCLC, it is less likely that an FDG-PET scan 3 months after therapy detects progression in a stage that is still curable.

As earlier response evaluation with FDG is limited by its uptake in inflammatory areas, other tracers, such as proliferation markers that are described below, may be better suitable for this purpose.

10.3 Novel PET tracers for the non invasive imaging of tumour characteristics

The supplementary role of FDG-PET in the diagnosis, staging and treatment of lung cancer is beyond doubt. The correlation between high FDG uptake and worse overall survival has been shown in multiple studies⁴²⁻⁴⁵, and was confirmed in a meta-analysis, with a combined HR for survival of 2.27³⁶. Nevertheless, the inherent properties of FDG limit its value in certain areas. Furthermore, the development and introduction of new therapeutic strategies specifically targeted at tumour cell characteristics provide novel opportunities for molecular imaging to specifically visualize one of these characteristics. This makes it worthwhile to investigate whether alternative tracers can complement FDG.

The limited ability of FDG to discriminate between tumour activity and inflammatory effects due to therapy, has forced the search for more specific markers of tumour cell proliferation. Two groups of proliferation markers have been evaluated for their ability to image proliferation during (chemo-)radiotherapy. Thymidine analogues, markers of DNA synthesis, of which ¹⁸F-fluorothymidine (¹⁸F-FLT) is most extensively applied, has been correlated with tumour proliferative activity in lung cancer⁴⁶⁻⁴⁹ and has the feasibility to image proliferation during chemoradiotherapy⁵⁰. In head and neck cancer patients, however, FLT has been shown to accumulate as well in reactive B-lymphocytes, which forms a potential drawback for its use in early response assessment⁵¹.

The second group of proliferation markers consists of amino-acid tracers, such as ¹¹C-methionine (¹¹C-Met) and ¹⁸F-fluoromethyltyrosine (¹⁸F-FMT). Data on their usefulness in evaluating treatment response are scarce⁵²⁻⁵⁵, but preclinical studies with ¹⁸F-FMT did show a rapid response to antitumour therapy with little accumulation in inflammatory cells^{56,57}.

Tumour hypoxia is an important marker of cancer prognosis, being associated with aggressive growth, metastasis, and resistance to anticancer therapy⁵⁸. Non-invasive PET imaging allowing detection and quantification of hypoxia could select patients who may benefit from hypoxic radio-sensitizers or dose-escalation. Although the uptake of glucose, and thus FDG, is increased by hypoxia, many other factors including proliferation and cell density also increase cellular glucose influx⁵⁹. Clinical studies in NSCLC regarding the correlation between FDG uptake and the degree of hy-

poxia within the tumour have shown contradictory results^{39, 60-63}. Therefore, specific hypoxia targeted tracers are required to image hypoxia in lung cancer.

[¹⁸F]HX4, a recently developed hypoxia marker of the 2-nitroimidazole family, has in preclinical models proven to be a good tracer for the detection and evaluation of tumour hypoxia. [¹⁸F]HX4 was cleared faster from normal tissues and better reflected tumour heterogeneity compared to commonly used hypoxia markers such as [¹⁸F]FMISO and [¹⁸F]FAZA, suggesting that [¹⁸F]HX4 may be a better alternative than these known hypoxia markers⁶⁴. We demonstrated in a phase I trial that PET imaging with [¹⁸F]HX4 is safe (Chapter 7). The median tumour to muscle ratio (TMR) at 120 minutes post-injection was 1.40 (range: 0.63-1.98). No imaging at later time points was performed to limit the burden for the patients, all suffering from end stage disease. Future trials are needed to determine optimal imaging parameters, as preclinical data suggest 240 minutes post-injection as the most optimal time-point of scanning, with a maximum tumour to blood ratio of 7.6⁶⁴.

Another area where non-invasive PET imaging could have additional clinical benefit is in the imaging of tumour expression of receptors that are targets for specific anti-cancer agents. One of these targets is the epidermal growth factor receptor (EGFR). Expression of this receptor has been correlated with tumour aggressiveness and treatment resistance⁶⁵. EGFR inhibitors, such as the monoclonal antibody cetuximab, are increasingly used in combination with RT and/or chemotherapy to improve treatment outcome compared to RT alone^{66, 67}. The expression of EGFR, however, is heterogeneous throughout the tumour, and can alter under the influence of anti-cancer treatment⁶⁸. Therefore, non invasive imaging of cetuximab binding to cancer cells before and during combined modality therapy could help to select the patients with the highest probability to benefit from treatment and would provide insight in intra-tumour characteristics associated with treatment resistance. Zirconium-89 (⁸⁹Zr) labelled cetuximab has been tested in pre-clinical animal models with excellent results (Figure 10.1)⁶⁹.

Safety results of the phase I trial in this thesis form the basis for future patient studies to evaluate its potential clinical efficacy (Chapter 8). In this study, the maximal tumour to blood ratio for cetuximab uptake was 1.6. Future clinical studies are planned in patients before the start of any antitumour therapy, to allow correlation of EGFR expression at histology with imaging results. These studies will include kinetic imaging to enable the measurement of tumour perfusion. Optimal imaging conditions, including the appropriate loading dose of unlabelled cetuximab, are to be defined.

Figure 10.1 Time series of representative small-animal PET images at indicated time points after injection of ^{89}Zr -cetuximab into HT-29 tumour bearing mouse

Grey arrows indicate tumours. Uptake levels plateaued from 72 h after injection onward. To allow comparison between different time points, images are shown at mid-plane cross-section through tumour. Images are corrected for injected dose and decay and represented as %ID/mL

10.4 Future perspectives

Future developments to further improve outcome of the combined modality treatment of locally advanced lung cancer should adhere to the following principle: Improving tumour control whilst keeping normal tissue toxicity at a constant level. Molecular imaging provides several opportunities to contribute to this goal in the future, which will be discussed below.

Accurate target volume definition is a prerequisite for the further improvement of conformal radiotherapy. PET-CT could optimize different aspects with regard to this subject: delineation of macroscopic tumour and lymph nodes encompassing the GTV, definition of the CTV margin to cover microscopic spread, and finally, the application of a PTV-margin appropriate to cover inaccuracies due to delineation uncertainty, set-up errors and tumour movement¹. Ideally, validation of the delineated tumour volume on PET AND CT should be obtained by correlating it with the tumour volume at pathologic examination, being the gold standard. Data that are currently available are only based on two-dimensional correlations in early stage disease⁷⁰⁻⁷². Three-dimensional models correlating PET and CT findings with pathology are under development, and results in large patient cohorts are pending^{6, 7, 73}. Individually adapted CTV and PTV margins could contribute significantly to personalized optimization of therapy. This thesis proved the feasibility to predict the presence of microscopic spread on basis of the pre-treatment PET/CT scan. Validation of the model is to be awaited, with the final aim to implement the use of individually adapted CTV margins.

The limitations of PET to define the exact tumour extent should be kept in mind. Blurring of the tumour edges does occur due to the poor resolution and motion

artefacts associated with the long acquisition time of PET⁷⁴. The long acquisition time is, however, advantageous with respect to determining the extent of tumour motion. In a phantom study, PET-based treatment volumes resulted in an adequate coverage of the tumour during the whole respiratory cycle, while CT-based volumes harboured the risk of a geographical miss⁷⁵. So-called four dimensional (4D) imaging techniques add respiration movements as a fourth dimension to conventional 3D CT and PET. It allows the incorporation of information on the extent of tumour motion, while optimizing image quality and quantification through reduction of the blurring effect. This provides the opportunity to apply personalized PTV margins depending on the extent of tumour motion. These techniques are presently being evaluated in clinical studies^{76,77}.

The incorporation of PET in RT planning has already shown the potential for dose escalation through a reduction of the radiation fields^{21, 22, 78}. Further optimization could be reached with the prescription of an individually determined maximal tolerable dose instead of applying the same radiation dose in all patients. The concept of individualized radiation dose escalation based on normal tissue constraints has recently been introduced in the clinic. This technique is an ultimate example of individualized treatment intensification at an acceptable toxicity rate. Survival rates of patients treated on basis of this concept with sequential chemo-radiation had survival rates comparable to results with concurrent chemo-radiation schedules, while less toxicity was observed⁷⁹. These results suggest that individual dose escalation with PET-based RT planning can ultimately lead to higher cure rates, which should be the subject of future randomized prospective studies.

Recently, the concept of intratumoral radiation dose distribution has been established as a counterpart to homogeneous irradiation. The rationale behinds this concept is that characteristics associated with radioresistance, such as hypoxia, cell density and proliferation, are heterogeneous across the tumour⁸⁰⁻⁸². Therefore, it is anticipated that selective boosting of these radioresistant areas, whilst decreasing the dose to the less resistant zones, would result in higher tumour control with similar side effects⁸³⁻⁸⁶. FDG is at present the most reasonable tracer to identify therapy-resistant areas within the tumour. Certain key issues before initiating a clinical trial on FDG-PET based dose redistribution have recently been addressed. First, it has been demonstrated that regions with high FDG uptake prior to radiotherapy correspond well with the location of recurrent or persistent tumour after sequential chemo-radiotherapy or radiotherapy alone^{69, 87}. Furthermore, it has been shown that those regions remain stable during a course of RT⁸⁸. Thus, selective boosting of areas of assumed radioresistance identified with FDG-PET before the start of RT appears to be feasible. A multicentre prospective trial has recently been started to evaluate whether selective boosting leads to better treatment out-

come. On basis of the currently available evidence and the wide availability of FDG as a tracer, FDG represents the most appropriate tracer for boosting subvolumes. Other tracers that are more specific to hypoxia (^{18}F -FMISO, [^{18}F]HX4) or proliferation (^{18}F -FLT), however, could be used complementary to FDG^{50, 89-92}, and deserve further investigation for this purpose.

The ultimate method to guide tumour dose distribution would be the development of a voxel control probability map on the basis of tumour characteristics identified on CT and PET with different tracers. For this purpose, pathology correlation studies are underway to examine the relation between the pre-treatment PET/CT characteristics of a voxel and the underlying histopathology (tumour cell density, hypoxia, proliferation). The resulting probability map could be used for dose distribution with the application of a dose modifying factor to each voxel depending on the relative radioresistance, resulting in an optimal “voxel control probability”.

Until now, the majority of patients still suffer from disease progression short after the completion of treatment^{33, 93-96}. In order to avoid ineffective treatment with the associated toxicity, extensive efforts have been made to select these patients before or early during treatment, enabling alternative therapy or treatment modification in cases where the expected benefit of the proposed treatment is insufficient. Different methodologies have been developed in the search for predictive factors of treatment outcome, such as genomics, cytomics, proteomics and identification of predictive imaging features. It remains a challenge to effectively select those parameters that are of up most predictive value. So-called “Computer assisted theranostics” (CAT) provide a method to incorporate different predictive parameters to determine the expected benefit of a particular treatment for each individual patient. Obviously, data obtained with molecular imaging should be included in CAT. Although in the overall patient group with NSCLC, pre-treatment FDG-uptake has prognostic value³⁶, results in advanced stage disease are conflicting, with the most recent study in the largest patient cohort not showing a significant correlation with survival^{42, 43, 97}. Data in SCLC are scarce, but indicate that pre-treatment SUV_{max} has prognostic value⁹⁸. The predictive value of an early metabolic response during induction chemotherapy has been established^{99, 100}. With respect to the predictive value of a metabolic response during radical (chemo-)RT itself, the limited available data show a correlation with survival^{101, 102}. Also in this regard, other tracers are worthwhile to be investigated. Especially proliferation markers, that are less susceptible to uptake in inflammatory tissue, are supposed to have additional value above FDG in response evaluation during and after treatment⁵⁰.

A potential drawback of PET is its associated costs in comparison to anatomic imaging modalities. Health care costs put an increasing burden on the overall economy. In the Netherlands, in 2008, 80 billion Euro was spent on health care, representing

13% of the gross domestic product ¹⁰³. At present, cancer care accounts for approximately 5% of the total health care costs, and this proportion is expected to increase ¹⁰⁴. Different countries increasingly request for evidence regarding the cost-effectiveness of novel therapeutic strategies in order to support its reimbursement, as only finite resources are available. In this light, the costs associated with the introduction of PET in different aspects of the combined modality treatment of lung cancer have to be weighed against its benefits. Information regarding cost-effectiveness can be obtained by an economic evaluation in which different treatment strategies including diagnostics can be compared with respect to both their costs and consequences on the basis of the currently available evidence ¹⁰⁵.

10.5 Conclusions

The aim of this thesis was to address the potential of molecular imaging with PET to optimize combined modality treatment in lung cancer.

FDG-PET improves target volume definition both with respect to the primary tumour and lymph nodes. The only way to accurately assess the extent of microscopic spread is by means of pathology correlation studies. This thesis proved the feasibility to predict the presence of microscopic spread on basis of the pre-treatment PET/CT scan. Finally, adapted CTV margins may be applied for low and high risk patients, resulting in an individually optimized sparing of normal tissue and improved coverage of all microscopic disease.

Selective nodal irradiation (SNI) of FDG-PET positive nodal stations has already been established as the preferred treatment in NSCLC. Results from this thesis suggest that FDG-PET based SNI is also safe in SCLC and is associated with a low toxicity rate, which may provide opportunities for dose escalation.

With regard to the role of PET scanning in the follow-up of lung cancer, it has been shown that an FDG-PET scan 3 months after combined modality therapy for NSCLC potentially improves survival through the detection of progression in a stage that radical treatment is still an option.

Tracers other than ¹⁸F-DG offer potential to select patients with the highest probability to benefit from treatment with hypoxic radio-sensitizers or anticancer agents targeted at receptors on the surface of cancer cells. Furthermore, these tracers could have additional value for treatment response assessment and the visualization of intra-tumour heterogeneity, but more research is needed before they can be clinically implemented.

10.6 References

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CHAPTER 11

Summary

English summary

Lung carcinoma is the third common malignancy in Europe and forms the major cause of cancer death. On basis of its histology, it is broadly divided in two main categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).

Combined modality treatment with radiotherapy (RT) and chemotherapy is the treatment of choice for locally advanced NSCLC patients and for SCLC patients without distant metastases. Traditionally, anatomical imaging modalities are applied for the diagnosis and staging, as well as in the follow-up of lung cancer patients. Anatomical imaging with computed tomography (CT) is very accurate with respect to anatomical information in lung cancer, but it has limitations in certain other areas, such as the distinction between vital tumour and non-malignant tissue. Recently, molecular imaging techniques have been developed, which allow the visualization of molecular processes inside tumour and normal tissues in a non-invasive manner.

In this thesis, different aspects of the potential of molecular imaging with positron emission tomography (PET) to optimize the combined modality treatment of lung cancer are assessed. **Chapter 1** provides a general introduction to the epidemiology and treatment of lung cancer, and the imaging modalities that are used. Furthermore, the outline of the thesis is described. The thesis consists of 3 main parts, which are summarized below.

Part I: FDG-PET-CT based target volume definition to optimize radiotherapy for locally advanced lung cancer

In RT planning, a margin of tissue surrounding the macroscopic tumour is added in all patients to ensure that the area with potential microscopic tumour spread is covered by the radiation field. Microscopic disease spread, however, does not occur in all patients with NSCLC. In **chapter 2**, risk factors for the presence of microscopic disease spread were identified on pre-treatment PET-CT. The pathological specimens of 34 NSCLC patients who underwent lobectomy were examined microscopically for microscopic disease extension outside the macroscopic tumour. Image based risk factors for microscopic disease were identified and a prediction model was developed based on these factors. Mean tumour density on CT and tumour volume on CT were predictive for the presence of microscopic disease. Finally, these risk factors could allow tumour tailored adaptation of the dose to the tissue surrounding the macroscopic tumour. In this way, the balance between local tumour control and sparing of normal tissue in individual patients can be optimised.

In chapter 3 and 4, selective irradiation of FDG-PET positive mediastinal lymph nodes in SCLC was evaluated. Traditionally, all mediastinal nodal areas are irradiated prophylactically, resulting in large treatment volumes. Selective nodal irradiation (SNI) on basis of CT has previously shown to result in an unacceptable amount (11%)

of isolated nodal failures in SCLC. On basis of the hypothesis that fluorodeoxyglucose (FDG)-PET based SNI would improve the coverage of involved lymph nodes, a planning study (**chapter 3**) was performed. Two conformal treatment plans were made with selective irradiation of involved lymph nodes, based on CT and on PET, respectively. A difference in the treatment plan resulting from PET- and CT-based SNI was seen in 24% of patients. Results of the subsequent prospective study are reported in **chapter 4**, in which the safety of PET-based SNI in SCLC was evaluated in 60 patients. Two patients (3%) experienced an isolated nodal failure. The median actuarial overall survival was 19 months. The treatment resulted in a remarkably low percentage (12%) of grade III or worse oesophageal toxicity.

It was concluded that this low rate of isolated nodal failures and toxicity supports the use of PET-based SNI in stage I-III SCLC. Results should be re-evaluated, however, with the application of more conformal RT techniques because these are associated with altered penumbra characteristics.

Part II: Value of FDG-PET-CT in the follow-up of locally advanced lung cancer

In the second part of this thesis, the added value of FDG-PET-CT after curative intent therapy for locally advanced NSCLC was evaluated. In **chapter 5**, we prospectively evaluated whether a PET-CT 3 months after therapy can detect potentially curable progression in 100 NSCLC patients treated with (chemo-)radiation. Progression amenable for retreatment with curative intent was detected in a small proportion of patients (2%), and only in the subgroup that did not have symptoms at the time of scanning. This progression was only detected with PET, not with CT alone.

The results of this study formed the basis for the economic evaluation described in **chapter 6**. The long-term cost-effectiveness of a PET-CT based follow-up was compared with the “usual” follow-up with either a CT scan or repeated chest X-rays. Cost-effectiveness of the different follow-up strategies was expressed in incremental cost-effectiveness ratios (ICERs), calculating the incremental costs per quality adjusted life year (QALY) gained. A PET-CT scan 3 months after treatment turned out to be potentially cost-effective, costing € 69.086 per QALY gained compared to conventional follow-up. As the advantage was confined to the asymptomatic patients, performing a PET-CT in this group only is probably as effective and more cost-effective (€ 42.265 per QALY gained). CT-based follow-up was only slightly more effective than conventional follow-up, resulting in an ICER of € 264.033 per QALY gained.

This part of the thesis thus indicates that a PET-CT scan 3 months after (chemo)radiotherapy with curative intent is a potentially cost-effective follow-up method, and is more cost-effective than CT alone. On basis of the currently avail-

able evidence, it is therefore suggested that an FDG-PET-CT scan 3 months after therapy is to be preferred above CT alone. It is worthwhile to perform additional research to reduce the uncertainty regarding the decision which imaging to perform in the follow-up of NSCLC.

Part III: Novel PET tracers for the non invasive imaging of tumour characteristics

Part III of this thesis consists of two trials evaluating the safety of new PET-tracers directed at two different biological characteristics of cancer cells. **Chapter 7** reports the results of a phase I trial in incurable cancer patients evaluating [^{18}F]HX4, a recently developed hypoxia marker of the 2-nitroimidazole family. A two-dose step study design was used, with 3 patients included in each dose step. PET-CT images of the largest tumour site were acquired at 30, 60 and 120 minutes after injection. No toxicity was observed in any of the patients at either dose level. The median tumour to muscle ratio (TMR) at 120 minutes post-injection was 1.40 (range: 0.63-1.98). In conclusion, [^{18}F]HX4 PET imaging is not associated with any toxicity. Trials are planned to determine the optimal time point of imaging, as in preclinical studies tumour to blood ratios up to 7.6 can be reached when imaging is performed at later time points post-injection.

In **chapter 8**, the safety of Zirconium-89 (^{89}Zr) labelled cetuximab, an antibody against the epidermal growth factor receptor, was evaluated in 7 patients with incurable cancer. The safety of two different dose schedules was tested. Labelled cetuximab administration was preceded by a standard loading dose of unlabelled cetuximab. PET-CT scans were acquired on day 4, 5 and 6 (step 1) and 5, 6, 7 (step 2) post injection. Five of six patients who completed the study experienced skin toxicity, a known side-effect from cetuximab administration. No additional toxicity was reported. The maximal tumour to blood ratio (TBR) was 1.6 (range: 0.42-1.60). Future trials are needed to define optimal imaging conditions, including the appropriate loading dose of unlabelled cetuximab. In the end, visualization and quantification of tumour uptake of cetuximab with PET before and during (chemo-)radiotherapy would have major benefit in the appropriate selection of patients for cetuximab treatment.

Finally, part IV of this thesis provides a discussion on the role of PET in the combined modality therapy of lung cancer. In **chapter 9**, the available literature regarding this subject is reviewed, while **chapter 10** describes the major results of this thesis in the context of the currently existing evidence. Furthermore, perspectives for future research to further improve outcome in locally advanced lung cancer are highlighted.

In conclusion, FDG-PET provides several opportunities to improve the combined modality treatment of locally advanced lung cancer, both in the field of defining the volume to be treated with RT, and in the follow-up after treatment. Prospective randomized trials are encouraged in this field. Tracers other than ^{18}F FDG offer potential to select patients with the highest probability to benefit from treatment with hypoxic radio-sensitizers or anticancer agents targeted at receptors on the surface of cancer cells, but additional research is needed before these tracers can be implemented in clinical practice.

Nederlandse samenvatting

Longkanker is de derde meest voorkomende maligniteit in Europa en is de belangrijkste oorzaak van kankersterfte. Op basis van de celkenmerken wordt longkanker ruwweg ingedeeld in 2 hoofdcategorieën: het niet-kleincellig longcarcinoom (non-small cell lung carcinoma, NSCLC) en het kleincellig longcarcinoom (small cell lung carcinoma, SCLC).

Gecombineerde behandeling met bestraling (radiotherapie, RT) en chemotherapie is de behandeling van keuze voor patiënten met lokaal gevorderd NSCLC of SCLC zonder uitzaaiingen op afstand. Van oudsher worden anatomische beeldvormingstechnieken gebruikt, zowel voor de diagnostiek en stadiëring van longkanker als voor de evaluatie na de behandeling. Anatomische beeldvorming met “computed tomography”, ofwel CT scans, is accuraat wat betreft anatomische informatie, maar kent beperkingen op andere gebieden, zoals het onderscheid tussen vitaal tumorweefsel en niet-kwaadaardig weefsel. Meer recent zijn moleculaire beeldvormingstechnieken ontwikkeld die het mogelijk maken moleculaire processen binnen de tumor en normale weefsels te visualiseren op een niet-invasieve manier. Positron emissie tomografie (PET) is een bekende moleculaire beeldvormingstechniek. PET maakt het mogelijk de verdeling van een radioactieve stof in het lichaam driedimensionaal in beeld te brengen. Voor de beeldvorming van kanker wordt verreweg het meest gebruik gemaakt van radioactief gelabelde suiker (^{18}F -fluorodeoxyglucose, FDG). Kankercellen gebruiken meer suiker dan de meeste niet-kwaadaardige cellen, en dit verschil in suikermetabolisme resulteert in een verhoogde opname van FDG ter plaatse van de tumor. Ook andere moleculen kunnen radioactief worden gemaakt door ze te binden aan een radioactieve tracer. Dit maakt het mogelijk om bepaalde eigenschappen van een tumor te visualiseren die geassocieerd zijn met de agressiviteit van de tumor en de te verwachten respons op antikankerbehandeling. In dit proefschrift werden verschillende mogelijkheden onderzocht om de gecombineerde modaliteitsbehandeling van longkanker te optimaliseren door middel van moleculaire beeldvorming met PET. **Hoofdstuk 1** geeft een algemene introductie in de epidemiologie en de behandeling van longkanker en de beeldvormingstechnieken die worden gebruikt. Ook wordt een overzicht gegeven van de opbouw van het proefschrift. De drie hoofdonderdelen van het proefschrift worden hieronder samengevat.

Deel 1: Definitie van het doelvolume op basis van FDG-PET-CT ter optimalisatie van de radiotherapie voor lokaal uitgebreide longkanker

Bij het plannen van de bestralingsbehandeling wordt altijd een marge weefsel rondom de macroscopisch zichtbare tumor meegenomen om te verzekeren dat het

gebied met mogelijk microscopische tumoruitbreiding wordt meebestraald. Microscopische ziekte-uitbreiding is echter slechts in een deel van de patiënten met NSCLC aanwezig. In **hoofdstuk 2** werden risicofactoren voor de aanwezigheid van microscopische tumoruitbreiding vastgesteld aan de hand van een PET-CT die voor de behandeling werd verricht bij 34 NSCLC patiënten die een lobectomie ondergingen. De pathologische preparaten van deze patiënten werden microscopisch onderzocht op ziekte-uitbreiding buiten de macroscopische tumor. Risicofactoren op PET en/of CT werden geïdentificeerd en op basis van deze factoren werd een predictie-model ontwikkeld. De gemiddelde tumordichtheid op CT en het tumorvolume op CT waren predictief voor de aanwezigheid van microscopische ziekte. Uiteindelijk zouden deze risicofactoren kunnen worden gebruikt om de bestralingsdosis op het weefsel rondom de macroscopische tumor per individu aan te passen. Op deze manier kan het evenwicht tussen lokale tumorcontrole en het sparen van het normale weefsel in elke individuele patiënt worden geoptimaliseerd.

In hoofdstuk 3 en 4 werden de resultaten geëvalueerd van selectieve klierbestraling van FDG-PET positieve mediastinale klieren in SCLC. Bij een conventionele bestraling worden alle mediastinale klierstations profylactisch bestraald, resulterend in grote bestralingsvolumes. In NSCLC is inmiddels aangetoond dat selectieve bestraling van klieren die positief zijn op CT of PET veilig is. Selectieve bestraling van CT-positieve klieren leidde in SCLC echter tot een onacceptabele hoeveelheid (11%) geïsoleerde klierrecidieven. Op basis van de hypothese dat FDG-PET betrouwbaarder is dan CT voor de detectie van positieve klieren in SCLC, werd in **hoofdstuk 3** een planning studie uitgevoerd. Er werden twee conformele bestralingsplannen ontwikkeld, één voor selectieve bestraling van CT-positieve klieren, de andere voor PET-gebaseerde selectieve klierbestraling. In 24% van de patiënten werd een verschil gevonden tussen de bestralingsplannen voor PET- en CT gebaseerde klierbestraling. Vervolgens werd een prospectieve studie uitgevoerd welke beschreven wordt in **hoofdstuk 4**. In deze prospectieve studie werd de veiligheid van PET-gebaseerde selectieve klierbestraling geëvalueerd in 60 SCLC patiënten. Twee van hen (3%) ontwikkelden een geïsoleerd klierrecidief. De mediane overleving bedroeg 19 maanden. De behandeling resulteerde in een opvallend laag percentage patiënten met een graad 3 of hogere slokdarmtoxiciteit.

Het lage aantal geïsoleerde klierrecidieven samen met een lage toxiciteit ondersteunt de toepassing van PET-gebaseerde selectieve klierbestraling in stadium I-III SCLC. Indien in de toekomst meer conformele bestralingstechnieken worden toegepast zullen resultaten opnieuw moeten worden geëvalueerd aangezien deze nieuwe technieken gepaard gaan met een andere dosisverdeling rondom het doelvolumen van de radiotherapie.

Deel II: Waarde van FDG-PET in de evaluatie na behandeling van het lokaal uitgebreide longcarcinoom

In het tweede deel van het proefschrift werd de toegevoegde waarde onderzocht van een FDG-PET-CT na curatieve behandeling van het lokaal uitgebreide longcarcinoom. In **hoofdstuk 5** werd bij 100 NSCLC patiënten prospectief beoordeeld of een PET-CT 3 maanden na de behandeling progressie kan detecteren die in aanmerking komt voor herbehandeling met curatieve opzet. In een klein aandeel (2%) van de patiënten werd progressie vastgesteld die in opzet curatief kon worden behandeld. Dit was alleen het geval bij de patiënten die asymptomatisch waren op het moment van de PET-CT scan. Progressie werd bij deze patiënten alleen gedetecteerd met PET, niet met uitsluitend de CT-scan.

De resultaten van deze studie vormden de basis van de economische evaluatie die wordt beschreven in **hoofdstuk 6**. In deze studie werd de kosteneffectiviteit op de lange termijn vergeleken van verschillende follow-up strategieën: de PET-CT gebaseerde follow-up, een follow-up met CT-scan, of een conventionele follow-up waarbij alleen een X-thorax wordt vervaardigd. De kosteneffectiviteit van de verschillende strategieën werd uitgedrukt in zogenaamde incrementele kosteneffectiviteitsratio's (ICER's). Deze ratio geeft de additionele kosten aan per gewonnen levensjaar gecorrigeerd voor de kwaliteit van leven gedurende dit jaar (quality adjusted life-year, QALY). Uit deze analyse kon worden afgeleid dat een PET-CT scan 3 maanden na behandeling een potentieel kosteneffectieve methode is vergeleken met conventionele follow-up, resulterend in een ICER van € 69.086 per gewonnen QALY. Aangezien het voordeel beperkt was tot de groep asymptomatische patiënten, is het waarschijnlijk even effectief en meer kosteneffectief om alleen een PET-CT te verrichten in deze patiëntengroep (€ 42.265 per QALY). CT-gebaseerde follow-up was in geringe mate effectiever dan conventionele follow-up, resulterend in een ICER van € 264.033 per QALY.

Concluderend geeft deel II van dit proefschrift aan dat een PET-CT 3 maanden na curatieve (chemo)radiotherapie een potentieel kosteneffectieve methode is voor de evaluatie na behandeling, en meer kosteneffectief is dan alleen een CT-scan. Op basis van het beschikbare bewijs is daarom een FDG-PET-CT te prefereren boven alleen een CT-scan 3 maanden na behandeling. Aanvullend onderzoek is zinvol ter reductie van de onzekerheid in de besluitvorming rond beeldvorming in de follow-up.

Deel III: Nieuwe PET-tracers voor de niet-invasieve beeldvorming van tumoreigenschappen

Deel III van dit proefschrift bestaat uit 2 studies die de veiligheid van nieuwe PET-tracers evalueren, beide gericht op specifieke biologische eigenschappen van kankercellen. **Hoofdstuk 7** beschrijft de resultaten van een fase I studie met ^{18}F -HX4 in incurabele kankerpatiënten. ^{18}F -HX4 is een recent ontwikkelde radioactieve merkstof voor cellen met zuurstoftekort (hypoxie), behorend tot de familie van 2-nitroimidazolen. Er werd een studieopzet met 2 dosisstappen gebruikt. In elke stap werden 3 patiënten geïncubeerd. PET-CT beelden van de grootste tumorlokalisatie werden verkregen op 30, 60 en 120 minuten na injectie van ^{18}F -HX4. In geen van de geïncubeerde patiënten werd toxiciteit geobserveerd. De mediane tumor-spiers ratio 120 minuten na injectie was 1.40 (range: 0.63-1.98). Uit deze studie kan worden geconcludeerd dat PET met ^{18}F -HX4 niet gepaard gaat met toxiciteit. Momenteel worden studies opgezet met als doel het optimale tijdstip voor de PET scan te bepalen. In preklinische studies met proefdieren zijn tumor-bloed ratio's tot een waarde van 7.6 gedetecteerd indien op latere tijdstippen na injectie werd gescand. In **hoofdstuk 8** wordt de veiligheid geëvalueerd van cetuximab gelabeld met de radioactieve tracer Zirconium-89 (^{89}Zr). Cetuximab is een antilichaam gericht tegen de epidermale groeifactor receptor (EGFR). Activatie en overexpressie van EGFR in kankercellen is geassocieerd met de ontwikkeling van resistentie voor radiotherapie en chemotherapie. De toxiciteit van twee verschillende doseringsschema's van ^{89}Zr -cetuximab werd onderzocht. In beide schema's werd de dosering van het gelabelde cetuximab voorafgegaan door een standaard "laaddosis" ongelabeld cetuximab. Op dag 4, 5 en 6 (stap 1), of dag 5, 6 en 7 (stap 2) na injectie werden PET-CT beelden verkregen. Vijf van de zes patiënten ontwikkelden huidtoxiciteit, een bekende bijwerking van cetuximab. Additionele toxiciteit ten gevolge van de toediening van het gelabelde cetuximab werd niet geobserveerd. De maximale tumor-bloedratio was 1.6 (range: 0.42-1.60). Toekomstige studies zijn nodig om de optimale beeldvormingsomstandigheden te definiëren, waaronder de optimale laaddosis ongelabeld cetuximab. Uiteindelijk kan de visualisatie en de kwantificatie van cetuximabopname door de tumor met PET voor en tijdens (chemo)radiotherapie een belangrijke invloed hebben op een juiste selectie van patiënten voor behandeling met cetuximab.

Tenslotte wordt in deel IV van dit proefschrift de rol van PET in de gecombineerde modaliteitsbehandeling van longkanker bediscussieerd. **Hoofdstuk 9** bestaat uit een review van de beschikbare literatuur over dit onderwerp. **Hoofdstuk 10** beschrijft de belangrijkste resultaten van het proefschrift in het licht van het momenteel beschikbare bewijs. Hiernaast worden toekomstperspectieven beschreven ten aanzien van verder wetenschappelijk onderzoek.

Concluderend biedt FDG-PET verschillende mogelijkheden om de gecombineerde modaliteitsbehandeling van het lokaal gevorderde longcarcinoom te verbeteren. Dit geldt zowel op het gebied van het definiëren van het doelgebied voor radiotherapie, als voor de evaluatie na de behandeling. Prospectieve gerandomiseerde studies op dit gebied worden aanbevolen. Andere tracers dan ^{18}F FDG bieden de mogelijkheid om patiënten te selecteren met de hoogste kans op baat van behandeling met radiosensitizers gericht op hypoxie of middelen gericht tegen receptoren op het oppervlak van kankercellen. Aanvullend wetenschappelijk onderzoek is echter noodzakelijk voordat deze tracers in de klinische praktijk kunnen worden geïntroduceerd.

Appendices

Dankwoord

Terugkijkend op 3 jaar onderzoek moet ik toch echt concluderen dat de tijd is omgevlogen. Dit wil natuurlijk niet zeggen dat alle onderzoeksresultaten zonder slag of stoot tot stand zijn gekomen. Ik wil dan ook iedereen bedanken die direct of indirect hieraan heeft bijgedragen.

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Curriculum vitae

Judith van Loon was born on the 29th of February, 1980, in Venray, the Netherlands and grew up in Overloon. In 1998, she graduated cum laude from the Raayland College in Venray. In the same year, she started her medical training at the Maastricht University. She was member of the administrative board of the Medical Inter-facultary Conference ("MIC") in 2001. In the academic year 2002-2003, she was treasurer of the Student Rowing Club "M.S.R.V. Saurus". Her final internship was performed at the radiation oncology department of the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam. After obtaining her medical degree in November 2005, she started her specialty training in radiation oncology at the Maastricht Clinic (dr. J. Jager and prof.dr. Ph. Lambin). During her residency, she got the opportunity to perform the PhD project described in this thesis, for which she suspended her training position for the period of three years. From August 2010, she continued her residency which she will finish at the end of 2013. She will perform an elective at the National Institute for Health and Clinical Excellence (NICE) in London for the period of November 2010 until January 2011 on clinical effectiveness and costs of innovations in radiation oncology.

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