# Patients with Resectable Lung Cancer:

# Preoperative Selection and Postoperative Function

Sietske Anke Smulders

Smulders, SA

Patients with resectable lung cancer: preoperative selection and postoperative function

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# Patients with Resectable Lung Cancer:

# Preoperative Selection and Postoperative Function

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door

**Sietske Anke Smulders**

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voor pap en mam,

en eigenlijk ook voor mezelf…

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# General Introduction and Outline of the Thesis

## Introduction

In the 20th century, the incidence and mortality of lung cancer has increased so dramatically that it can be considered one of the major epidemics of the former century[1]. Lung cancer continues to be the leading cause of death from cancer throughout the world, with a median survival rate of only 8 months and 13% of patients still alive five years after the diagnosis[2-4]. Highest cure rates result from surgical resection, especially for stage I and II non-small cell lung cancer (NSCLC) patients, with 5-year survival rates of 40-50%. However, a potentially curative resection is only possible in about 25% of new cases. Whether or not patients are eligible for surgery, depends on the tumors' resectability (stage of the disease) and the patients' operability (physical condition).

### *Resectability and NSCLC staging*

TNM-stages for NSCLC are classified as I-IV, with decreasing survival rates (Tables 1 and 2). Generally, patients with stages I and II (T1 and T2 tumors without mediastinal lymph node involvement, N0-1 disease) are considered to be eligible for potentially curative surgical resection. The presence of mediastinal lymph node metastases (N2-3 disease, stages IIIA and IIIB) and locally advanced tumor growth are ominous prognostic signs and considered contraindications for primary surgical resection. Stages III and IV (distant metastases) are generally considered incurable and are predominantly treated with chemo- and/or radiotherapy in clinical or experimental settings, or not treated at all. Because of these different survival rates and the impact on choice of therapy, proper staging is of utmost importance. Staging of NSCLC is done by imaging modalities (*computed tomography* (CT) *scanning*, *F-18-deoxyglucose positron emission tomography* ($^{18}$FDG-PET) *scanning*, *magnetic resonance* (MR) *imaging*) and by (minimally) invasive tools like *bronchoscopy, transbronchial needle aspiration* (TBNA), *mediastinoscopy* and, more recently, *transoesophageal ultrasound-guided fine needle aspiration* (EUS-FNA) and *endobronchial ultrasound* (EBUS).

**Table 1 TNM Descriptors**

| | |
|---|---|
| **Primary tumor (T)** | |
| **Tx** | Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy |
| **T0** | No evidence of primary tumor |
| **Tis** | Carcinoma *in situ* |
| **T1** | Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus * (*ie*, not in the main bronchus) |
| **T2** | Tumor with any of the following features of size or extent:<br>> 3 cm in greatest dimension<br>Involves main bronchus, ≥ 2 cm distal to the carina<br>Invades the visceral pleura<br>Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung |
| **T3** | Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung |
| **T4** | Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural or pericardial effusion ǂ, or with satellite tumor nodule(s) within the ipsilateral primary tumor-lobe of the lung |
| **Regional lymph nodes (N)** | |
| **Nx** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumor |
| **N2** | Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s) |
| **N3** | Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |
| **Distant metastases (M)** | |
| **Mx** | Presence of distant metastasis cannot be assessed |
| **M0** | No distant metastasis |
| **M1** | Distant metastasis present § |

** The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.*

*ǂ Most pleural effusions associated with lung cancer are due to tumor. However, there are few patients in whom multiple cytopathologic examinations of pleural fluid show no tumor. In these cases, the fluid is nonbloody and is not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2 or T3. Pericardial effusion is classified according to the same rules.*

*§ Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1.*

**Table 2 Stage groupings - TNM subsets ***

| Stage | TNM subset |
|---|---|
| **0** | *Carcinoma in situ* |
| **IA** | T1N0M0 |
| **IB** | T2N0M0 |
| **IIA** | T1N1M0 |
| **IIB** | T2N1M0 |
| | T3N0M0 |
| **IIIA** | T3N1M0 |
| | T1N2M0 |
| | T2N2M0 |
| | T3N2M0 |
| **IIIB** | T4N0M0 |
| | T4N1M0 |
| | T4N2M0 |
| | T1N3M0 |
| | T2N3M0 |
| | T3N3M0 |
| | T4N3M0 |
| **IV** | Any T any N M 1 |

** Staging is not relevant for occult carcinoma, designated TxN0M0*

A whole body $^{18}$FDG-PET to evaluate the mediastinum is recommended for NSCLC patients who are candidates for surgery[5]. Controversy exists among the use of PET imaging in patients with peripheral cT1N0 tumors because evidence indicates that the incidence of finding either unsuspected distant or mediastinal metastases on PET in these patients is quite low. In patients with mediastinal lymph node enlargement on CT, mediastinoscopy (or other invasive biopsy) is likely to be indicated regardless of the PET findings in the mediastinum[6]. Especially in certain subgroups of patients (those with tumors adjacent to the mediastinum, adenocarcinomas, or N1 nodal involvement), physicians seem to argue whether or not mediastinoscopy is needed in case of a negative PET result.

Cervical mediastinoscopy, considered as 'the gold standard' for detecting N2-3 disease, is recommended to confirm metastatic disease in patients with a PET scan that is positive (15-20% false positive[6]) in the mediastinum and in patients with a PET scan negative in the mediastinum in whom confirmation of the absence of mediastinal lymph node metastases is deemed desirable[5-7]. Ideally, cervical mediastinoscopy at least requires sampling of lymph nodes from stations 4 (left and right lower paratracheal) and 7 (subcarinal) routinely, along with the nodes from station 2 (left and right upper paratracheal), if accessible, as described in the American Thoracic Staging system[8] (Figure 1). In case of a primary pulmonary tumor without evidence for distant or mediastinal metastases, patients are considered eligible for resection. Patients will only benefit from a complete resection, which means complete removal (macro- and microscopically) of all malignant tissue (pulmonary and lymph nodes).

*Operability and physical condition*

Whether or not to perform a resection depends, besides the stage of the disease, on the patients' physical condition, comorbidity and cardiopulmonary function (operability). The pulmonary physician preoperatively tries to predict which patients will survive a pulmonary resection and not be left a respiratory cripple, experiencing incapacitating dyspnoea and being unable to carry out activities of daily living, with obviously very poor quality of life. On the other hand, what is an unacceptable morbidity and surgical mortality in a disease with a 100% mortality unless treated surgically[9]? In the past, numerous studies have addressed this issue and have tried to identify the pulmonary function limits below which patients are defined inoperable[10-14]. This has led to widely accepted algorithms for the assessment of the cardiorespiratory reserves of lung resection candidates, like the one introduced by Bolliger et. al. in 1998[15].

Since lung cancer patients are often old and almost always smokers, presence of comorbidity (presence of other diseases besides lung cancer) in these patients is frequent. Just like decreased (cardio)pulmonary function, presence of comorbidity may lead to complications during or after treatment (surgically or systemic). Because of this,

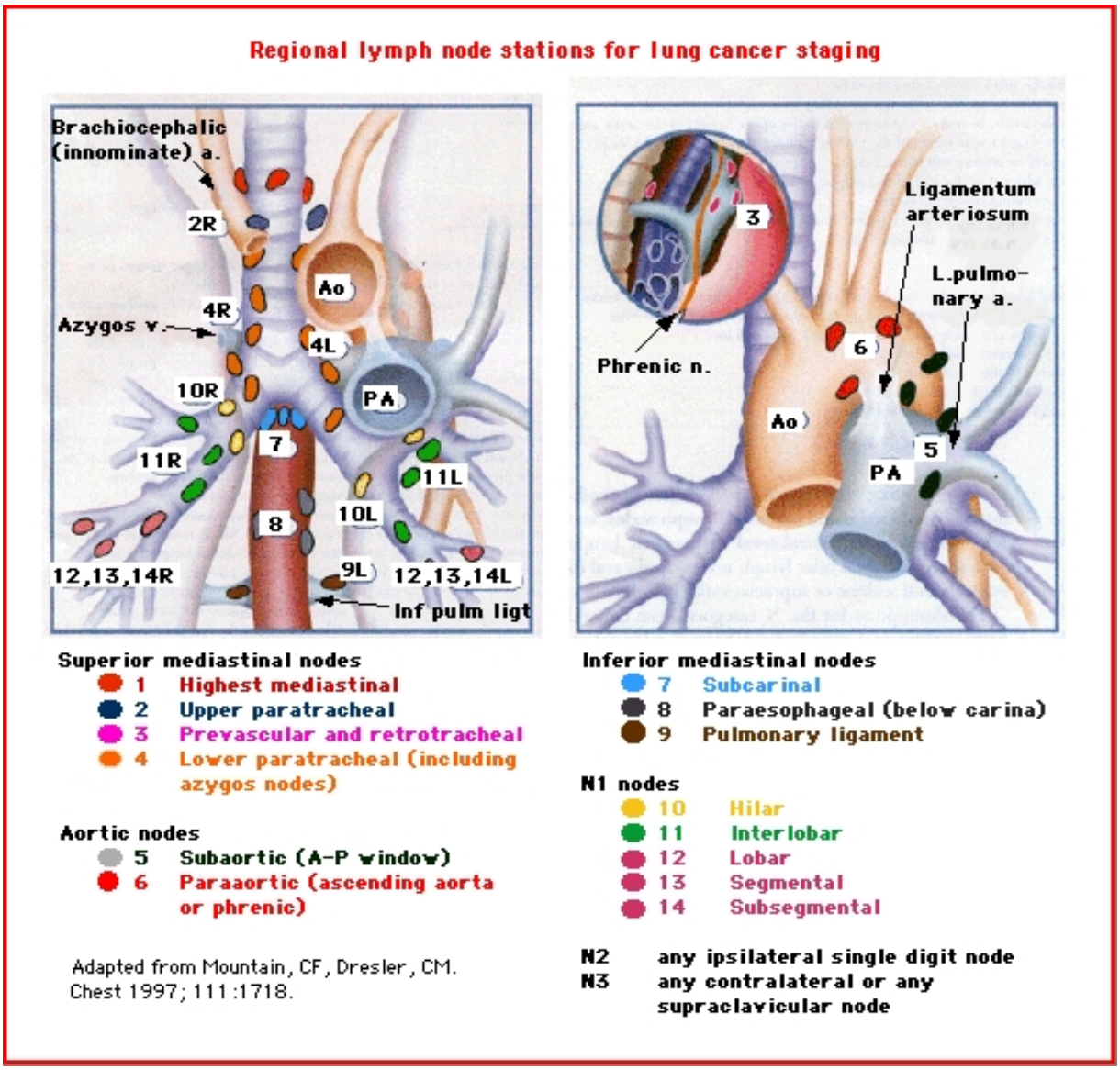


***Figure 1***

*Regional lymph node stations for lung cancer staging. Adapted from Mountain CF, Dresler CM, Chest 1997; 111: 1718*

elderly patients and patients with comorbidity are often treated less aggressively compared to younger patients or patients without comorbidity[16;17].

*Postoperative aspects*

Depending on the size and localisation of the tumor, more or less pulmonary tissue will have to be removed, in order to obtain a complete resection. Major lung resection,

especially pneumonectomy, causes a significant decrease in cardiopulmonary function and still has a high mortality rate of approximately 10-12% for right-sided procedures and 0-3,5% for left-sided procedures[18]. Right-sided pneumonectomy is more likely associated with the development of complications, like bronchopleural fistula, empyema and postpneumonectomy pulmonary edema, and therefore has higher mortality rates. Normally, after pneumonectomy, forced vital capacity (FVC) and forced expiratory volume in 1 second ($FEV_1$) decrease by 30-40% while maximum oxygen uptake during exercise ($VO_2$max) decreases by approximately 20%[18].

Furthermore, immediately after pneumonectomy, right ventricular (RV) dysfunction occurs[19-23]. Several studies have shown RV enlargement and a decreased RV ejection fraction the first few days after surgery[21-23]. Increasing RV afterload, due to rising pulmonary artery pressure and pulmonary vascular resistance, is supposed to be the main cause of this RV dysfunction. Successful adaptation of the RV to increased pulmonary blood flow depends upon the ability of the pulmonary vascular bed to expand. Failure of this mechanism results in increased intravascular pressure which can lead to the development of pulmonary hypertension and eventually RV failure[24]. Nowadays, cardiovascular magnetic resonance (CMR) imaging offers a unique possibility to study the cardiac function in an altered geometric position of the heart. CMR not only is accurate and reproducible in normal as well as abnormal ventricles[25], but also free of ionising radiation and independent of the geometric assumptions and acoustic windows that limit echocardiography[26].

In summary, several different aspects (like the TNM stage, the patients' cardiopulmonary condition and the presence of comorbidity) influence treatment choice in patients with NSCLC. Highest cure rates result from surgical resection, however major lung resection, especially pneumonectomy, extensively influences cardiac and pulmonary function and still has one of the highest mortality rates that may be encountered by patients submitted to non-emergent surgery.

**Outline of the Thesis**

This thesis contains studies on two different aspects in lung cancer patients, described in two parts. In the first part, aspects influencing the preoperative selection of patients that are eligible for resection are studied. The second part consists of studies regarding postoperative cardiopulmonary function in surgically treated patients.

**Part I** consists of studies on aspects influencing treatment choice, like the TNM stage and comorbidity. With the rising mean age more patients will be diagnosed with one or more other serious diseases at the time of lung cancer diagnosis (comorbidity). Little is known about either the best way to treat elderly patients with comorbidity or the outcome of treatment. The effect of comorbidity on treatment choice and prognosis of elderly patients with NSCLC is studied in **Chapter 1**.

Even after the introduction of $^{18}$FDG-PET, mediastinoscopy remains the gold standard for detecting N2-3 disease. However, with an accuracy of 92% or better, mediastinoscopy is not always perfect and its result may be surgeon dependent. Also, results from large studies in academic centers are probably not totally concordant with all-day clinical practice. In **Chapter 2**, we investigated the accuracy of mediastinal staging procedures in daily practice. For this, we studied the degree of adherence of treating physicians to the accepted staging procedures in their hospitals. And, in case mediastinoscopy was performed, how often this was performed according to gold standards.

In the past years, $^{18}$FDG-PET is increasingly used to stage NSCLC patients. Addition of FDG-PET to conventional workup of NSCLC patients who are possible candidates for surgical resection can be very useful in guiding mediastinal biopsy during mediastinoscopy and reduces the number of futile thoracotomies[27]. Because $^{18}$FDG-PET became available in our hospital in 2002, we also studied (**Chapter 3**) whether the implementation of PET in daily practice has resulted in improved performance and adherence to preoperative surgical mediastinal staging procedures, compared to the results from **Chapter 2**. Results from PET studies pertaining to its accuracy in

mediastinal staging are robust, but as the technique is disseminating and becoming more available in even the smaller hospitals, observer variation and learning curves need to be documented (**Chapter 4**).

**Part II** consists of studies regarding cardiac and pulmonary function after pneumonectomy for lung cancer. Several formulas are in use aiming to predict postoperative lung function after resection. These formulas were validated relatively soon after the operation and in a small number of patients after pneumonectomy, nevertheless, they are worldwide accepted in guidelines. Since recruitment occurs after lung resection, especially after pneumonectomy, it is still unclear what the validity of these formulas might be for predicting lung function at a much later stage. In **Chapter 5** we investigated the validity of these formulas in pneumonectomy patients surviving for more than two years after the operation.

In contrast to postoperative pulmonary function studies, relatively few studies have investigated postoperative cardiac function in patients after pneumonectomy. Immediately after pneumonectomy, right ventricular (RV) enlargement occurs due to increased RV afterload. We wondered whether and to what extent the RV function recovers and how long it takes before this recovery is complete. Also, does cardiac function differ between patients after left- or right-sided pneumonectomy? The literature agrees to the fact that pulmonary artery pressure and pulmonary vascular resistance are normal or slightly increased at rest, but increase on exertion. However, whether or not this chronically increased state of stress also causes RV hypertrophy, is unclear. Therefore, to answer all these questions, we studied cardiac function in patients immediately after and three months after pneumonectomy (**Chapter 6**) and also, more than 5 years after pneumonectomy (**Chapter 7**). Next to this, we investigated whether the extreme anatomical changes that sometimes occur after pneumonectomy have influence on cardiac function and whether these changes differ between patients after right- or left-sided pneumonectomy (**Chapter 7**). At the end of this thesis, in **Chapters**

**8.1**, **8.2 and 8.3**, several patients with unusual features after pneumonectomy are presented and discussed.

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# Part I

# Preoperative Selection

Chapter 1

# Effect of Comorbidity on the Treatment and Prognosis of Elderly patients with NSCLC

Maryska LG Janssen-Heijnen [1], Sietske A Smulders [2]

VEPP Lemmens [1], Frank WJM Smeenk [2]

HJAA van Geffen [3], JWW Coebergh [1,4]

**Thorax 2004; 59: 602-607**

[1] Eindhoven Cancer Registry, Comprehensive Cancer Center South (IKZ), Eindhoven

[2] Department of Pulmonary Diseases, Catharina Hospital, Eindhoven

[3] Jeroen Bosch Hospital, Department of Surgery, 's-Hertogenbosch

[4] Erasmus University Medical Center, Department of Public Health, Rotterdam

The Netherlands

**Abstract**

*Background:* With the rising mean age more patients will be diagnosed with one or more other serious diseases at the time of lung cancer diagnosis. Little is known about the best way to treat elderly patients with comorbidity or the outcome of treatment. This study was undertaken to evaluate the independent effects of age and comorbidity on treatment and prognosis in patients with non-small cell lung cancer (NSCLC).

*Methods:* All patients with NSCLC diagnosed between 1995 and 1999 in the southern part of the Netherlands (N=4072) were included.

*Results:* The proportion of patients with localised NSCLC who underwent surgery was 92% in patients younger than 60 years and 9% in those aged 80 years or older. In patients aged 60-79 years this proportion also decreased with comorbidity. In patients with non-localised NSCLC the proportion receiving chemotherapy was considerably higher for those aged less than 60 years (24%) than in those aged 80 years or older (2%). The number of comorbid conditions had no significant influence on the treatment chosen for patients with non-localised disease. Multivariable survival analyses showed that age, tumor size and treatment were independent prognostic factors for patients with localised disease, and stage of disease and treatment for those with non-localised disease. Comorbidity had no independent prognostic effect.

*Conclusions:* It is questionable whether the less aggressive treatment of elderly patients with NSCLC is justified.

## Introduction

Lung cancer occurs mainly in the elderly. Because of a demographic shift towards an older population and improved survival of patients with cardiovascular diseases, more elderly people are at risk of developing lung cancer. The proportion of patients aged 70 years or older has increased from 26% in 1970 to 43% in 2000[1]. With the rising mean age, more patients will be diagnosed with one or more other serious diseases at the time of lung cancer diagnosis (comorbidity)[2]. Comorbidity may lead to complications during or after surgical and/or systemic treatment[3-6]. The clinical management of lung cancer is therefore becoming increasingly complex. Furthermore, these patients are often excluded from clinical trials. This means that little is known about the best way to treat elderly patients with comorbidity and about the outcome of treatment such as complications and survival.

Population based cancer registries are able to facilitate studies of these patients if they collect data directly from medical records. The Eindhoven Cancer Registry, at the request of clinicians, has been collecting data on clinically relevant concomitant diseases for all cancer patients diagnosed since 1993 in the southern part of the Netherlands. We report here on the influence of age, stage of disease and comorbidity on the choice of treatment and survival of patients with non-small cell lung cancer (NSCLC).

## Patients and Methods

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with about two million inhabitants. Since 1993 serious comorbidity with an impact on prognosis has also been recorded for all patients according to a slightly adapted version of the index developed by Charlson et al. (Table 1)[7]. The data were extracted from previous admissions, letters from and to other specialists, medical history and preoperative screening. Comorbidity was defined as diseases that were present at the time of cancer diagnosis.

**Table 1 Classification of comorbidity, according to an adapted version of the list of Charlson et al. (1987)**

| |
|---|
| Chronic Obstructive Pulmonary Diseases (COPD) |
| Cardiovascular diseases |
| - myocardial infarction, cardiac decompensation, angina pectoris |
| - peripheral arterial disease, intermittent claudication, abdominal aneurysm |
| Cerebrovascular diseases (cerebrovascular accident, hemiplegia) |
| Other malignancies (except basal cell skin carcinoma) |
| Hypertension (medically treated) |
| Diabetes mellitus |
| Other: |
| - soft tissue diseases (Besnier Boeck disease, Wegener's disease, SLE (systemic lupus erythematosis)) |
| - rheumatoid arthritis (only severe) |
| - kidney diseases (chronic glomerulonephritis, chronic pyelonephritis) |
| - bowel diseases (Crohn's disease, ulcerative colitis) |
| - liver diseases (cirrhosis, hepatitis) |
| - dementia |
| - chronic infections |

Patients with NSCLC diagnosed between 1995 and 1999 (N=4076) were included. Those with cancer diagnosed at post mortem examination (N=138) were excluded.

Clinical tumor staging was performed according to the Tumor-Node-Metastasis (TNM) system of the Union Internationale Contre le Cancer, version 4[8]. Tumors were classified as localised (stages I and II) and non-localised (stages III and IV).

Non-small cell lung tumors were classified as squamous cell carcinoma, adenocarcinoma and large cell undifferentiated carcinoma, according to the WHO classification[9].

Treatment for localised disease was classified as surgery (with or without adjuvant radiotherapy), radiotherapy alone and 'other or none'. Treatment was only classified as surgery when the tumor was resected during surgical intervention; diagnostic surgery was

not included. For patients with non-localised disease treatment was classified as surgery (with or without radiotherapy), radiotherapy alone, chemotherapy (with or without radiotherapy) and 'other or none'.

Data on vital status were available up to 1 April 2002. In addition to passive follow up via the hospitals, information was also obtained from the municipal registries in the area of the Eindhoven Cancer Registry and the Central Bureau for Genealogy, an institution that collects data on all deceased Dutch citizens via the civil municipal registries. In this way, information on patients who moved outside the registry area was also obtained. Patients who died outside the Netherlands were lost to follow up. The estimated proportion of these patients was 0.2%. Of 4076 patients with NSCLC 637 (16%) were still alive and 3439 (84%) were dead at the end of the study.

*Analysis of data*

Overall survival rates were computed (3 year for patients with localised disease and 1 year for patients with non-localised disease). Survival time was defined as the time from diagnosis to death or the end of the study (if the patient was still alive on 1 April 2002). The log rank test was performed to evaluate significant differences between survival curves in univariate analyses. For evaluation of the independent effects of the prognostic factors, a multivariable Cox regression model was built. The models were stratified according to stage. This was done because both the guidelines for treatment of localised NSCLC and the survival rates are clearly different from those for non-localised NSCLC. Since interaction terms with age were not statistically significant, multivariable analyses were not stratified according to age. The independent prognostic effects of age, sex, stage of disease and comorbidity were first estimated using a model without treatment. Treatment was then included in the model to investigate whether the prognostic effects of age and comorbidity could be fully explained by less aggressive treatment. With respect to comorbidity, the prognostic effects of both the

**Table 2 General characteristics of the patients**

| | | Age <60 | | Age 60-69 | | Age 70-79 | | Age 80+ | |
|---|---|---|---|---|---|---|---|---|---|
| | | **N** | ***(%)*** | **N** | ***(%)*** | **N** | ***(%)*** | **N** | ***(%)*** |
| Gender | Male | 732 | ***(68)*** | 1230 | ***(84)*** | 1095 | ***(86)*** | 230 | ***(85)*** |
| | Female | 344 | ***(32)*** | 233 | ***(16)*** | 172 | ***(14)*** | 40 | ***(15)*** |
| Histology | Squamous cell | 389 | ***(36)*** | 725 | ***(50)*** | 657 | ***(52)*** | 158 | ***(58)*** |
| | Adenocarcinom | 388 | ***(36)*** | 376 | ***(26)*** | 287 | ***(23)*** | 40 | ***(15)*** |
| | Large cell undiff. | 299 | ***(28)*** | 362 | ***(25)*** | 323 | ***(25)*** | 72 | ***(27)*** |
| Stage | Localised [1] | 251 | ***(23)*** | 403 | ***(28)*** | 366 | ***(29)*** | 82 | ***(30)*** |
| | Non-localised | 710 | ***(66)*** | 848 | ***(58)*** | 694 | ***(55)*** | 128 | ***(48)*** |
| | Unknown | 115 | ***(11)*** | 212 | ***(14)*** | 207 | ***(16)*** | 60 | ***(22)*** |
| Comorbidity (N) | 0 | 555 | ***(52)*** | 462 | ***(32)*** | 303 | ***(24)*** | 66 | ***(24)*** |
| | 1 | 302 | ***(28)*** | 506 | ***(35)*** | 449 | ***(35)*** | 88 | ***(33)*** |
| | 2+ | 134 | ***(12)*** | 397 | ***(27)*** | 463 | ***(37)*** | 95 | ***(35)*** |
| | Unknown | 85 | ***(8)*** | 98 | ***(7)*** | 52 | ***(4)*** | 21 | ***(8)*** |
| Comorbidity (type) [2] | COPD | 159 | ***(15)*** | 362 | ***(25)*** | 349 | ***(28)*** | 72 | ***(27)*** |
| | Cardiovascular | 122 | ***(11)*** | 338 | ***(23)*** | 382 | ***(30)*** | 80 | ***(30)*** |
| | Previous cancer | 88 | ***(8)*** | 191 | ***(13)*** | 230 | ***(18)*** | 50 | ***(19)*** |
| | Hypertension | 84 | ***(8)*** | 209 | ***(14)*** | 191 | ***(15)*** | 29 | ***(11)*** |
| | Diabetes | 47 | ***(4)*** | 110 | ***(8)*** | 130 | ***(10)*** | 31 | ***(11)*** |
| | Other | 93 | ***(9)*** | 188 | ***(13)*** | 231 | ***(18)*** | 44 | ***(16)*** |

[1] *Stage I or II*

[2] *More diseases per patient possible*

number of comorbid conditions and the specific diseases/combinations of diseases were evaluated. Survival generally decreases with age and the prevalence of comorbidity increases with age. We therefore also calculated relative survival rates for each age group according to stage. Relative survival is an estimation of disease specific survival. It reflects survival of cancer patients, adjusted for survival in the general population with the same age structure. Relative survival is calculated as the ratio of the observed to the expected rates[10].

Expected survival rates were calculated from life tables for regional male and female populations with the same 5 year age distribution.

**Results**

The general characteristics of the patients are shown in Table 2. The male:female ratio increased dramatically from 2.1 for patients younger than 60 years to 6.4 for patients aged 70-79 years and then decreased to 5.8 for patients aged 80 years or older. The proportion with squamous cell carcinoma was clearly higher among the elderly. The prevalence of concomitant diseases for NSCLC patients clearly increased with age; in patients aged 70 years or older the prevalence of comorbidity was 73% for men and 61% for women. The most frequent comorbid conditions in men aged 70 or older were cardiovascular diseases (31%) and COPD (29%); in older women the most common conditions were cardiovascular diseases (22%), hypertension (22%) and COPD (20%).

The proportion of patients with localised NSCLC who underwent surgery with or without radiotherapy was only 9% of those aged 80 or older versus 92%, 79% and 61% of the age groups <60, 60-69 and 70-79, respectively. In patients aged 60-69 and 70-79 the proportion who underwent surgery also decreased with comorbidity (Figure 1a). In patients aged 60-69 the proportion who underwent surgery was especially low in the presence of COPD alone (67%), COPD and cardiovascular disease (58%) or COPD and previous cancer (33%), compared to 88% in patients without comorbidity. For patients aged 70-79 the proportion who underwent surgery was 78% of those without comorbidity but only 59% in patients with cardiovascular disease, 55% of those with previous cancer, 53% of those with previous cancer in combination with COPD and 40% of those with COPD. Most patients with non-localised NSCLC received radiotherapy alone (Figure 1b). The proportion receiving chemotherapy (with or without radiotherapy) was considerably higher in patients younger than 60 years (24%) than in those aged 80 or older (2%). More elderly patients did not receive any treatment. The number of comorbid conditions had no significant influence on

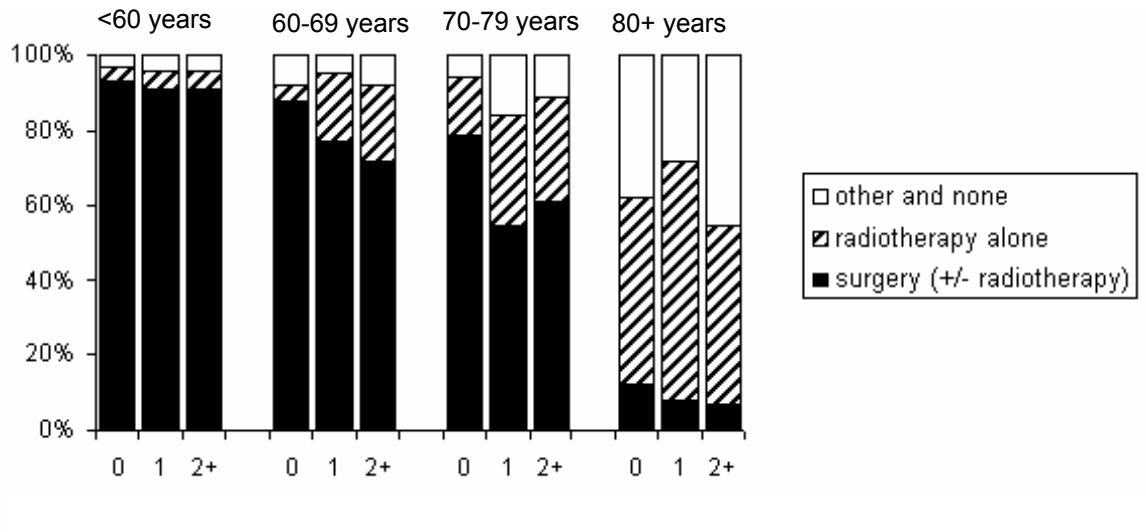


**Figure 1A**

*Treatment of localised NSCLC, according to age, comorbidity and stage*

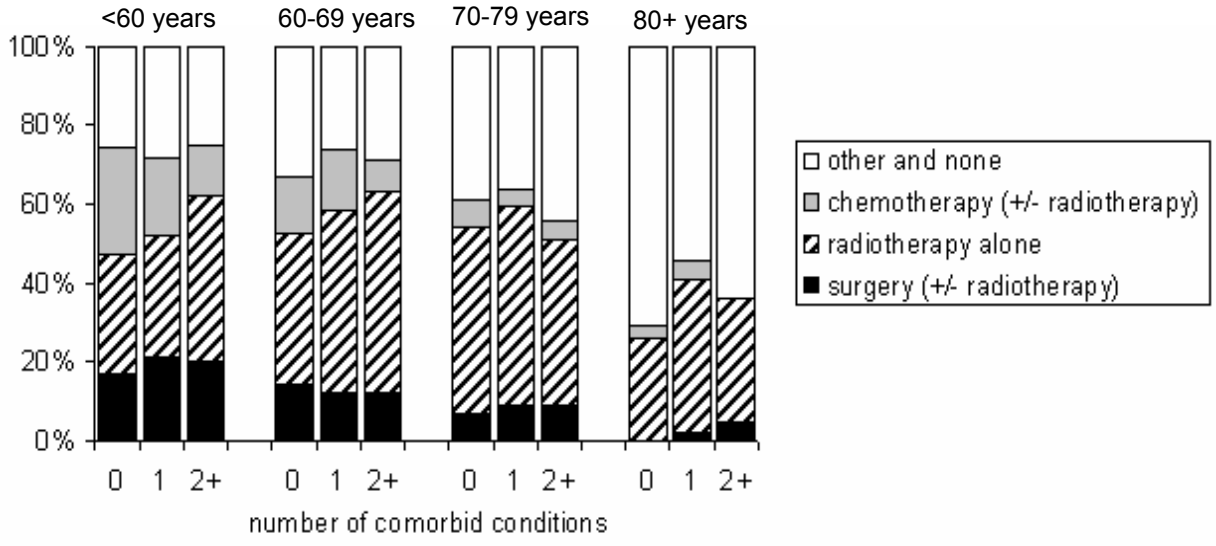


**Figure 1B**

*Treatment of non-localised NSCLC, according to age, comorbidity and stage*

the treatment chosen for patients with non-localised disease. However, for patients with stage IIIa aged 70-79 the presence of COPD lowered the proportion who underwent surgery (10% versus 19% of patients without comorbidity, results not shown).

Table 3 shows univariate and multivariable analyses of survival for patients with localised NSCLC. Three year survival decreased significantly with age ($p<0.0001$) with relative 3 year survival of 62% for patients younger than 60 and 13% for those aged 80 or older. The 3 year overall survival decreased from 61% to 8%. Among patients aged 70-79 the prognosis for those with adenocarcinoma was better than for those with squamous cell carcinoma or large cell undifferentiated carcinoma. Survival was better for T1 tumors and was also better after surgery. The number of comorbid conditions seemed to have no significant influence on survival, but the 3 year survival for patients aged 70-79 was especially low for those with COPD in combination with previous cancer (11% compared with 38% for patients without comorbidity). In multivariable analyses age, subtype, tumor size and the presence of two or more comorbid conditions were independent prognostic factors. The effects of age and tumor size remained significant after treatment was included, but the prognostic effects of subtype and comorbidity disappeared (Table 3). In the model with the specific diseases and combinations of diseases only the combination of a previous tumor and COPD had a negative influence on survival. However, this prognostic effect disappeared when treatment was included in the model. This means that the effect of the combination of a previous tumor and COPD might be ascribed to the less aggressive treatment of these patients.

Table 4 shows univariate and multivariable analyses of survival for patients with non-localised NSCLC. One year survival decreased significantly with age ($p<0.0001$) with 1 year relative survival of 31% for patients younger than 60 and 13% for those aged 80 or older. One year overall survival decreased from 31% to 11%. Furthermore, histological subtype (only for age group 70-79), stage and treatment were prognostic factors in univariate analyses. Comorbidity had no influence on survival nor did the specific diseases or combinations of diseases.

**Table 3 Univariate and multivariable analysis of overall survival for patients with localised* NSCLC, according to age, sex, histology, tumor size, comorbidity and treatment**

| | **Age <60** | | **Age 60-69** | | **Age 70-79** | | **Age 80+** | | **All ages** | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total (N) | 251 | | 403 | | 366 | | 82 | | 1102 | |
| Alive at 3 yrs (N) | 154 | | 198 | | 117 | | 7 | | 476 | |
| *Relative 3-yr survival (%)* | *62* | | *52* | | *38* | | *13* | | *47* | |
| | **Overall 3-year survival (%) and univariate p-values** | | | | | | | | **Multivariable** | |
| | **%** | ***P*** | **%** | ***P*** | **%** | ***P*** | **%** | ***P*** | **HR[2]** | ***P*** |
| ***Age*** | | | | | | | | | | |
| <60 | 61 | | | | | | | | 0.84 | ***0.1*** |
| 60-69[1] | | | 49 | | | | | | 1 | |
| 70-79 | | | | | 32 | | | | 1.28 | ***.007*** |
| 80+ | | | | | | | 8 | | 1.31 | ***0.07*** |
| ***Gender*** | | | | | | | | | | |
| Female[1] | 69 | | 51 | | 43 | | 18 | | 1 | |
| Male | 57 | ***0.1*** | 48 | ***0.8*** | 30 | ***0.1*** | 6 | ***0.7*** | 0.86 | ***0.2*** |
| ***Histology*** | | | | | | | | | | |
| Squamous cell[1] | 66 | | 49 | | 30 | | - | | 1 | |
| Adenocarcinoma | 60 | | 53 | | 44 | | - | | 1.10 | ***0.4*** |
| Large cell undiff. | 37 | ***0.1*** | 38 | ***0.5*** | 24 | ***0.03*** | - | | 1.08 | ***0.4*** |
| ***Tumor size*** | | | | | | | | | | |
| T1[1] | 78 | | 69 | | 42 | | - | | 1 | |
| T2 | 51 | ***<.001*** | 39 | ***<.001*** | 27 | ***.007*** | - | | 1.62 | ***<.001*** |
| ***Comorbidity*** | | | | | | | | | | |
| 0[1] | 53 | | 53 | | 38 | | 10 | | 1 | |
| 1 | 66 | | 48 | | 33 | | 4 | | 0.94 | ***0.5*** |
| 2+ | 59 | ***0.2*** | 43 | ***0.2*** | 30 | ***0.2*** | - | ***0.5*** | 1.13 | ***0.2*** |
| ***Treatment*** | | | | | | | | | | |
| Radiotherapy[1] | - | | 21 | | 10 | | - | | 1 | |
| Surgery (+/-) RT | 63 | | 57 | | 47 | | - | | 0.49 | ***<.001*** |
| Other/none | - | | - | ***<.001*** | 2 | ***<.001*** | - | | 1.35 | ***0.02*** |

** Stage I or II*

*[1] Reference category*

*[2] Hazard Ratio for death*

**Table 4 Univariate and multivariable analysis of overall survival for patients with non-localised* NSCLC, according to age, sex, histology, stage, comorbidity and treatment**

| | Age <60 | | Age 60-69 | | Age 70-79 | | Age 80+ | | All ages | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total (N) | 710 | | 848 | | 694 | | 128 | | 2380 | |
| Alive at 1 yrs (N) | 219 | | 219 | | 146 | | 14 | | 598 | |
| *Relative 1-yr survival (%)* | *31* | | *26* | | *22* | | *13* | | *26* | |
| | **Overall 1-year survival (%) and univariate p-values** | | | | | | | | **Multivariable** | |
| | **%** | ***P*** | **%** | ***P*** | **%** | ***P*** | **%** | ***P*** | **HR[2]** | ***P*** |
| ***Age*** | | | | | | | | | | |
| <60 | 31 | | | | | | | | 0.93 | ***0.2*** |
| 60-69[1] | | | 26 | | | | | | 1 | |
| 70-79 | | | | | 21 | | | | 1.05 | ***0.3*** |
| 80+ | | | | | | | 11 | | 1.14 | ***0.2*** |
| ***Gender*** | | | | | | | | | | |
| Female[1] | 32 | | 20 | | 11 | | 14 | | 1 | |
| Male | 30 | ***0.6*** | 27 | ***0.08*** | 23 | ***0.06*** | 10 | ***0.9*** | 1.04 | ***0.5*** |
| ***Histology*** | | | | | | | | | | |
| Squamous cell[1] | 35 | | 29 | | 28 | | 12 | | 1 | |
| Adenocarcinoma | 28 | | 28 | | 18 | | 13 | | 1.07 | ***0.2*** |
| Large cell undiff. | 29 | ***0.3*** | 20 | ***0.08*** | 14 | ***0.01*** | 8 | ***0.6*** | 1.03 | ***0.6*** |
| ***Stage*** | | | | | | | | | | |
| III[2] | 41 | | 35 | | 28 | | 13 | | 1 | |
| IV | 19 | ***<.001*** | 13 | ***<.001*** | 10 | ***<.001*** | 9 | ***0.7*** | 1.14 | ***0.01*** |
| ***Comorbidity*** | | | | | | | | | | |
| 0[1] | 31 | | 25 | | 23 | | - | | 1 | |
| 1 | 31 | | 29 | | 22 | | - | | 1.01 | ***0.8*** |
| 2+ | 25 | ***0.4*** | 25 | ***0.6*** | 19 | ***0.5*** | - | | 1.05 | ***0.4*** |
| ***Treatment*** | | | | | | | | | | |
| Radiotherapy[1] | 28 | | 29 | | 28 | | - | | 1 | |
| Surgery (+/- RT) | 55 | | 49 | | 37 | | - | | 0.69 | ***<.001*** |
| Chemo (+/- RT) | 39 | | 35 | | 38 | | - | | 0.90 | ***0.2*** |
| Other/none | 9 | ***<.001*** | 8 | ***<.001*** | 8 | ***<.001*** | - | | 1.13 | ***0.03*** |

** Stage III or IV*

*[1] Reference category*

*[2] Hazard Ratio for death*

In a multivariable analysis age and stage were independent prognostic factors. After inclusion of treatment the prognostic effect of age disappeared and that of stage became weaker but remained significant. In a model with the specific diseases and combinations of diseases, none of the concomitant diseases had an independent effect on survival.

**Discussion**

In this population based study we found that the prevalence of serious comorbidity in patients with NSCLC was high, especially in elderly patients and in men. Furthermore, elderly patients were treated less aggressively than younger patients. In patients with localised disease a lower proportion of patients with comorbidity underwent surgery. The survival of patients with localised disease was lower for older patients but the effect of comorbidity on the prognosis was small.

In 2003 the completeness and accuracy of the data on comorbidity were validated in a series of 500 consecutive patients with lung cancer aged 40 and older and diagnosed between 1995 and 1999. Comorbidity scored by the registry team was compared with that scored by a team consisting of a surgeon and an epidemiologist. Recording of comorbidity was correct for about 70% of patients. There was some underregistration, especially of cardiovascular diseases (internal report). This means that the effects of comorbidity on treatment and survival, as described here, are probably weaker than the real effects.

*Prevalence*

The higher prevalence of comorbidity in older patients was expected because the prevalence of diseases generally increases with age. The prevalence of comorbidity in older patients may even be underestimated due to ascertainment bias. Younger patients underwent surgery more often, which means that the prevalence of comorbidity reported by the chest physician may be higher in patients with resectable disease because of the required preoperative examination.

The high risk of cardiovascular diseases and COPD for patients with lung cancer can be explained by the high proportion of smokers among these patients, especially men.

*Treatment*

Patients with localised disease underwent surgery less often when they were older and when comorbidity was present. The resection rate was very low for those with COPD, probably because of the expected higher incidence of postoperative complications and mortality[11]. However, in everyday practice the resectability is not determined primarily by comorbid conditions but by the effects of comorbidity, such as pulmonary and cardiac function.
Age seemed to have more influence on the choice of treatment than comorbidity, especially for patients with localised disease. Apparently, comorbidity alone does not entirely explain why elderly patients with localised disease undergo surgery less often and why those with non-localised disease receive systemic chemotherapy less often. The lower proportion of elderly patients who undergo surgery or chemotherapy was also reported in another area of the Netherlands[12]. The lower proportion of surgery in elderly patients may be explained by an increased risk of surgical mortality[13-15]. In previous studies less aggressive treatment of patients with comorbidity was also shown for breast cancer, prostate cancer and lymphoma[16-19]. In contrast, age and comorbidity had a negligible influence on the resection rate in patients with colorectal cancer[20]. It seems that when surgery is inevitable, as in patients with colorectal cancer, or when no alternative treatment is available, age and comorbidity have a negligible influence on the resection rate. In our study elderly patients received chemotherapy less often than younger patients. In previous studies, however, treatment with vinorelbine was shown to be well tolerated by elderly patients with non-localised NSCLC[21,22]. The effects of age and comorbidity on the application of chemotherapy for NSCLC in our study may be underestimated because we did not have any information on dose reduction or delay of chemotherapy.

*Survival*

Age, stage of disease and treatment were prognostic factors for patients with NSCLC, independent of sex, histology and comorbidity. Since age and treatment were both independent prognostic factors for patients with localised disease, the effect of age on the prognosis cannot be completely explained by less aggressive treatment of the elderly. Overall survival of older patients with lung cancer is worse because of the lower expected survival rate for the elderly in the general population. However, the effect of age remained significant when relative survival rates (adjusted for survival in the general population with the same age structure) were calculated. Since we also adjusted for comorbidity, the lower survival rate for the elderly should be explained by prognostic factors other than comorbidity, such as performance status, decreased organ reserves, worse pulmonary function, or psychic and social factors[23-27], which were not available for analysis in the Eindhoven Cancer Registry.

Comorbidity seemed to have a negligible influence on survival of patients with lung cancer, despite less aggressive treatment in case of comorbidity. This contradicts the findings in some other studies where comorbidity was found to be an independent prognostic factor for surgically resected stage I NSCLC, stage III NSCLC and all lung cancer patients, respectively[26-29]. However, these studies were not population based and they used other scales for measuring comorbidity (the Kaplan-Feinstein Index[30] and the Cumulative Illness Rating Scale-Geriatric (CIRS-G)[31]). In one of the studies, comorbidity influenced overall survival in surgically resected patients with stage I NSCLC in whom comorbidity was rated according to CIRS-G but not according to the Charlson scale[26]. In another American study comorbidity count and the Charlson index were significant predictors for lung cancer survival, but explained only 2.5% and 2.0%, respectively, of the variation in survival[32]. The influence of comorbidity on survival is probably of less importance in lethal diseases such as lung cancer. Most of these patients die of lung cancer before they have a chance to die of the comorbid condition.

A possible shortcoming of all the studies is the classification of total severity in cases of two or more comorbid conditions. More conditions may have a multiplicative effect rather than an additive effect. Classifying comorbidity as the number of diseases present, or as the sum of scores, or as the most severe condition present may miss the burden of multiple diseases on prognosis. In our data set we also analyzed the prognostic effect of the individual diseases and their combinations. However, none of the (combinations of) diseases had an independent effect on prognosis. A negative effect of comorbidity on prognosis may also be cancelled out by earlier detection, with lung cancer possibly being detected at an earlier stage during routine examination for the comorbid condition. Treatment was a strong prognostic factor, even after adjustment for age. The question therefore arises whether the less aggressive treatment of elderly patients is justified. For careful preoperative selection, studies of the complications during and after treatment should be performed, including data on performance status and pulmonary function.

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Chapter 2

# Surgical Mediastinal Staging in Daily Practice

A retrospective analysis in four general hospitals

Sietske A Smulders, Frank WJM Smeenk
Maryska LG Janssen-Heijnen, Pascal LML Wielders [1]
Dirk RAJ de Munck [2], Pieter E Postmus [3]

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[1] Department of Pulmonary Diseases, Catharina Hospital, Eindhoven
[2] Department of Pulmonary Diseases, Máxima Medical Center, Veldhoven
[3] Department of Pulmonary Diseases, VU University Medical Center, Amsterdam
The Netherlands

**Abstract**

*Background:* An adequately staged mediastinum remains obligatory in patients with NSCLC prior to surgery. In this study, we investigated the accuracy of preoperative surgical mediastinal staging procedures in 4 hospitals.

*Setting:* Non-university teaching hospital and three surrounding community hospitals in Eindhoven, The Netherlands.

*Methods and results:* Patients with NSCLC who underwent mediastinoscopy and/or thoracotomy, between 1993 and 1999. Adherence to guidelines for indicating and performing mediastinoscopy were investigated and compared in four hospitals. Guidelines for indicating mediastinoscopy were adequately followed in two-thirds of cases. Mediastinoscopy was performed according to gold standards in 40% of cases. The hospital with the smallest number of evaluated patients scored the worst. Postoperatively, 17% of patients appeared to have unforeseen N2-3 disease. In approximately 18% of these "upstaged" patients, thoracotomy could have been prevented, if guidelines had been followed adequately.

*Conclusions:* In clinical practice the adherence to staging guidelines with respect to mediastinoscopy is insufficient in 1/3 of patients. Furthermore, mediastinoscopy was performed according to gold standards in 40% of patients.

## Introduction

Lung cancer continues to be the leading cause of death from cancer throughout the world. It is the second most common type of cancer in both men and women[1-3]. Surgical resection results in 5-year survival in 40-50% of patients with early stage non-small cell lung cancer (NSCLC). After radical radiotherapy only a small number is alive after 5 years. However, a potentially curative resection is only possible in about 25% of new cases. Involvement of mediastinal lymph nodes (MLN) is a negative prognostic factor for both resectability and survival rate.

Surgical biopsy of MLN by mediastinoscopy has to be considered as the gold standard for thorough preoperative, minimally invasive mediastinal staging[4]. Based on historical data, mediastinoscopy can only be omitted in patients with small (< 3 cm) peripheral squamous cell tumours without MLN enlargement on CT scan[5-7]. This was considered common daily practice in most hospitals in the Netherlands in that period, as described in these manuscripts[5-7].

Ideally, cervical mediastinoscopy at least requires sampling of nodes from stations 4 (left- and right lower paratracheal) and 7 (subcarinal) routinely along with the nodes from station 2 (left- and right higher paratracheal), if accessible, as described in the American Thoracic Society staging system[8]. However, with an accuracy of 92% or better, mediastinoscopy is not always perfect and its result may be surgeon dependent[9;10]. Also, results from large studies in academic centres are probably not totally concordant with all-day clinical practice. Surgeons may refrain from biopsy of nodal stations because MLN cannot be visualized, due to lack of experience[11], or due to risk of bleeding from adjacent large vessels. In cases where positive MLN were not biopsied by mediastinoscopy, wrong therapeutic decisions might be made.

In view of the increasing demand for adequate preoperative mediastinal staging of highly suspected or proven lung cancer, we analyzed the results of mediastinoscopy and thoracotomy of three general hospitals and one teaching hospital in the Netherlands. Our

main study objective was to investigate the accuracy of preoperative surgical mediastinal staging procedures, which we divided and formulated as follows:

1) To investigate the degree of adherence of treating physicians to the accepted staging procedures in their hospitals.

2) To study, in case mediastinoscopy was performed, how often this was performed according to gold standards in normal clinical practice settings.

For all objectives the results from the different hospitals were compared.

Next to this main research question we investigated whether non-adherence to guidelines and not performing mediastinoscopies according to gold standard procedures might have had clinical implications. For this, in all patients postoperatively diagnosed having N2/N3-disease localized at Naruke stations[12] accessible for mediastinoscopy, we checked whether preoperative mediastinal surgical staging was adequately done. By doing so, we tried to obtain an indication about how many thoracotomies might have been prevented if protocols were followed adequately.

**Patients and Methods**

In a retrospective study data were evaluated of all patients who had mediastinoscopy and/or thoracotomy for lesions proven or highly suspicious for malignancy. From a non-university, teaching hospital and three surrounding community (non-teaching) hospitals, data of patients treated between 1993 and 1999, were included. At that time, fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) was not yet available in these hospitals. Of all participating hospitals data were collected by the regional cancer registry of the IKZ. Of this registry, several studies have been published in the area of lung cancer[13;14]. Surgery for proven N2 or N3 disease was not considered beneficial and therefore not performed in these patients during this study. The described staging procedures were not changed during the investigated period.

From the patient records we gathered: demographic data, preoperative diagnosis (known or unknown), results of preoperative CT-scan, results of mediastinoscopy and thoracotomy, tumour histology, final staging data (cTNM data, in case of thoracotomy

pTNM data) and follow up data. Preoperative CT-scans were reviewed in case the radiologists' report was unclear regarding the presence of enlarged MLN. Only patients diagnosed with NSCLC were included for analysis. When lymph node metastases were present, attention was given to whether metastases were limited to lymph nodes only, or also capsular involvement was present. Microscopic examination of MLN by the pathologist was standardized and slices were taken every 5 mm.

*Accuracy of preoperative surgical mediastinal staging procedures*

1) Adherence to staging management guidelines for indicating mediastinoscopy.

Three of the four hospitals used the following guideline for indicating a mediastinoscopy: mediastinoscopy should be performed in all patients with NSCLC, except in case of a peripheral clinically staged (c)T1N0 squamous cell carcinoma. In the other non-teaching hospital, mediastinoscopy should be performed in all patients with NSCLC, except in case of a peripheral cT1N0 NSCLC in the right upper lobe. According to these guidelines, in case of the presence of a coin lesion suspicious for malignancy without histological proof, mediastinoscopy should be done, especially when enlarged MLN were present at preoperative CT-scan. We analyzed results of all investigated hospitals. For each patient, we compared clinical practice to the corresponding guidelines. These guidelines were agreed upon and accepted for use in clinical practice during a weekly conference between surgeons, radiologists and pulmonologists. Treatment plans were made according to these guidelines as described.

2) Performance of mediastinoscopy according to gold standards in each hospital.

From the files of the surgeon and the pathologist all information concerning site of biopsies and specification of tissue present in biopsies with the results of pathologic examination were registered. Locations of MLN were classified as 2 right/left, 4 right/left, 7 and 'other', according to Naruke[12]. In case of doubt concerning localizations from which biopsies were taken, surgeons were additionally consulted. We considered mediastinoscopy to be performed according to gold standards if lymph node stations 4

(right and left) and 7 were biopsied with lymph node tissue present in all three biopsies. All other results were not considered to be performed according to gold standards. We did not include lymph nodes 2 right and 2 left (often difficult to reach), because it was felt that adherence to this method would be unfeasible in all-day clinical practice. On the other hand, we believe it is obligatory for adequate preoperative mediastinal staging to sample at least one contralateral lymph node.
Again, results from individual hospitals were compared.

*Postoperative upstaging and adequacy of preoperative staging*
Thoracotomies done more than 28 days after mediastinoscopy were not included for analysis of final staging. In the hospitals no specific guidelines existed concerning MLN sampling during thoracotomy. In general, only MLN that were found to be enlarged were removed. In case of upstaging post-thoracotomy, we investigated which MLN were found to be positive during thoracotomy. Next, we investigated whether mediastinoscopy was performed according to gold standards in these cases and whether positive MLN found during thoracotomy would have been accessible for mediastinoscopy in these particular patients.

*Statistical analysis*
We used SPSS 11.0 for statistical analysis. To determine accuracy of preoperative surgical mediastinal staging procedures, adequacy of mediastinal lymph node sampling during thoracotomy and to compare results from different hospitals, we performed chi-square test. Statistical significance was defined at $p < 0.05$.

**Results**
In total, 2177 patients were diagnosed having lung cancer (1562 NSCLC, 397 small-cell and 218 'other') in our study cohort. From 1993 to 1999, 671 patients suspected of having malignant pulmonary lesions in these four hospitals were evaluated by either mediastinoscopy or thoracotomy, or both. The diagnosis of lung malignancy was

histologically proven in 635 patients (90%), of which 569 were NSCLC. These 569 patients were included for analysis. Mean age was 64.0 years (ranging from 37-81 years) and 460 (81%) were men. Out of 569 NSCLC, 308 were squamous cell carcinoma, 128 adenocarcinoma, 40 bronchoalveolair cell carcinoma, 4 adenosquamous carcinomas, and 89 large cell undifferentiated carcinomas.

Mediastinoscopy was performed in 387 patients. In 317 of these the diagnosis of NSCLC was known prior to the diagnostic procedure. Out of the 182 (32%) patients without a mediastinoscopy, 98 did not have a diagnosis of NSCLC established prior to surgery.

*Accuracy of preoperative surgical mediastinal staging procedures*

1) Adherence to staging management guidelines for indicating mediastinoscopy.

Table 1 presents accuracy data for indicating a mediastinoscopy in the different hospitals, tested according to the corresponding guideline for that hospital. This table shows that in 373 out of 569 (66.1%) patients, guidelines for indicating mediastinoscopy were followed correctly. Comparing the different hospitals, we found that the percentage of correctly indicated mediastinoscopies was lowest (26%) in the one hospital with the smallest number of evaluated patients (Table 1). This was significantly different from the other hospitals ($p < 0.0001$). No other significant differences could be detected between the hospitals.

Surprisingly, in almost all (175 of the 182) patients without a mediastinoscopy, a mediastinoscopy should have been performed if guidelines were used strictly. Of all 569 patients whom were evaluated, 387 underwent mediastinoscopy. In 13 out of these 387 patients, mediastinoscopy could have been omitted according to corresponding guidelines. Nonetheless, one of these demonstrated mediastinal metastases of squamous cell carcinoma.

**Table 1 Accuracy data for indicating mediastinoscopy, comparing different hospitals**

| | GFC[1] | GNFC[2] | Total patients evaluated | % Correct |
|---|---|---|---|---|
| **1 (Teaching)** | 190 | 83 | 273 | 69.6 |
| **2 (Non-Teaching 1)** | 113 | 45 | 158 | 71.5 |
| **3 (Non-Teaching 2)** | 61 | 31 | 92 | 66.3 |
| **4 (Non-Teaching 3)** | 12 | 34 | 46 | 26.1 |
| **Total** | 376 | 193 | 569 | 66.1 |

[1] *GFC = Guidelines Followed Correctly*

[2] *GNFC = Guidelines Not Followed Correctly*

**Table 3 Results from mediastinal lymph node sampling during thoracotomy**

| | Number of locations from which MLN were sampled during thoracotomy | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Hospital** | **None (%)** | **1** | **2** | **3** | **4** | **5** | **6** | **Total thoracotomies performed** |
| **1 (Teaching)** | 98 (44 [1]) | 65 | 37 | 16 | 3 | 2 | 1 | 222 |
| **2 (Non-Teaching 1)** [2] | 39 (30 [1]) | 58 | 26 | 8 | 1 | - | - | 132 |
| **3 (Non-Teaching 2)** | 54 (66 [1]) | 22 | 5 | 1 | - | - | - | 82 |
| **4 (Non-Teaching 3)** | 36 (82 [1]) | 7 | 1 | - | - | - | - | 44 |
| **Total** | 227 (47) | 152 | 69 | 25 | 4 | 2 | 1 | 480 |

[1] *All significantly different from each other*

[2] *Significantly best, p = 0.007 compared to the teaching hospital and p = 0.0001 compared to the other two non-teaching hospitals*

2) Performance of mediastinoscopy according to gold standards in each hospital.

Performance results of all mediastinoscopies, according to hospital are presented in Figure 1. Out of all 387 mediastinoscopies, 151 (39.0%) were done according to gold standards and 60 (15.5%) were positive for mediastinal metastases. Table 2 presents detailed information about localizations from which MLN were biopsied at mediastinoscopy, comparing different hospitals. Mean overall amount of biopsied

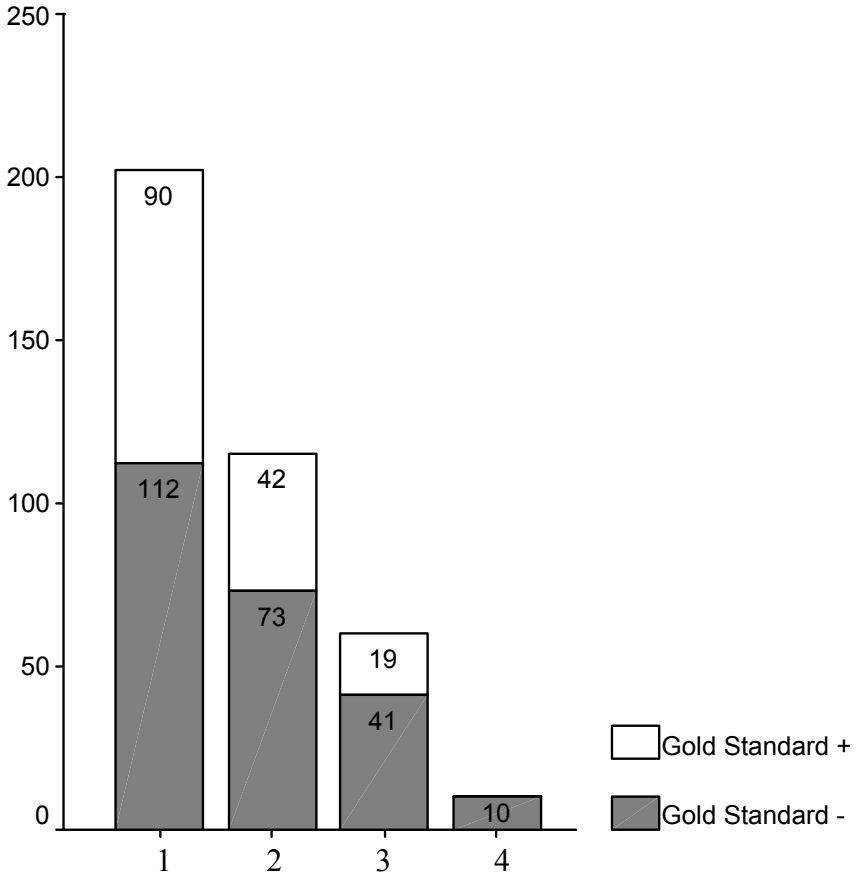


**Figure 1**

*Results from all mediastinoscopies, comparing different hospitals*

localizations was 2.63 (±0.9, range 0-5). Figure 1 and Table 2 show that the more patients are evaluated, the better MLN are sampled during mediastinoscopy.

*Postoperative upstaging and adequacy of preoperative staging*

MLN (Naruke 1-9) were sampled in 253 (53%) out of 480 patients during thoracotomy. In Table 3 results from MLN sampling during thoracotomy are shown, comparing the different hospitals, which were all significantly different from each other.

**Table 2 Details on localizations from which MLN were sampled at mediastinoscopy, comparing different hospitals**

| (n) Localizations of biopsies | Hospital | | | |
|---|---|---|---|---|
| | 1 (Teach) | 2 (Non-Teach 1) | 3 (Non-Teach 2) | 4 (Non-Teach 3) |
| **Amount (Mean (SD))** [1] | 2.63 (0.9) | 2.7 (0.9) | 2.58 (0.8) | 1.0 |
| **Combinations of MLN sampled at MS** [2] | | | | |
| **4R+4L+7** | 90 | 42 | 19 | - |
| **4R+7** | 29 | 35 | 9 | - |
| **4L+7** | 5 | 8 | 9 | - |
| **4R+4L** | 16 | 14 | 2 | - |
| **4R** | 13 | 9 | 1 | 2 |
| **4L** | 5 | - | 1 | 1 |
| **7** | 19 | 1 | 15 | - |
| **None** [3] | 22 | 2 | 3 | - |
| **2R** | 17 | 21 | 4 | - |
| **2L** | 7 | 4 | 5 | - |
| **2R+2L** | 15 | 3 | 2 | - |
| **'Other'** | 17 | 11 | 24 | - |
| **Unknown** | 3 | 4 | 1 | 7 |
| **MS performed** [4] | 202 | 115 | 60 | 10 |

*[1] Mean amount of different localizations that were biopsied at mediastinoscopy. Maximum amount = 6 (Naruke stations 2 right/left, 4 right/left, 7 and 'other'). SD = Standard error of mean.*

*[2] Biopsies without lymph node tissue present were excluded from this table. Localizations are according to Naruke. MS = Mediastinoscopy.*

*[3] None of the MLN at gold standard locations (4R, 4L or 7) was sampled.*

*[4] Numbers do not add up because of possible combinations between localizations.*

Mean amount of localizations from which MLN were sampled was 1.5 (range 1-6). Again, in the hospitals where most patients were evaluated and operated on (numbers 1 and 2 in Table 3), MLN were generally sampled more often and more thorough. Table 4 presents data on localizations of sampled MLN during thoracotomy, according to Naruke.

**Table 4 Frequency of MLN sampled at different lymph node stations, according to Naruke, of all patients that underwent thoracotomy and MLN sampling (n = 253)**

| Naruke | 2R | 3 | 4R | 4L | 5 | 6 | 7 | 8 | 9 | UK [1] |
|---|---|---|---|---|---|---|---|---|---|---|
| **Frequency** | 2 | 1 | 62 | 34 | 98 | 10 | 54 | 38 | 49 | 48 |
| **Of which positive result** | 1 | - | 9 | 2 | 15 | 1 | 6 | 3 | 5 | 8 |

[1] *UK = Unknown localization*

Overall, in 43 out of the 253 (17.0%) patients in whom MLN were sampled during thoracotomy, one or more MLN proved to be malignant. Maximum time interval of 28 days was exceeded in 20 patients, so data of 233 out of 253 patients were available for analysis of upstaging. Mean time interval between mediastinoscopy and thoracotomy was 14 days (range 2 – 28 days). Table 5 presents an overview of the presence of "unforeseen N2 disease", in these 233 patients.

Mediastinoscopy was performed in 156 of these 233 patients. Postoperatively, 27 patients had N2- and 1 patient had N3 disease. Out of these 28 upstaged patients, 10 had MLN positive at thoracotomy that would have been accessible for mediastinoscopy. Amongst these 10 patients, mediastinoscopy was not done according to gold standards in 3 patients. One of these 3 patients was upstaged because of a positive MLN found at thoracotomy which was not biopsied during mediastinoscopy.

Theoretically, this upstaging might have been prevented if this MLN station was adequately biopsied during mediastinoscopy. Furthermore, mediastinoscopy was also not performed according to gold standards in another 3 out of the 28 upstaged patients, but accessibility of MLN in these 3 patients could not be determined due to lack of information about localization of excised MLN at thoracotomy in these patients' records.

Mediastinoscopy was not performed in 77 patients of these 233 patients. Almost half (37) of these 77 patients underwent thoracotomy without a preoperative histological diagnosis.

**Table 5 Presence of "unforeseen N2 disease" in all 233 patients that had thoracotomy and sampling of MLN with adequate time interval between mediastinoscopy and surgery**

| (n) | MS [1] + | | MS – | | Total |
|---|---|---|---|---|---|
| | GS [3] + | GS - | + Indicated | - | |
| **Amount** | 66 | 90 | 77 | 0 | **233** |
| **Unforeseen N2/3 disease (intranodal)** | 14 (10) | 14 (12) | 11 (8) | - | **39 (30)** |
| **Positive MLN accessible for MS (Y/N/UK) [2]** | 7/5/2 | 3/8/3 | 6/4/1 | - | **16/17/6** |
| **Accessible MLN biopsied at MS** | 7 | 2 | | | **9** |
| **N of thoracotomy that might have been prevented** | 0 | 1/0/3 | 6/0/1 | - | **7** |

[1] *MS = Mediastinoscopy*

[2] *Y/N/UK = Yes / No / Unknown*

[3] *GS + = According to gold standards*

Postoperatively, 10 patients had N2- and 1 patient had N3 disease. Out of these 11 upstaged patients, 6 had MLN positive at thoracotomy, which would have been accessible for mediastinoscopy. In another patient, accessibility could not be determined, due to lack of information about localization of excised MLN in patients' record. All these patients should have had mediastinoscopy if guidelines for indicating mediastinoscopy would have been followed adequately.

Table 5 shows that overall, 39 out of 233 (16.7%) patients who had some kind of mediastinal staging during thoracotomy appeared to have "unforeseen N2/3-disease" postoperatively. Thirty of those 39 were limited to intranodal metastases. Theoretically, upstaging and thoracotomy could have been prevented in at least 7 out of these 39 (17.9%) patients, maybe even in 11 (28.2%) if the patients with positive MLN of unknown localization at thoracotomy had positive MLN at localizations accessible for mediastinoscopy.

**Discussion**

This study shows that in all-day clinical practice, guidelines to perform or to skip mediastinoscopy in patients suspected for malignant lung lesions were adequately followed in approximately two-third of cases in four general hospitals. Physicians were especially reluctant to perform mediastinoscopy in patients with peripheral lesions without a preoperative histological diagnosis. Within the four hospitals the one with the smallest number of evaluated patients scored the worst percentage of correctly indicated mediastinoscopies, which was significantly different from the other hospitals.
This study also shows that of all mediastinoscopies performed, 40% were done according to gold standards with regard to sampling of lymph nodes. There was a close relation between the number of mediastinoscopies done and the percentage of mediastinoscopies performed according to gold standards.
Finally, sampling of MLN during thoracotomy was done more often and more thorough in the hospitals were most patients were evaluated and operated on. We found that MLN sampling during thoracotomy was done in approximately 50% of cases, which led to upstaging in 17% of patients. In almost one out of every five cases, upstaging and surgical intervention could theoretically have been prevented when mediastinoscopy would have been indicated and performed according to gold standards.

Even nowadays, an adequately staged mediastinum remains obligatory in patients with NSCLC prior to surgery. N2 disease at mediastinoscopy is generally considered as an absolute contraindication to primary surgical resection. The few exceptions being unexpected N2 disease after *adequate* negative cervical mediastinoscopy, limited intranodal disease in the aortopulmonary nodes for a left upper lobe squamous cell carcinoma and in case complete resectability is anticipated by the surgeon[15;16].
Incidence of pN2 disease in cT1N0 squamous cell carcinomas is approximately 4%, varying from 0-8% in different studies[5;17-20]. For other carcinomas, for example adenocarcinomas, this percentage in cT1N0 is higher, varying from 10-20%[17;21].
Therefore, physicians in most Dutch hospitals at the time of this study felt that

mediastinoscopy can be omitted in patients with a preoperatively identified cT1N0 squamous cell carcinoma without enlarged MLN on CT[5-7;22]. Nonetheless, many controversies still exist concerning invasive staging procedures for possibly resectable NSCLC, as is reflected in the literature[19;23-25]. Nowadays, after introduction of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, mediastinoscopy in most Dutch centres is omitted when MLN on FDG-PET are negative and the primary tumour is located peripherally[26]. On the other hand, mediastinoscopy remains obligatory to confirm all FDG-PET positive lymph nodes[27].

We found that in approximately one-third of cases, guidelines for indicating mediastinoscopy were not adequately followed. This can partly be explained by the 183 thoracotomies that were performed in patients without prior mediastinoscopic examination of the MLN. Almost half of these patients went directly to thoracotomy without a preoperative histological diagnosis. When we excluded patients with peripheral lesions without a histological diagnosis and without mediastinoscopy (n = 97), the percentage of correctly followed guidelines for indicating mediastinoscopy rose from 66% to 79.5% (data not shown).

Comparing the different hospitals, we found that the one hospital with the smallest number of evaluated patients scored the worst percentage (28%) of correctly indicated cases, which was significantly different from the other hospitals ($p < 0.0001$). After excluding data from this hospital, no significant differences could be detected. This finding is consistent with an American study[11], in which authors suggested that the quality of care relates to the number of procedures performed in an hospital.

Data from this study, as presented in Figure 1 and Table 1, also show that the more mediastinoscopies were performed in a specific center, the better MLN were sampled during the procedure. This difference might in part be explained by the fact that in the teaching hospital, mediastinoscopies are performed by cardiothoracic surgeons, in contrast to general surgeons in the non-teaching hospitals. Cardiothoracic surgeons may be more familiar and experienced with thoracic surgery and can therefore be more

thorough in performing mediastinoscopies. Results from our study could suggest that it is better to centralize mediastinoscopy and thoracotomy for NSCLC to larger hospitals with better results. In a recently published study by Birkmeyer[28], an inverse association was found between surgeon volume and operative mortality for lung cancer resection. They therefore suggested that selected operations (including lung resection surgery) should be restricted to a smaller number of surgeons. Also, in a review article on this subject, Hillner et al[29] suggested that, for all forms of cancer, efforts to concentrate its initial care would be appropriate.

Nonetheless, overall, 40% of all mediastinoscopies were done according to gold standards. Apparently, in many cases, surgeons refrain from biopsy of one or more (Naruke 4R, 4L and 7) 'gold standard' mediastinal lymph nodes. Most often because no (enlarged) MLN were visible or could be visualized.

In our study, only 60 out of 387 (16%) mediastinoscopies were positive for mediastinal metastases. Other studies present a higher percentage of positive mediastinoscopies, varying from 25-30% overall, to 7-10% in stage I NSCLC alone[18;19;23;30]. This difference in results from our study compared to the literature might be caused by our liberal guidelines for indicating mediastinoscopy which makes mediastinoscopy necessary in almost every patient with (suspected) lung cancer eligible for surgical resection. On the other hand, it can also be explained by the fact that in our study the mediastinum was not sampled as thorough as might be desirable.

Considering the fact that in general patients with stage IIIA-B NSCLC are not cured by thoracotomy, this study provides important information. After thoracotomy and/or mediastinoscopy, 39 patients (17%) appeared to have N2 or N3 disease, of which at least 16 had MLN accessible for mediastinoscopy. Theoretically, at least 7 out of these 39 thoracotomies could have been prevented because staging procedures were not adequately followed in these cases. We believe however, taking also into account that in 47% of thoracotomies no MLN were sampled, that the actual number of patients having

"unforeseen N2-3 disease", and thus possible 'futile thoracotomy', in our study was in fact higher.

On the other hand, most (30/39) false negative mediastinoscopies in our study proved to be minimal N2 disease (Table 5) at thoracotomy. Because several studies show that survival is significantly better in unforeseen, intranodal N2 disease when complete surgical resection is possible, the clinical relevance of this finding remains unclear[7;31]. In patients with NSCLC, it would be interesting to investigate whether the recent introduction of FDG-PET scanning will result in an improved staging process and better selection of patients for surgical resection in clinical practice.

Of course, our results might be biased due to the retrospective nature of our study. Our results are very much dependent on completeness of data in patient' and pathologist' records and accuracy of documentation on localizations of MLN by surgeons. Nevertheless, we believe that by using the Eindhoven Cancer Registry, which records data on all patients newly diagnosed with lung cancer in the southern part of the Netherlands with a completeness exceeding 95%, as our primary data source, our data were accurate[14]. Furthermore, we feel the results on upstaging are important because it gives us an *impression* on how often postoperative upstaging might have been prevented in our study population.

**Conclusion**

This study shows that in clinical practice, accuracy of preoperative surgical mediastinal staging procedures and sampling of MLN during thoracotomy is not as adequate as one should hope for. Furthermore, non-adherence to protocols for indicating and performing mediastinoscopy and surgical sampling was significantly higher in the smallest hospital. Because of this finding it might be recommended to perform these procedures only in those centres where one has sufficient experience. Local monitoring of these aspects of care in each center is of great importance, firstly to see whether problems in these areas might be present and secondly to instigate procedures to improve this, if necessary.

Whether this will be effective and whether this might also have implications on clinical outcome calls for further prospective studies.

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Chapter 3

# Influence of Introduction of PET on Adherence to Mediastinal Staging Protocols and Performance of Mediastinoscopy

Martijn Goosens [1], Sietske A Smulders
Frank WJM Smeenk, Alette W Daniels-Gooszen [2]
Astrid B Donkers-van Rossum [2], Michela A Edelbroek [3]
Dyde A Huysmans [3], Arent-Jan Michels [4], Pieter E Postmus

**(Submitted)**

[1] Department of Pulmonary Diseases, Catharina Hospital, Eindhoven
[2] Department of Radiology, Catharina Hospital, Eindhoven
[3] Department of Nuclear Medicine, Catharina Hospital, Eindhoven
[4] Department of Pulmonary Diseases, St Anna Hospital, Geldrop
The Netherlands

**Abstract**

*Background:* In this study we investigated the impact of implementation of FDG-PET in daily practice on adherence to mediastinal staging protocols and performance of mediastinoscopy in NSCLC patients who are possible candidates for surgical resection.

*Methods:* From a non-university teaching hospital and three surrounding community hospitals in Eindhoven, the Netherlands, we studied data of 143 patients with NSCLC who underwent mediastinoscopy and/or thoracotomy in three consecutive periods (I: 9 months, II: 9 months and III: 13 months) after introduction of PET. Adherence to surgical mediastinal staging guidelines and performance of PET and mediastinoscopy were investigated and compared between the three periods and with our previous study before introduction of PET.

*Results:* Guidelines for indicating mediastinoscopy were adequately followed in significantly more (80%) cases after introduction of PET, compared to the period before PET (66%). 'Optimal' harvest (N7, N4 right and left nodes) of mediastinoscopy (in 27% of cases) was not significantly different form the period before PET (39% of cases). Compared with the historical data, the percentage of positive mediastinoscopies increased from 15.5 to 17.6 (NS). We found no significant differences between the three consecutive periods with regard to adequacy of indicating and performance of mediastinoscopy.

*Conclusions:* After introduction of PET, adherence to staging guidelines with respect to mediastinoscopy improved. Although fewer mediastinoscopies had an optimal harvest, more proved to be positive for metastases. Nevertheless, when mediastinoscopy is indicated, surgeons must be encouraged to reach an optimal harvest because PET positive nodes might be false negative.

## Introduction

In patients presenting with non-small cell lung cancer (NSCLC), one of the earliest and most important issues is determining resectability and operability, since complete resection offers the best prospects for patients with NSCLC. Resectability depends mainly on the presence of mediastinal lymph node metastases, which is an ominous prognostic sign and generally a contraindication to primary surgical resection. Even nowadays, after introduction of F-18-deoxyglucose positron emission tomography (FDG-PET), mediastinoscopy remains the gold standard for detecting N2-3 disease.

In a former study, we found that adherence to staging guidelines and performance of mediastinoscopy in general practice is not as high as one should hope for[1]. Addition of FDG-PET to conventional workup of NSCLC patients who are possible candidates for surgical resection can be very useful in guiding mediastinal biopsy during mediastinoscopy and reduces the number of futile thoracotomies[2]. PET scanning is becoming more and more available, even in the smaller hospitals. Recently (October 2002), FDG-PET scanning became available in our hospital. In this present study we investigated whether the non-supervised implementation of FDG-PET in daily practice resulted in improved performance and adherence to preoperative surgical mediastinal staging procedures. Secondly, we compared these results with our previous study before introduction of PET[1]. Thirdly, we studied in patients who were upstaged post-operatively whether upstaging might have been prevented in case preoperative staging protocols would have been followed correctly

## Patients and Methods

Study design

Data of all NSCLC patients who had mediastinoscopy and/or thoracotomy were collected. From a non-university teaching hospital and three surrounding community (non-teaching) hospitals, data of NSCLC patients evaluated between October 2002, after the introduction of FDG-PET scanning, and April 2005, were included. To find out whether the

degree of adherence to staging guidelines or performance of mediastinoscopy improved as time after implementation of PET progressed, three arbitrarily chosen consecutive periods were analyzed: the first 9 months after FDG-PET became available (October 2002-June 2003, period I), the second 9 months (July 2003-March 2004, period II) and the final 13 months (April 2004-April 2005, period III). Accessibility to PET was made known to physicians at its introduction and repeatedly mentioned during the weekly treatment planning conference of physicians involved in the treatment of lung cancer patients. The described staging procedures were not changed during the investigated period.

Preoperative CT scans in the non-university teaching hospital were prospectively reviewed by two independent radiologists (ADG, ADR). Presence of pathologically enlarged mediastinal lymph node stations, defined as > 10 mm (or > 15 mm for subcarinal nodes) in short axis diameter, was systematically documented for all Naruke stations[3]. Furthermore, all preoperative PET scans were reviewed by two independent nuclear medicine physicians (ME, DH), in presence of CT scans. The localization of the primary tumor on PET was classified as: 'peripheral' or 'central / adjacent to the mediastinum'. Mediastinal lymph nodes were localized according to Naruke. Criteria for PET positivity were the presence of focally enhanced uptake versus background. Whenever radiologists or nuclear medicine physicians disagreed, scans were reviewed again till agreement was obtained, which was possible in all cases. Results regarding adherence to mediastinal staging procedures and performance of mediastinoscopy were compared between the three consecutive periods and with the results from our previous study.

Accuracy of surgical mediastinal staging procedures

*1) Adherence to staging management guidelines*

According to staging protocols in the four hospitals, PET should be performed in all patients with (suspicious) malignant lesions that were eligible for surgical resection. In all

four hospitals at the time of this study, PET was generally used to evaluate the mediastinum and to detect distant metastases.

All four hospitals used the following guideline to decide whether or not to perform a mediastinoscopy: only in case of a peripheral tumor, without evidence of mediastinal lymph node metastases on PET and CT, mediastinoscopy could be omitted. In case no PET was performed, only in patients with histologically proven clinical(c) T1N0 squamous cell carcinomas, mediastinoscopy could also be omitted (like during the period before introduction of PET[1]). For each patient, we compared clinical practice to the corresponding guidelines. Surgery for proven N2 or N3 disease was considered non-beneficial and therefore not performed in these patients during this study. There were no specific guidelines existed concerning mediastinal lymph node sampling during thoracotomy in the participating hospitals. In general, enlarged nodes were removed. In case of upstaging we analyzed whether preoperative mediastinal staging guidelines were adequately followed and if not, whether upstaging could have been prevented in case guidelines would have been followed correctly.

*2) Performance of mediastinoscopy*

Of all mediastinoscopies, information concerning site of biopsies and histopathologic diagnosis were registered. Locations of mediastinal lymph nodes were classified according to Naruke[3]. We considered the harvest of mediastinoscopy optimal, in case lymph node stations 4 (right and left) and 7 were biopsied with lymph node tissue present in all three biopsies. If these 3 sites were not biopsied results were considered to be non-optimal. In case PET showed positive mediastinal lymph nodes that were accessible for mediastinoscopy, we investigated whether these nodes were actually biopsied during mediastinoscopy.

*3) Upstaging*

In case of upstaging post-thoracotomy, we investigated whether these positive mediastinal lymph nodes found during thoracotomy would have been accessible for

mediastinoscopy and if so, whether this "false negative" staging procedure might have been caused by non-adherence to staging guidelines.

Statistical analysis

We used SPSS 13.0 for statistical analysis. To determine accuracy of preoperative surgical mediastinal staging procedures and to compare results from this study with the ones from our previous study, we performed chi-square test. Statistical significance was defined at $p < 0.05$.

**Results**

From October 2002 to April 2005, 143 patients with histologically proven NSCLC undergoing either mediastinoscopy, thoracotomy or both, were evaluated. Mean age was 65 years ± 9 (range 41-84) and 107 (74.8%) were men. Of the 143 NSCLC patients, 46 had squamous cell carcinoma, 64 adenocarcinoma, 4 bronchiolo-alveolair cell carcinoma and 28 large cell undifferentiated carcinoma; 52 (36.4%) were analyzed in period I, 46 (32.2%) in II and 45 (31.5%) in III.

Accuracy of surgical mediastinal staging procedures

*1) Adherence to staging management guidelines*

Table 1 presents data on adherence to staging guidelines and the number of diagnostic procedures that were performed in each period of time. There were no differences between these three periods. Overall, guidelines for indicating mediastinoscopy were adequately followed in 80% of patients.

Mediastinal lymph nodes were sampled in 75 out of 122 patients (61.5%) during thoracotomy (Table 1). Maximum time interval of 28 days between mediastinoscopy and thoracotomy was exceeded in 9 patients, so data from 66 out of 75 patients were available for analysis on upstaging. Mean time interval between mediastinoscopy and thoracotomy was 17.2 days (range 7 – 26 days). In 8 out of the 66 (12.1%) patients, one or more sampled mediastinal lymph nodes proved to be malignant.

**Table 1 Adherence to staging guidelines and the number of diagnostic procedures that were performed in each period of time after implementation of PET**

| Period | PET[1] | MS (HO)[2] | GFC/GNFC[3] | Surgery | Sampling[4] | Upstaged[5] |
|---|---|---|---|---|---|---|
| **I (n = 52)** | Y 34 | Y 18 (5) | 16 / 2 | Y 15 | Y 12 | 0 |
| | | N 16 | 14 / 2 | Y 16 | Y 9 | 0 |
| | N 18 | Y 12 (3) | 12 / 0 | Y 9 | Y 4 | 2 |
| | | N 6 | 2 / 4 | Y 6 | Y 3 | 1 (GNFC)* |
| **Total %** | 65.4 % | 30 (8)(26.7%) | HO 84.6 % | 46 | 60.9 % | 11.5 % |
| **II (n = 46)** | Y 33 | Y 13 (5) | 13 / 0 | Y 8 | Y 6 | 1 |
| | | N 20 | 13 / 7 | Y 20 | Y 15 | 2 (GFC) |
| | N 13 | Y 7 (2) | 7 / 0 | Y 2 | Y 1 | 0 |
| | | N 6 | 0 / 6 | Y 6 | Y 1 | 0 |
| **Total %** | 71.7 % | 20 (7)(35%) | HO 71.7 % | 36 | 63.9 % | 14.3 % |
| **III (n = 45)** | Y 31 | Y 16 (4) | 16 / 0 | Y 13 | Y 9 | 1 |
| | | N 15 | 13 / 2 | Y 15 | Y 8 | 1 (GFC) |
| | N 14 | Y 8 (1) | 8 / 0 | Y 6 | Y 4 | 0 |
| | | N 6 | 0 / 6 | Y 6 | Y 3 | 0 |
| **Total %** | 68.9 % | 24 (5)(20.8%) | HO 82.2 % | 40 | 60 % | 10.5 % |
| **Overall** | **68.5 %** | **Y 74 (27%)** | **HO 79.7 %** | **Y 122** | **61.5 %** | **12.1 %** |

*[1] Y = procedure performed; N = procedure not performed*

*[2] Number of mediastinoscopies (MS) performed (between brackets, the number and/or percentage of mediastinoscopies with optimal harvest (HO; HNO = harvest not optimal)*

*[3] Guidelines followed correctly/Guidelines not followed correctly (GFC/GNFC)*

*[4] Percentage of thoracotomies during which mediastinal lymph nodes were sampled*

*[5] Percentage of patients diagnosed having N2-3 disease after thoracotomy (between brackets whether guidelines were followed correctly)*

** Mediastinal lymph nodes that proved positive for metastases during thoracotomy were not accessible for mediastinoscopy*

In the one patient where mediastinal staging guidelines were not followed correctly (GNFC) (Table 1), mediastinal lymph nodes that proved to be involved during thoracotomy were not accessible for mediastinoscopy. So upstaging could not have been prevented in this patient if guidelines would have been adequately followed.

*2) Performance of mediastinoscopy*

In Table 2 results of PET and mediastinoscopy are presented. The number of separate mediastinal lymph nodes that were positive on PET and accessible for mediastinoscopy was respectively 15, 13 and 3 for the three consecutive periods. There were no differences between these three periods with regard to upstaging.

We found that out of all 74 mediastinoscopies, 20 (27%) were done with an optimal harvest (Table 1) and 13 (18%) were positive for mediastinal metastases (Table 2). Overall, out of 49 separate PET positive nodes that were accessible for mediastinoscopy, 31 (63%) were actually biopsied (Table 2). During all 74 mediastinoscopies, a total of 163 separate mediastinal lymph node localizations were biopsied, of which 14 (9%) separate nodes proved positive for metastases (data not shown). This was not significantly different compared to the results from our previous study[1], where a total of 981 mediastinal lymph node localizations were biopsied during 387 mediastinoscopies, of which 97 (10%) proved to be positive for metastases.

Overall, data from 66 patients could be analyzed for upstaging; PET was performed in 54 of these patients. PET appeared to be false negative for mediastinal lymph node metastases in 3 patients (5.6%) with PET-positive (peripherally located) adenocarcinomas (Table 2).

<u>Comparison to period before introduction of PET[1]</u>

In Table 3 an overview comparing the results from this study with those from our previous study is presented. After the introduction of PET in our study cohort, adherence to guidelines on whether or not to perform mediastinoscopy increased significantly ($p = 0.002$) from 66% to 80%. The percentage of mediastinoscopies performed with an optimal harvest decreased and the number of thoracotomies where mediastinal lymph nodes were sampled increased, however, for both this did not reach significance.

**Table 2 Results of PET and mediastinoscopy in each period of time after implementation of PET**

| Period | PET [1] | Separate MLN [2] | Accessible MLN biopsied [3] | MS | Upstaged |
|---|---|---|---|---|---|
| **I (n = 52)** | P 16 | 23 | 15 (65.2%) | P 1<br>N 14<br>ND 1 | -<br>0<br>0 |
| | N 18 | - | - | P 0<br>N 3<br>ND 15 | -<br>0<br>0 |
| | ND 18 | - | - | P 2<br>N 10<br>ND 6 | -<br>2<br>1 |
| | | | | | |
| **II (n = 46)** | P 20 | 18 | 13 (72.2 %) | P 3<br>N 10<br>ND 7 | -<br>1<br>0 |
| | N 13 | - | - | P 0<br>N 0<br>ND 13 | -<br>1<br>1 |
| | ND 13 | - | - | P 4<br>N 3<br>ND 6 | -<br>0<br>0 |
| | | | | | |
| **III (n = 45)** | P 16 | 8 | 3 (37.5 %) | P 1<br>N 13<br>ND 2 | -<br>1<br>0 |
| | N 15 | - | - | P 0<br>N 2<br>ND 13 | -<br>0<br>1 |
| | ND 14 | - | - | P 2<br>N 6<br>ND 6 | -<br>0<br>0 |
| | | | | | |
| **Overall Total** | 98 | 49 | 31 (63.3 %) | P 13 | 8 |

*[1] Results from PET pertaining to the mediastinum (P: positive → either separate mediastinal lymph nodes were positive or presence of a tumor adjacent to the mediastinum; N: negative)*

*[2] Number of separate mediastinal lymph nodes that were positive on PET and accessible for mediastinoscopy*

*[3] Number of separate positive mediastinal lymph nodes on PET that were actually biopsied during mediastinoscopy*

*Abbreviations: MS mediastinoscopy; MLN mediastinal lymph nodes; P positive result; N negative result; ND not done*

**Table 3 Influence of introduction of PET on adherence to mediastinal staging protocols and performance of mediastinoscopy, in percentages**

| % | Pre-PET period n = 569* | Post-PET period n = 143 | p |
|---|---|---|---|
| **% correctly indicated MS [1]** | 66.1 | 79.7 | 0.002 |
| **% MS according to gold standards** | 39.0 | 27.0 | 0.083 |
| **% positive MS** | 15.5 | 17.6 | NS [2] |
| **% thoracotomies with nodes sampled [3]** | 52.7 | 61.5 | 0.082 |
| **% patients upstaged after thoracotomy** | 16.7 | 12.1 | NS |

*[1] MS = mediastinoscopy*

*[2] NS = not significant*

*[3] in case surgery was performed*

** Smulders SA. Lung Cancer 2005; 47(2): 243-2*

**Discussion**

In this study PET scan was pre-operatively performed in 69% of patients undergoing mediastinoscopy and/or thoracotomy for NSCLC. We found that in daily practice, guidelines on whether or not to perform mediastinoscopy were correctly followed in 4 out of every 5 patients. This was significantly better compared to the period before the introduction of PET (p = 0.002). In only 27% of mediastinoscopies harvest of mediastinal lymph nodes was considered optimal, however 18% of mediastinoscopies proved to be positive for metastases. Overall, 63% of separate positive mediastinal lymph nodes on PET that were accessible for mediastinoscopy were actually biopsied. Finally, sampling of mediastinal lymph nodes during thoracotomy was done in 62% of cases, which led to upstaging in 12% of patients. PET proved to be false negative for mediastinal lymph node metastases in 6% of cases.

In this study we found that adherence to guidelines on whether or not to perform mediastinoscopy was significantly (p = 0.002) increased after the introduction of PET.

Perhaps shortly after the implementation of such a promising new diagnostic imaging tool like the PET scan, clinicians are more aware of the current literature and try extra hard to adhere to existing guidelines. Furthermore, it is possible that these guidelines after the introduction of PET were simply easier to adhere to than before. However, in contrast to what we expected, the number of patients that underwent PET, did not increase in time. Results from our study might furthermore be influenced because in 1 out of every 3 patients, PET was not done, possibly due to non acquaintance of some physicians with PET in the beginning of this study and because of problems implementing its use in practice, like long waiting lists.

Although we hypothesized that performance of mediastinoscopy would improve, because of the awareness of our previous study and the introduction of PET, the opposite appeared to be true. In fact, the number of mediastinoscopies with an optimal harvest decreased, although not significantly, from 39% to 27%. This may be caused by the fact that results of PET are considered as a guide to biopsy only one or two PET positive nodes, rather than trying to get an optimal harvest during mediastinoscopy.
Furthermore, we found that not all positive mediastinal lymph nodes on PET were actually biopsied during mediastinoscopy. Despite this we found in our present study a slightly higher percentage of positive mediastinoscopies (17.6%), compared to our former study (15.5%) (NS).
Herder et al. demonstrated that use of PET for all lung cancer patients is not better than the normal staging procedures[4]. On the other hand it was demonstrated that the use of PET in NSCLC patients considered for surgery is cost-effective[2]. Despite this proven cost-effective use, introducing a new diagnostic tool, without additional measures for optimal implementation, does not automatically result in significant change of attitude of physicians and incorporation of new guidelines in daily routine. As such, this is well-known from other areas of pulmonary medicine, such as introduction of guidelines for optimal use of diagnostic techniques for pulmonary embolism[5-8]. For the introduction of expensive new drugs resulting in improvement of medical treatment despite additional

costs, regulatory boards like FDA and EMEA have to evaluate this and consider whether the benefit is sufficiently large to have significant impact on outcome. For the introduction of new diagnostic techniques there is no comparable standard procedure and it needs more than simply making the technique available, to come to optimal use. Professional organizations should not only develop guidelines but need to evaluate its use as well and, if insufficient, stimulate optimal use by supervised introduction within quality care projects. Governmental health care and/or insurance companies need to stimulate these by supplying financial support for the introduction of cost-effective diagnostic algorithms and treatment[9,10]. Furthermore, clinicians have their own responsibility to be aware of the characteristic performance of the new tool used in their institution before integrating it into diagnostic algorithms[11].

**In summary after the introduction of PET we found that:**

1. Staging protocol is followed in 80% of all cases.
2. One out of three patients did not underwent a PET scan.
3. Optimal harvest in mediastinoscopy in only 27% of all cases.
4. Only 62% of positive PET nodes accessible for mediastinoscopy were actually biopsied.
5. Introducing optimal use of a new diagnostic technique fails if not actively supported.

We believe that monitoring these aspects of care is extremely important but sadly in most hospitals not performed.

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Chapter 4

# Observer Variation of $^{18}$FDG-PET in Mediastinal Staging of NSCLC as a function of Experience, and its potential Clinical Impact

Sietske A Smulders, Chad M Gundy [1]

Arthur van Lingen [2], Emile FI Comans [2]

Frank WJM Smeenk, Otto S Hoekstra [1-2]

**(Submitted)**

[1] Departments of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam

[2] Department of Nuclear Medicine and PET research, VU University Medical Center, Amsterdam

The Netherlands

**Abstract**

*Background:* $^{18}$FDG-PET scans are obtained to stage non-small cell lung cancer (NSCLC). Lymph node status at PET is important to guide the further staging procedure, especially with the introduction of new less invasive biopsy techniques such as endoscopic ultrasound. This study was designed to test the extent of variation among nuclear medicine physicians with respect to this aspect of NSCLC staging at PET, and to assess how their interpretations differed from that of expert readers.

*Methods:* Two groups of nuclear medicine physicians with different levels of PET experience ('experienced' (n=7) and 'inexperienced' (n=7)) reviewed thirty PET scans of patients with suspected operable NSCLC. They were requested to identify and localise suspicious mediastinal lymph nodes (MLN) on each scan and to formulate a clinical management advise using standardized algorithms. Results were compared between the 2 groups, between individuals and with expert reading.

*Results:* Overall, 80% of the management recommendations and 68% of N-stage classifications were correct, with moderate and good interobserver agreement (kappa 0.59 and 0.65, respectively). Detection rate (72% versus expert reading) and most common mislocalisations of separate MLN stations were equally distributed between the 2 groups. Experience with PET translated into a better ability to localise MLN stations (68% versus 51%, respectively), and experienced readers appeared to be more familiar with translating PET readings into clinically useful statements.

*Conclusions:* Although our results suggest that clinical experience with PET increases observers' ability to read and interpret results from PET adequately, there is still room for improvement, even among experienced observers. Education with structured databases in a skill's lab setting supported by expert feedback might be an effective instrument of knowledge transfer.

## Introduction

In non-small cell lung cancer (NSCLC), proven ipsi- (N2) or contralateral (N3) mediastinal lymph node involvement precludes cure by surgery. F-18-deoxyglucose positron emission tomography ($^{18}$FDG-PET) is increasingly used to stage NSCLC patients. The yield of whole-body PET pertains to typing the primary pulmonary lesion and on the preoperative identification of distant and lymph node metastases. Moreover, PET may simplify and improve lymph node evaluation by setting the indication for biopsy and improving its yield. Mediastinoscopy is the standard technique of invasive lymph node staging but the results in daily practice are quite variable[1]. It has been suggested that the proportion of tumor positive procedures increases if guided by PET[2;3]. So far, mediastinoscopy is the most often used invasive method, but more recently endoscopic techniques (like EUS-FNA) have been developed. Since the mediastinal areas covered by mediastinoscopy and EUS-FNA are largely complementary, proper localisation of possible malignant nodes is important to assign patients to the appropriate procedure. $^{18}$FDG-PET criteria of test positivity for mediastinal lymph node staging are based on recognition of focally enhanced uptake ('hot spots') versus background, rather than on quantitative assessment (like the 1 cm short axis criterion with CT scanning). Results from PET studies pertaining to its accuracy in mediastinal staging are robust[4], but as the technique is disseminating, observer variation and learning curves need to be documented.
The aim of the present study was to measure the observer agreement and accuracy versus expert readings of mediastinal lymph nodes in NSCLC staging with $^{18}$FDG-PET, at various levels of complexity and as a function of experience.

## Materials and Methods

*Study Design*

We used a set of 30 PET scans from the study by Joshi et al.[5] of consecutive patients referred for staging to the Department of Nuclear Medicine and PET Research of the VUmc. To obtain an adequate case mix, we included scans of patients with a range of

mediastinal lymph node sizes at CT scanning: 1) ≤ 10 mm short axis diameter (n = 10), 2) 10.1-15 mm (n = 10) and 3) > 15 mm (n = 10). PET scans had been performed according to the standard protocol in our institution using a full ring BGO PET scanner (ECAT EXACT HR+, CTI/Siemens, starting 60 min. after 370 MBq $^{18}$FDG)[5].
The scans were analysed by 14 nuclear medicine physicians, who had extensive experience with SPECT but variable expertise with PET and mediastinal lymph node staging in NSCLC: 7 had no personal experience with PET (the 'inexperienced group') whereas the others had at least one year of experience with PET in NSCLC patients in their own clinical practice which comprised access to mobile PET once every one or two weeks (the 'experienced group'). On average, the inexperienced group had reviewed 0-15 PET scans each compared to a 100-150 (with at least 50% NSCLC) each in the experienced group. Prior to this study, the observers had been instructed in workshops by two expert PET readers, a pulmonologists and a surgeon about the concepts, principles and practice of mediastinal staging in NSCLC by PET and other methods. The results of the observers were compared to the combined judgement of the two expert nuclear medicine physicians (EFC, OSH), and the latter readings were used as the gold standard. The expert readers had been working together in the same university hospital for numerous years and had a broad experience with PET[6-8].

We developed a software tool running Matlab 5.3, which allowed simultaneous visualisation of PET images in the axial, coronal and sagittal planes (at 5 or 10 mm slice thickness), with possible cross linking. Each observer was requested to identify and interpret any abnormal hot spot representing primary tumor or lymph node, blinded for the results of the other readers. This software tool was installed on the personal computer of each observer, and the results were electronically stored for analysis. In order to be able to accurately relate results of different observers, the coordinates of each hot spot identified by an observer were stored and linked to the assigned interpretation. Since none of the observers had worked with this software before, we provided a test set (derived from the original data set) of three scans to each observer

**Table 1 Classification system of tumor and lymph nodes**

| **Primary tumor** | **Lymph node localisation** [a] |
|---|---|
| **- Presence** | * No lymph nodes present |
| * No tumor present | * N1 L / R |
| * Primary tumor | * N2 L / R |
| * Second primary | * N3 |
| | * N4 L / R |
| **- Localisation** | * N5 / * N6 / * N7 |
| * Peripheral | * N8 L / R |
| * Adjacent to mediastinum | * N9 L / R |
| * Adjacent to hilus | * N10 L / R |
| | * Clavicular L / R |
| **Likelihood of malignancy** | |
| * Definitely benign | |
| * Probably benign | |
| * Equivocal | |
| * Probably malignant | |
| * Definitely malignant | |
| **Management recommendation** | |
| * Invasive lymph node evaluation | |
| * Thoracotomy | |
| * Expectative policy | |

[a] *According to Naruke's map of lymph node definitions (Figure at page 16)*

prior to the study. These three scans comprised 29 separate abnormal mediastinal lymph node localisations and therefore provided an adequate way to practice working with Naruke's map of lymph node localisations (Figure adapted from Mountain, page 16 of this thesis)[9]. Observers had knowledge of the clinical information provided with the original PET scan referral, except for the mediastinal stage at CT.

*Data acquisition*

The observers were asked to interpret abnormal hot spots pertaining to the primary tumor and lymph nodes in terms of their *localisation* and *likelihood of malignancy* using the classification systems shown in Table 1 and the figure at page 16. Criteria for test positivity was the presence of focally enhanced uptake vs. background. Furthermore, observers were asked to formulate a *recommendation* with respect to the next *management step* to the referring clinician (Table 1). In this context, we instructed them to use the following protocol: 1) recommend biopsy of mediastinal lymph nodes in case of suspected (hilar or mediastinal) lymph node involvement, and in case of tumors adjacent to the mediastinum or hilus; 2) recommend thoracotomy in case of a peripheral primary tumor without suspicious mediastinal lymph nodes at PET; 3) recommend an expectative policy in case PET shows no abnormal uptake in either the primary site nor in lymph nodes. For the purpose of the present investigation, they were instructed to ignore possible suspicious extrathoracic localisations in these management considerations.

*Data analysis*

Using the individual scores of the observers, we assigned an 'N-stage according to PET' for each observer and each patient using the following classification:

1. N0 (peripheral primary tumor, no mediastinal hot spot)
2. N1 (peripheral primary tumor and separate hot spot considered to be a hilar lymph node)
3. N0-N1 (primary tumor within hilar area, no separate mediastinal hot spot)
4. N0-N2 (primary tumor adjacent to mediastinum, no separate mediastinal hot spot)
5. N2 (hot spot compatible with ipsilateral mediastinal lymph node)
6. N3 (hot spot compatible with contralateral mediastinal or clavicular lymph node)

We performed a more detailed analysis of the nature of the errors in the 'management recommendation' classification versus the expert reading, identifying whether these errors followed the observers' own interpretation of suspicious lymph node stations, or

resulted from true errors (protocol violation). For example, the former situation occurred if, in case of a peripheral primary tumor, an observer considered the ipsilateral right lower tracheobronchial station to be positive at PET, whereas the expert only identified the primary lesion. The resulting discrepant management recommendations (mediastinoscopy versus thoracotomy, respectively) directly flow from these classifications. We coined such an incorrect answer as a *mistake* (M). However, if this observer would have advised to proceed directly to thoracotomy, this was considered a *protocol violation* (P).

We also measured the accuracy of defining and localising suspected mediastinal lymph node stations at PET. Compatible with known limitations of PET with respect to spatial resolution and accounting for different levels of clinical relevance, we accepted the following differences of nodal classifications (Figure at page 16): Naruke stations 1 and 2 (left (L) / right (R) respectively); 4R and 10R; 4L and 10L and 5; 8 and 9 (L / R, respectively). Using this simplified system, we analysed whether observers defined and localised suspected lymph node metastases versus the expert reading 'correctly', 'incorrectly' or 'not at all'.

*Statistical Analysis*

Statistical analysis was done by SPSS 13.0 software. To determine interobserver agreement regarding 'management recommendation' and 'N-stage', and to compare this to expert readings, we calculated the Kappa coefficients, using AGREE 7.2. We used weighted kappa's for the N-stage analysis. Furthermore, to detect potential differences between the two groups of observers with different PET experience with respect to the nature of the management recommendation errors, and the classification of separate mediastinal hot spots, we used the Wilcoxon-Mann-Whitney test. Statistical significance was set at $p < 0.05$.

**Table 2 Inter observer agreement and accuracy as a function of experience with respect to the classification of 'N-stage' and 'management recommendation'**

| | Inexperienced Observers (n = 7) | Experienced Observers (n = 7) | Overall |
|---|---|---|---|
| **Management recommendation** [a] | | | |
| **- Agreement versus expert** | 0.60 (0.42 – 0.77) | 0.58 (0.37 – 0.79) | 0.59 (0.42 – 0.76) |
| **- Pair wise agreement** | 0.48 (0.35 – 0.62) | 0.56 (0.41 – 0.71) | 0.50 (0.37 – 0.63) |
| **N-stage** [b] | | | |
| **- Agreement versus expert** | 0.58 (0.36 – 0.80) | 0.72 (0.55 – 0.88) | 0.65 (0.47 – 0.83) |
| **- Pair wise agreement** | 0.56 (0.44 – 0.68) | 0.61 (0.49 – 0.74) | 0.58 (0.46 – 0.69) |

[a] *Kappa (95% confidence interval)*

[b] *Weighted kappa (95% confidence interval)*

**Results**

The 30 PET scans comprised a total of 89 locations of suspected malignancy, according to the gold standard (expert reading). Thirty-four represented tumor locations, 55 were lymph nodes (10 hilar, 39 mediastinal and 6 supraclavicular). According to expert readers, there was a mean of three sites (primary lesion and lymph nodes) per patient (range 1-13). The experts classified 82 lesions as 'definitely malignant', 5 as 'probably malignant' and 2 as 'equivocal'. In the final analysis, these 'probably' and 'definitely' malignant locations were classified as malignant. The expert N-stage classifications included 9 'N0', 3 'N1', 1 'N0-N1', 3 'N0-N2', 9 'N2' and 5 'N3', according to the definitions mentioned earlier.

**Table 3 Details on N-stage (using the classification system described in the methods section) in 30 scans for each inexperienced observer**

| Inexperienced observers | N-stage classified correctly [% (n)] [a] | N-stage overestimated [% (n)] [b] |
|---|---|---|
| **INEXP 1** | 70.0 (21) | 20.0 (6) |
| **INEXP 2** | 56.7 (17) | 20.0 (6) |
| **INEXP 3** | 70.0 (21) | 13.3 (4) |
| **INEXP 4** | 63.3 (19) | 23.3 (7) |
| **INEXP 5** | 66.7 (20) | 20.0 (6) |
| **INEXP 6** | 66.7 (20) | 20.0 (6) |
| **INEXP 7** | 66.7 (20) | 10.0 (3) |
| **Total** | 65.7 (138) | 18.1 (38) |
| **Experienced observers** | | |
| **EXP 1** | 63.3 (19) | 30.0 (9) |
| **EXP 2** | 76.7 (23) | 6.7 (2) |
| **EXP 3** | 73.3 (22) | 10.0 (3) |
| **EXP 4** | 73.3 (22) | 20.0 (6) |
| **EXP 5** | 73.3 (22) | 13.3 (4) |
| **EXP 6** | 73.3 (22) | 16.7 (5) |
| **EXP 7** | 60.0 (18) | 20.0 (6) |
| **Total** | 70.5 (148) | 16.7 (35) |

[a] *Percentage of N-stages classified correctly versus expert reading*

[b] *Percentage of overestimated N-stages versus expert reading*

*Management recommendations* were correct in 80% of cases (86 errors out of 420 recommendations, 42 in the experienced group and 44 in the inexperienced group). The accuracy versus expert reading was moderate (kappa 0.59) at either level of experience (Table 2). The level of agreement among inexperienced observers tended to be lower, but did not reach significance. Four scans accounted for a total of 38 errors (44%) while not a single mistake by any observer was made in eight.

**Table 4 Accuracy of inexperienced and experienced observers to detect and localise the 26 mediastinal lymph node stations present according to the expert reading**

| Inexperienced observers | Identified [% (n)] [a] | Correctly localised [% (n)] [b] |
|---|---|---|
| **INEXP 1** | 76.9 (20) | 30.0 (6) |
| **INEXP 2** | 84.6 (22) | 63.6 (14) |
| **INEXP 3** | 61.5 (16) | 62.5 (10) |
| **INEXP 4** | 80.8 (21) | 23.8 (5) |
| **INEXP 5** | 69.2 (18) | 55.6 (10) |
| **INEXP 6** | 65.4 (17) | 64.7 (11) |
| **INEXP 7** | 57.7 (15) | 66.7 (10) |
| **Total** | 70.9% (129) | 51.2% (66) |
| **Experienced observers** | | |
| **EXP 1** | 76.9 (20) | 65.0 (13) |
| **EXP 2** | 61.5 (16) | 81.3 (13) |
| **EXP 3** | 69.2 (18) | 83.3 (15) |
| **EXP 4** | 73.1 (19) | 89.5 (17) |
| **EXP 5** | 84.6 (22) | 77.3 (17) |
| **EXP 6** | 80.8 (21) | 42.9 (9) |
| **EXP 7** | 69.2 (18) | 38.9 (7) |
| **Total** | 73.6% (134) | 67.9% (91) |

[a] *Percentage of identified nodal stations versus expert reading*

[b] *Percentage of correctly localised nodal stations versus expert reading (e.g. INEXP 1 identified 20 out of the 26 stations, and 6 out of 20 were localised correctly).*

In the group of inexperienced readers, 29 (of 44; 66%) of the incorrect management recommendations were protocol violations (type 'P'), versus 17 (of 42; 40%) in the experienced readers group (p = 0.12). On the contrary, errors that directly flow from reading errors (type 'M') were significantly more prevalent in the group of experienced readers (25 out of 42 = 59%), versus 15 out of 44 (34%) in the inexperienced readers group (p = 0.03). Common errors (type 'P', protocol violations) were e.g. to recommend 'expectative policy' or 'directly to thoracotomy' in a patient without enhanced PET uptake

in primary tumor and mediastinal lymph nodes. However, the provided clinical information stated that bronchoalveolar cell carcinoma had been proven histologically. Therefore, 'mediastinal lymph node evaluation' should have been recommended, because the mediastinum in a patient with adenocarcinoma without $^{18}$FDG uptake of the primary tumor cannot be reliably evaluated so that histological confirmation of the mediastinum is required.

*N-stage* classifications were correct in 68% of cases (286 out of 420 assigned N-stages, 138 in the inexperienced group and 148 in the experienced group). Experienced observers tended to have a better agreement with the expert reading than inexperienced ones (weighted kappa's 0.72 and 0.58, respectively). N-stages were overestimated in 17.4% (16.7% by the experienced and 18.1% by the inexperienced observers) and underestimated in 14.5% of cases (12.9% and 16.2%, respectively). The individual scores of the observers (Table 3) reveal that errors in either direction were made by most of them.

Since we used three scans to practice on localising mediastinal lymph nodes, 27 scans remained with 26 separate lymph node localisations. The detection rate of individual mediastinal lymph node stations was similar for inexperienced and experienced observers (71% and 74%, respectively, Table 4), and the variation within the groups was also comparable. However, experienced readers were better at localising the stations than inexperienced readers were (correct in 68% versus 51%, respectively). The most common mislocalisations (Table 5 and the figure at page 16) were to classify right tracheobronchial stations (4R) as upper right paratracheal (2R), subcarinal (7) as right tracheobronchial (4R) and left para-esophageal (8/9L) as left tracheobronchial (4L).

**Discussion**

Observer variation is the Achilles' heel of diagnostic imaging[10], and especially of tests that apply visual interpretation. It is therefore surprising that the clinical PET literature contains few studies on observer variation beyond the level of occasional reports on

**Table 5 Mediastinal lymph node stations * by experienced and inexperienced observers, according to Naruke**

| Expert (CA) | Experienced and Inexperienced Observers | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **2 R** | **3** | **4 L** | **4 R** | **6** | **7** | **8 R** | **8 L** | **SC** | **T †** | **Missed** |
| **2 R (1 R)** | **4** | | | | | | | | | 1 | 9 |
| **3** | **7** | | | 3 | | | | | | 1 | 3 |
| **4 L (5, 10 L)** | | | **24** | | 1 | | | | | 14 | 31 |
| **4 R (10 R)** | **18** | 1 | | **85** | | 1 | 1 | | 1 | 14 | 19 |
| **7** | | 1 | 2 | **13** | | **15** | | | | 1 | 25 |
| **8 R (9 R)** | | | | 4 | | | **8** | | | 1 | 1 |
| **8 L (9 L)** | | | **9** | | 1 | | | **8** | | 1 | 9 |
| **SC** | 2 | | | 2 | | | | | **14** | 6 | 3 |

** Using the simplified system mentioned in the methods section regarding the acceptance of different lymph node classifications, consistent with clinical practice, for expert and both groups of observers*

*† T Tumor: observer identified pertaining mediastinal lymph node as primary or second primary tumor*

*CA Correct Alternative, according to simplified system; SC Supra- or infraclavicular lymph nodes;*

variation between two observers participating in an accuracy study. The present study reports on the results of 14 observers stratified by their experience with PET, and it accounts for several aspects of the clinical context of NSCLC staging (management recommendation, N-stage, nodal stations). We found that the accuracy (versus expert reading) was moderate to substantial at moderate levels of interobserver agreement. Our results suggest that clinical experience with PET improves the ability of readers to localise mediastinal hot spots correctly, and this is relevant with respect to the next clinical step: i.e. to decide which invasive verification method should follow and to enhance the yield of such procedures. Moreover, within the more experienced group, the

agreement of assigning N-stages and management recommendations tended to be better. Finally, familiarity with clinical practice and staging protocols for NSCLC patients may have contributed to fewer inconsistencies in management recommendations. Our management advice constructs were designed to account for generally recognized limitations of PET in mediastinal staging.

With slightly different endpoints the interobserver agreement of CT reading appears to be similar to what we have reported: in CT evaluation of mediastinal lymph node size, Guyatt et. al. reported a kappa of 0.61 regarding the presence of any nodes greater than 1 cm on CT scan[11]. However, agreement in different nodal groups varied widely and it appeared to be far more difficult for the left superior mediastinal nodes. In our study we found that some mistakes were made relatively more often regarding localising separate lymph nodes (Table 5). With the increasing clinical methods to verify imaging findings (transesophageal, transbronchial ultrasound guided fine-needle aspiration, mediastinoscopy, video-assisted thoracoscopy), the relevance of interpreting images at the nodal level is growing. PET-CT may help to improve the yield of PET and CT reading, in patients newly presenting with lung cancer, but also in restaging after neo-adjuvant therapy. Limitations of our study were the lack of co-reading of PET with CT scans, the relative unfamiliarity of the observers with the display and registration software, and perhaps the lack of standardized computer screens.

In the Netherlands, the availability of $^{18}$FDG-PET is rapidly expanding, even in smaller hospitals, and this has major implications for local nuclear medicine physicians as well as for residents. To our knowledge, the duration of time that is needed before results on PET are adequately reviewed and interpreted (´the learning curve´) by nuclear medicine physicians is unknown. We had anticipated striking differences between experienced and inexperienced readers, but this was not the case. However, there was obvious room for improvement in the experienced group and we suggest that optimal performance is not acquired by experience alone but requires higher levels of direct feedback[12]. We propose that such feedback could be achieved efficiently in experimental settings like applied in

our study. We believe that datasets like the present should play a key role in training of residents since they can learn and demonstrate improving skills at any time during their training. However, for example in the Dutch setting, this requires that residents should spend more time in such skills labs and less in daily clinical production.

**Conclusion**

Emerging alternatives to invasively stage the mediastinum in NSCLC puts high levels of skill to interpret PET and CT scans in NSCLC patients. Observer variation of PET and CT reading in mediastinal staging appear to be similar, with obvious room for improvement. Training of imaging specialists may require higher levels of feed-back which can more efficiently be obtained in skills labs using existing databases than currently achievable in local daily clinical practice.

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# Part II

# Postoperative Function

Chapter 5

# Actual and Predicted Postoperative Changes in Lung Function after Pneumonectomy

A retrospective analysis

Sietske A Smulders, Frank WJM Smeenk

Maryska LG Janssen-Heijnen, Pieter E Postmus

**Chest 2004; 125: 1735-1741**

**Abstract**

*Background:* Little is known about long-term effects of pneumonectomy on lung function and exercise tolerance. We evaluated the long-term validity of two formulas frequently used to predict postoperative lung function as well as trends in postoperative lung function and late postoperative exercise capacity.

*Setting:* Non-university teaching hospital of Eindhoven, The Netherlands.

*Patients:* Patients who underwent pneumonectomy between 1993 and 1998 and survived for more than one year after the operation.

*Methods and Results:* Lung function and exercise test data of 32 patients were analyzed. Postoperative forced vital capacity (FVC) and forced expiratory volume in one second ($FEV_1$) according to Kristersson/Olsen (split function of resected lung) and Juhl and Frost (number of segments to be resected) were calculated and compared with observed values measured in the third postoperative year. Calculated values correlated well with observed values, whereas Kristersson/Olsen appeared to be more accurate than Juhl and Frost. When considering trends in $FEV_1$, we found a mean decline of 44 ml/year; only 3 patients (12%) showed a rapid decline of more than 100 ml/year. Of 14 patients (44%), postoperative maximal exercise capacity was impaired due to ventilatory limitation.

*Conclusions:* The Kristersson/Olsen formula was more accurate in predicting postoperative lung function in the third postoperative year in pneumonectomy patients. Although the annual decline in $FEV_1$ in these patients is almost the same as in healthy, non-COPD patients, pneumonectomy has serious implications on exercise capacity in many patients.

## Introduction

Lung cancer is currently the most common cause of cancer mortality throughout the world. It is the second most frequent type of cancer among men and women[1;2]. Non-small cell lung cancer (NSCLC) accounts for 80% of all newly diagnosed lung cancers. At present, complete resection offers the best prospects and results in cure in a substantial number of patients with NSCLC. In order to determine whether lung resection is feasible in NSCLC patients and to what extent, resectable patients need to be carefully screened for their cardiopulmonary reserve. The best and most frequently used indicators for postoperative lung function are the forced expiratory volume during first second$_{\text{-predicted postoperative}}$ ($FEV_{1\text{-ppo}}$)[3-6], diffusion capacity of the lung for carbon monoxide$_{\text{-ppo}}$ ($D_{LCO\text{-ppo}}$)[6-9] and maximal oxygen uptake during exercise$_{\text{-ppo}}$ ($VO_2max_{\text{-ppo}}$)[4;10;11]. There is consensus in the literature that lobectomy leads to very little permanent functional deficit after 6 months[4]. Pneumonectomy causes a more permanent deficit which is higher for pulmonary function (i.e. forced vital capacity FVC and $FEV_1$) than for exercise capacity ($VO_2max$)[4]. FVC and $FEV_1$ are lowered by approximately 33% whereas $VO_2max$ is decreased by approximately 20%. However, little is known about long-term (more than one year postoperative) effects of pneumonectomy on lung function and exercise tolerance.

Several formulas are in use aiming to predict postoperative lung function after resection[12-14]. In general these formulas can be divided into two categories. The first category of formulas calculates postoperative FVC and $FEV_1$ by the number of segments to be resected[13]. The second category of formulas includes the function of these segments by measuring their actual perfusion preoperatively[12;14;15]. These formulas proved reasonably valid when the predicted lung function was compared with the one measured relatively soon, within three months, after the operation. Since recruitment of underperfused or overventilated lung segments may occur after lung resection, especially after pneumonectomy[16;17], it is still unclear what the validity of these formulas might be for predicting lung function at a much later stage. Furthermore, these formulas were

validated in a small number of patients after pneumonectomy. Nevertheless, they are worldwide accepted in guidelines[3;4;18]. Therefore, our main study objective was to investigate the validity of these formulas in pneumonectomy patients surviving for more than two years after the operation. Subsequently, we studied trends in postoperative lung function and examined the implications of pneumonectomy on exercise capacity in patients surviving for more than one year after the operation.

**Patients and Methods**

In a retrospective study all data of patients who underwent pneumonectomy in a non-university teaching hospital between 1993 and 1998 and survived for more than one year after the operation, were evaluated. Informed consent was obtained.

From the patient records the following characteristics were gathered: demographic data, tumour histology and stage, date of surgery, site of operation and presence of chronic obstructive pulmonary disease, according to American Thoracic Society criteria[19]. We used these data to answer our three research questions.

*Predicting postoperative lung function*

The predicted postoperative lung function, $FEV_1$ and FVC, were calculated by using the two most commonly used formulas:

1) $FEV_{1\text{-ppo}}$ (or $FVC_{\text{-ppo}}$) = $FEV_{1\text{-preop}}$ (or $FVC_{\text{-preop}}$)* × (1- fractional contribution of resected lung segments)[12;14]

2) $FEV_{1\text{-ppo}}$ (or $FVC_{\text{-ppo}}$) = $FEV_{1\text{-preop}}$ (or $FVC_{\text{-preop}}$)* × (1- (S × 0.0526))[13]
   S being the number of resected lung segments, each segment accounts for 1/19 of total lung function.

*$FEV_{1\text{-preop}}$ = preoperative $FEV_1$ (or FVC)

The predicted and observed postoperative lung function data measured in the third year after the pneumonectomy were compared. We used the last available data in that third postoperative year for analysis.

*Trends in postoperative lung function*

If more than two postoperative lung function tests were available, the changes in postoperative lung function over time were analyzed. These lung function tests had to be done at least more than 6 months postoperative and with a minimum time interval of 12 months between the first and last available test.

*Exercise capacity*

The pre- and postoperative maximal incremental exercise test results, performed according to European Respiratory Society criteria[20], were compared. The postoperative test had to be done more than one year after the operation. Ventilatory limitation of exercise capacity was defined as[21]:

1) pCO2 at maximum exercise being > 45mmHg or
2) Ventilation at maximum exercise ($V_E$max) ≥ 37.5 × $FEV_1$

*Statistics*

SPSS 9.0 was used for statistical analysis. For the evaluation of the two formulas for predicting postoperative lung function, scatterplots were made and regression analysis performed with the predicted postoperative lung function as the independent variable and the observed postoperative lung function as the dependent variable. Long-term trends in lung function after pneumonectomy were studied by linear regression analysis[22;23].

**Results**

*Patients*

From 1993 until 1998, 76 patients underwent pneumonectomy in our hospital. Forty-four patients were excluded from the study, 17 patients because of missing data, 26 patients died within one year after the operation and 1 patient refused to participate.

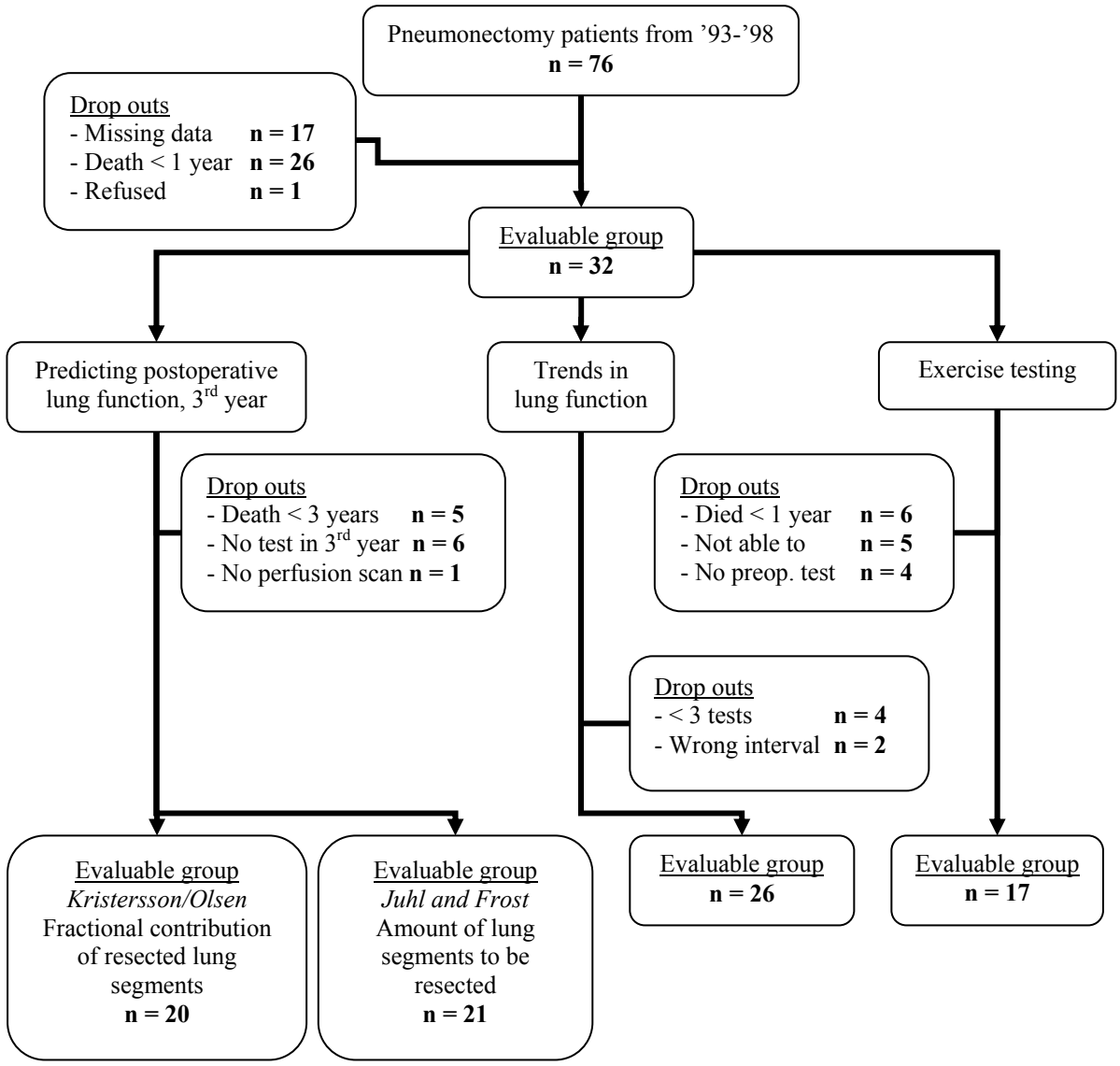


**Figure 1**

*Schematic overview of included patients and drop-outs for each research question.*

Table 1 presents initial patient characteristics of the 32 included patients compared to the drop outs and the total patient group. There were no statistical significant differences between the groups. Figure 1 shows a schematic overview of evaluable postoperative data and drop outs for each separate research question.

The diagnosis of lung malignancy was confirmed histologically in 31 patients; one patient underwent pneumonectomy because of an abscess with persisting empyema. Of

**Table 1 Initial patient characteristics of included patients (n=32) and total patient group**

| | Value Study group | Value Drop outs | Value Total group |
|---|---|---|---|
| **Patient Characteristics** | **n=32** | **n=35** | **n=67** [3] |
| **Male / Female (n)** | 24 / 8 | 32 / 3 | 56 / 11 |
| **Mean age (year) (range)** [1] | 62.4 (42-75) | 62.1 (37-76) | 62.3 (37-76) |
| **Median survival (months postoperative) (range)** | 64.5 (19-110) | 6.0 (1-21) | 19.0 (1-110) |
| **COPD + (n)** [1] | 9 | 11 | 20 |
| **Pneumonectomy Right / Left (n)** | 13 / 19 | 18 / 17 | 31 / 36 |
| **Preoperative Lung Function Data** [2] | n=32 | n=35 | n=67 [3] |
| **FVC (L)** | 3.41 ± 0.8 | 3.39 ± 1.0 | 3.40 ± 0.9 |
| **FVC % predicted** | 89.8 ± 14.3 | 84.9 ± 19.1 | 87.2 ± 17.0 |
| **$FEV_1$ (L)** | 2.48 ± 0.7 | 2.44 ± 0.7 | 2.46 ± 0.7 |
| **$FEV_1$ % predicted** | 83.5 ± 18.9 | 78.7 ± 18.8 | 81.0 ± 18.9 |
| **$FEV_1$/FVC** | 69.0 ± 11.3 | 70.2 ± 9.6 | 69.5 ± 10.4 |
| **Preoperative Exercise Test Data** [2] | n=28 | n=29 | n=57 |
| **Wmax (W)** | 121.2 ± 32.2 | 111.5 ± 24.1 | 116.3 ± 28.5 |
| **Wmax % predicted** | 99.3 ± 26.3 | 89.5 ± 19.2 | 94.3 ± 23.3 |
| **$VO_2$max (ml/min/kg)** | 19.9 ± 5.7 | 19.2 ± 3.3 | 19.5 ± 4.6 |
| **$VO_2$max % predicted** | 73.8 ± 23.0 | 73.0 ± 11.9 | 73.4 ± 18.1 |
| **Ventilation at maximum exercise (L/min)** | 51.9 ± 13.2 | 57.8 ± 12.5 | 54.9 ± 13.1 |

[1] *at time of surgery*

[2] *mean ± standard error of mean*

[3] *of which complete preoperative data could be obtained (n=67), 9 missing because of missing data*

all 31 malignant tumours, 20 were squamous cell carcinoma, 7 adenocarcinoma, 2 large cell undifferentiated carcinoma, 1 adenocystic carcinoma and 1 carcinoid tumour. Adjuvant radiotherapy was given to 10 patients, 9 because of residual disease and 1 because of adenoid cystic carcinoma of the left main bronchus; 3 patients were treated with adjuvant chemotherapy.

*Predicting postoperative lung function*

Scatterplots of predicted lung function data according to both formulas versus observed postoperative lung function data obtained in the third year after pneumonectomy are depicted in Figures 2 and 3, as well as the results of the linear regression analysis. These figures show that in patients surviving for more than two years after pneumonectomy, calculation of predicted postoperative FVC and $FEV_1$ by both formulas correlates well with the observed postoperative FVC and $FEV_1$. Linear regression analysis showed that the coefficient of determination ($R^2$) was higher for the Kristersson/Olsen formula than the Juhl and Frost formula. This indicates that the formula by Kristersson/Olsen[12;14] was more accurate in predicting postoperative FVC and $FEV_1$ than the formula by Juhl and Frost[13] for the investigated postoperative year. Furthermore, the formula by Juhl and Frost predicted postoperative $FEV_1$ roughly 300 ml lower than the Kristersson/Olsen formula.

*Trends in postoperative lung function*

Long-term postoperative changes in lung function of individual patients could be analyzed in 26 patients. The number of postoperative lung function tests varied between 3 and 12 tests (mean: 7 tests) and the mean time interval between the operation and most recent lung function test over which trends were analyzed was 9.9 ± 63.0 months. The mean annual decline in $FEV_1$ was 44 ml. Of 26 patients, 6 patients had improvement in $FEV_1$ postoperatively, 10 patients had a decline of 0-50 ml/year in $FEV_1$, 7 patients had a decline of 50-100 ml/year in $FEV_1$ and 3 patients had a decline over 100 ml/year in $FEV_1$.

*Exercise capacity*

Table 2 shows the results of the pre- and postoperative exercise tests. These were available in 17 of 32 patients, with a mean time interval between the operation and the postoperative exercise test of 38 months (± 21.4; range 12–77 months). The decrease in workload at maximum exercise (Wmax) and $VO_2$max was 27%, respectively 30%.

**Table 2 Mean maximum incremental exercise test results preoperative and postoperative (n=17)**

| | Preoperative [2] | Postoperative [2] |
|---|---|---|
| **Wmax (W)** | 123.6 ± 22 | 90 ± 24.2 |
| **Wmax (% predicted)** | 102.1 ± 19.8 | 75.5 ± 17.3 |
| **$VO_2$max (ml/kg/min)** [1] | 20.3 ± 4 | 14.2 ± 3.8 |
| **$VO_2$max (% predicted)** [1] | 75.4 ± 16.9 | 53.6 ± 14.7 |
| **Dyspnea Index** | 0.57 ± 0.15 | 0.67 ± 0.17 |
| **Ventilatory Limited** | 4 | 5 |

[1] *n=16, because of defective equipment*

[2] ± *standard error of the mean*

Preoperatively, maximal exercise tolerance was restricted due to a limited ventilatory capacity in 4 out of these 17 patients, whereas postoperatively this was the case in 5 out of these 17 patients. In all cases it was concluded that maximal exercise was restricted due to a limited ventilatory capacity because pCO2 exceeded the 45 mmHg limit at maximum exercise.

## Discussion

This study shows that calculation of $FVC_{\text{-ppo}}$ and $FEV_{1\text{-ppo}}$ by both the Kristersson/Olsen and the Juhl and Frost formula correlated well with the observed postoperative FVC and $FEV_1$ in the third year (mean 31.4 ± 3.7 months) after pneumonectomy. The formula by Kristersson/Olsen appeared to be more accurate in predicting postoperative FVC and $FEV_1$ than the formula by Juhl and Frost. Roughly seen, the formula by Juhl and Frost, estimated $FEV_{1\text{-ppo}}$ in the third postoperative year about 300 ml lower than the formula by Kristersson/Olsen. When considering the long-term trend in lung function we found that the mean decrease in $FEV_1$ was about 44 ml/year. Only three patients showed a rapid decline of more than 100 ml/year. No evidence for regeneration capacity in

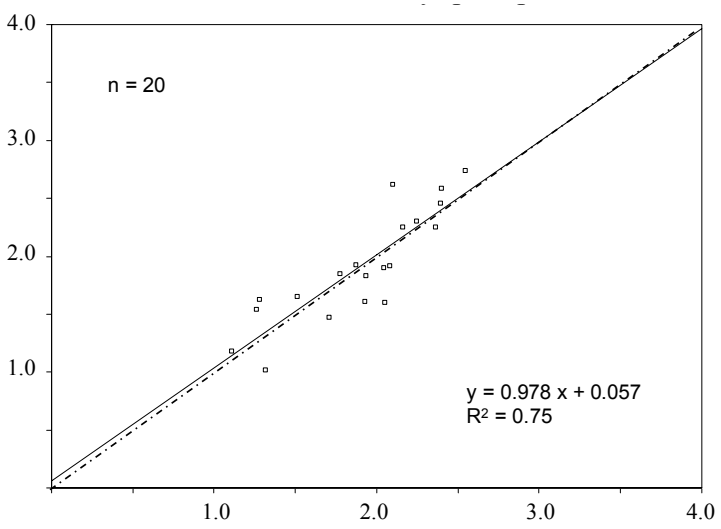


**Figure 2 A; FVC**

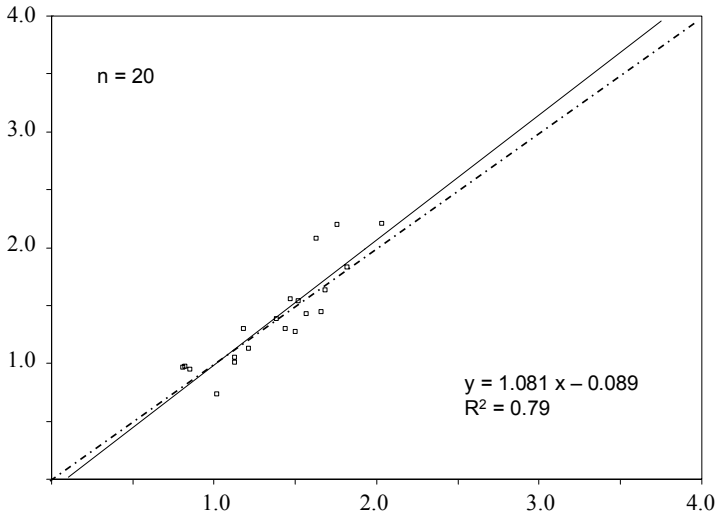


**Figure 2 B; $FEV_1$**

**Figures 2 A and 2 B**

*Scatterplots of predicted FVC (Liters) versus observed postoperative FVC (Liters) (**Figure 2 A**) and of predicted $FEV_1$ (Liters) versus observed postoperative $FEV_1$ (Liters) (**Figure 2 B**), according to **Kristersson/Olsen** (using split function tests to determine the fractional contribution of resected lung segments to overall lung function) of 20 patients in the third year after pneumonectomy. Predicted postoperative $FVC/FEV_1$ is on the x-axis and observed postoperative $FVC/FEV_1$ is on the y-axis. Dots represent separate patients. The continuous line (regression line) represents results of the linear regression analysis. The dotted line represents the line of identity. $R^2$ represents coefficient of determination.*

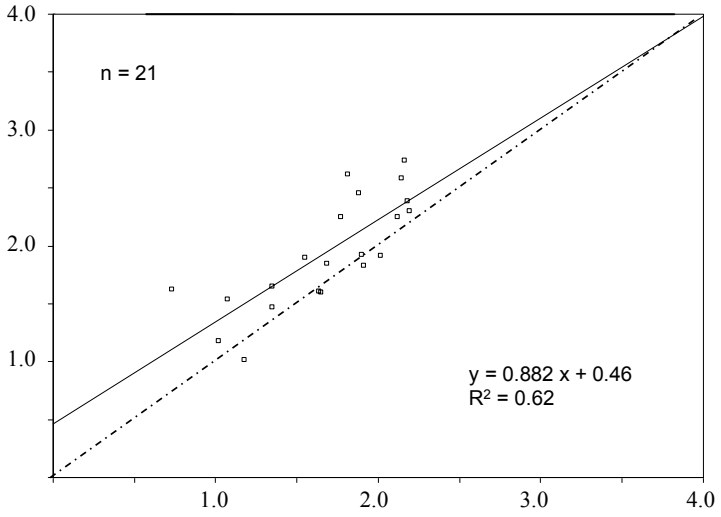


**Figure 3 A; FVC**

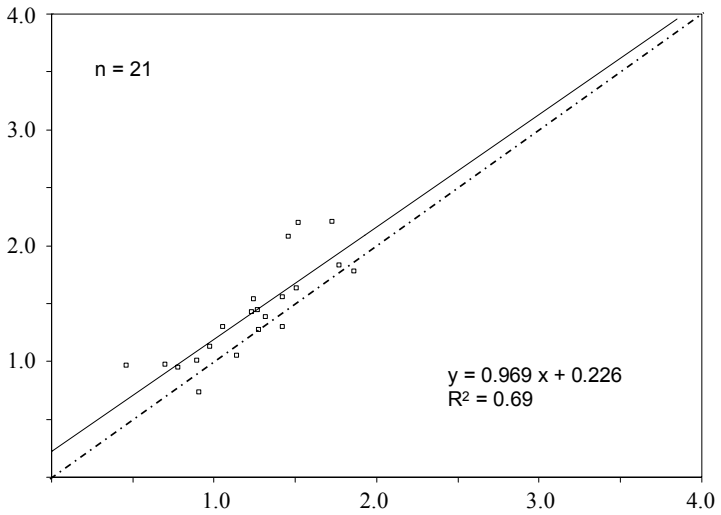


**Figure 3 A; $FEV_1$**

**Figures 3 A and 3 B**

*Scatterplots of predicted FVC (Liters) versus observed postoperative FVC (Liters) (**Figure 3 A**) and of predicted $FEV_1$ (Liters) versus observed postoperative $FEV_1$ (Liters) (**Figure 3 B**), according to **Juhl and Frost** (using the amount of resected lung segments to determine postoperative lung function) of 21 patients in the third year after pneumonectomy. Predicted postoperative FVC/$FEV_1$ is on the x-axis and observed postoperative FVC/$FEV_1$ is on the y-axis. Dots represent separate patients. The continuous line (regression line) represents results of the linear regression analysis. The dotted line represents the line of identity. $R^2$ represents coefficient of determination.*

pneumonectomy patients could be detected. Finally, pneumonectomy appears to lower Wmax at least by 27% and $VO_2$max by 30%. At least 40% of the patients experience impaired maximum exercise capacity due to ventilatory limitation.

The lower postoperative FVC and $FEV_1$ predicted by the Juhl and Frost formula compared to the observed FVC and $FEV_1$, might be explained by the fact that this formula does not take into account the function of the segments that will be removed. Zeiher et al.[24] found this underestimation of $FEV_{1\text{-ppo}}$ to be approximately 500 ml at 7.2 months (mean, ranging 24 days to 5 years) after pneumonectomy. In our study, we found an underestimation of $FEV_{1\text{-ppo}}$ of 225 ml, indicating further decrease in $FEV_1$ in this period of time or a better prediction of $FEV_{1\text{-ppo}}$ by the Juhl and Frost formula a few years after pneumonectomy. Bolliger et al.[25] recently found that both predictions of postoperative cardiopulmonary function by perfusion scan and quantitative CT scan (6 months postoperatively) were useful irrespective of the extent of resection. Unfortunately, we did not choose the use of quantitative CT scan for long-term prediction in our study, which would be very interesting to do.

In healthy non-smokers, $FEV_1$ physiologically decreases with approximately 30 ml/year. In current heavy male cigarette smokers (>25 cigarettes/day) this decline can increase to approximately 60 ml/year[26;27]. The mean annual decline in $FEV_1$ was 44 ml in our study. No clear correlation between the amount of decline and presence of chronic obstructive pulmonary disease, adjuvant radiotherapy or adjuvant chemotherapy could be detected. When looking at the patients individually we found that 6 out of 26 patients showed an improvement in their $FEV_1$ in time after their pneumonectomy whereas 3 patients showed a rapid deterioration of more than 100 ml/year. One of the possible explanations for these findings might be the past and current smoking status of the patients. Unfortunately, we were not able to determine the exact past and current smoking status in our patients because of the retrospective nature of our study. A possible explanation for the improvement in $FEV_1$ we observed in 6 of our patients might

be a better treatment of an underlying obstructive pulmonary disease or the occurrence of recruitment and distention of alveoli and capillaries after a pneumonectomy. Some investigators have suggested that this might be the main adaptive mechanism of the lung to the new situation after pneumonectomy[16;17]. Laros et al.[28] found that because of recruitment and alveolar distention the vital capacity increased slightly during the first few years after pneumonectomy.

In our study, Wmax and $VO_2$max decreased with 27% and 30% at approximately 38 months after the operation. Probably this decrease is an underestimation of the real decrease because 9 patients postoperatively could not be tested due to death or shortness of breath. Our data compare well with those of Nugent et al.[29]. They found that pneumonectomy was associated with impaired exercise performance and reduced $VO_2$max by 28% 6 months after the operation. Others found reductions of 16%[30] and 20%[4;31] at 6 months after the operation. These results suggest that long-term exercise performance might already be predicted at 6 months postoperatively.
Only 17 out of the 32 patients were able to perform a postoperative exercise test, of which 5 tested to be ventilatory limited to exercise. When also taking into account the 15 patients who were not available for postoperative exercise testing, we believe the actual number of ventilatory limited patients might be higher. Out of these 15 patients, 5 patients were not able to perform this test because of poor lung function and shortness of breath, indicating that exercise limitation might be due to ventilatory problems. Six patients, of whom 4 had preoperative ventilatory limited exercise tests, died before having performed a postoperative exercise test. Death was attributed to respiratory failure in 4 out of these 6 patients also indicating ventilatory limitation postoperatively. Adding these 9 patients without a postoperative exercise test to the 5 with a test, results in 14 out of 32 (44%) patients probably being ventilatory limited to exercise after pneumonectomy. Two out of these 9 patients also experienced cardiac comorbidity, besides their pulmonary limitations, which probably contributed to their limited exercise capacity. The preoperative FVC and $FEV_1$ of the 9 patients who were not able to perform

an exercise test postoperative, were compared to the preoperative FVC and $FEV_1$ of the patients in whom it was proven that ventilatory problems were the reason for postoperative exercise limitation. The preoperative lung function results in these 9 patients were worse, which makes it very likely that these 9 also have (had) ventilatory limitation as a reason for a restricted exercise capacity.

When considering our results, it might be argued that our results are biased because of missing data. Because we found no indications for selective drop out when comparing the final study group and the drop out group on their initial patient characteristics we have no indication that this might be the case. This study was conducted solely to answer our three research questions in long-term survivors. Also, compared to previous studies[6;24], we were able to include a relatively large number of patients which make our results more robust. Nevertheless, because of the retrospective character of this study, our results need to be confirmed by a prospective one.

**Conclusion**

In conclusion, this study showed that the Kristersson/Olsen formula was a better predictor of postoperative FVC and $FEV_1$ than the Juhl and Frost formula in patients surviving for more than two years after pneumonectomy. Secondly, the annual decline in $FEV_1$ in these patients is almost the same as in healthy, non-COPD patients. Finally, we found that Wmax more than one year after pneumonectomy (mean interval of 38 months) decreased by 27% and $VO_2$max by 30%, at least. Knowledge of these changes in lung function and exercise tolerance in these patients is extremely useful for the preoperative assessment and counseling of patients who are eligible for pneumonectomy.

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Chapter 6

# Underfilling of the Left Ventricle is the primary cause of a Low Stroke Volume after Pneumonectomy

Sietske A Smulders, Anton Vonk Noordegraaf [1]

Sebastiaan Holverda [1], Frank WJM Smeenk

Harrie CM van den Bosch [2], Johannes C Post [3]

Pieter E Postmus

**(Submitted)**

[1] Department of Pulmonary Diseases, VU University Medical Center, Amsterdam

[2] Department of Radiology, Catharina Hospital, Eindhoven

[3] Department of Cardiology, Catharina Hospital, Eindhoven

The Netherlands

**Abstract**

*Background:* To study the adaptation of the right ventricle and pulmonary vascular bed shortly after pneumonectomy by cardiac MRI.

*Setting:* Non-university teaching hospital of Eindhoven and VU University Medical Center in Amsterdam, the Netherlands.

*Methods:* In 8 patients undergoing pneumonectomy (4 right-, 4 left), lung function and cardiac function were measured before surgery (t = 0), at two weeks (t = 1) and at three months (t = 2) postoperatively.

*Results:* At t = 1, stroke volume and left ventricular end-diastolic volume were decreased (p = 0.036) and heart rate increased (p = 0.017), indicating depressed cardiac function. At t = 2, these values were normalised indicating that adaptation had been successfully completed. No signs of right ventricular enlargement or – hypertrophy were found.

*Conclusions:* This study shows that despite a sudden amputation of the pulmonary vascular bed, leading to an underfilling of the LV and a subsequent decrease in stroke volume shortly after pneumonectomy, RV and LV function remain stable in the postoperative phase. Within three months stroke volume, LV and RV structure and function are normalised compared to preoperative values.

## Introduction

In patients with non-small cell lung cancer (NSCLC), complete resection offers the best prospects and results in cure in a substantial number of patients. In case a pneumonectomy is required, this will lead to a sudden significant reduction of the pulmonary vascular bed demanding a quick adaptation of the heart. Successful adaptation of the heart to increased blood flow through the remaining lung and altered pressure relationships within the thorax after pneumonectomy depends upon the ability of the pulmonary vascular bed to expand[1]. Early and late effects of pneumonectomy on right ventricular (RV) function have been studied by echocardiography and thermodilution[2-4]. It was found that in patients with little or no lung disease in the remaining lung, in the long term, pulmonary artery pressure and pulmonary vascular resistance remain normal or are slightly increased at rest due to these adaptive mechanisms[5-7].

In contrast, the left side of the heart has been less studied in postpneumonectomy patients. We hypothesized that a reduction of the pulmonary vascular bed might lead to a decrease of pulmonary compliance and thereby directly altering left ventricular (LV) inflow[8]. According to Frank-Starling's law, a decrease in preload will result in a decrease in stroke volume. For this reason, LV underfilling might also contribute to the depressed cardiac function postoperatively.

In the present study we measured the consequences of a pneumonectomy on RV and LV filling and volumes, using MRI techniques in patients with normal lung parenchyma on the HRCT of the remaining lung. Furthermore, the ability of the LV to adapt in time will be investigated.

## Patients and Methods

We prospectively studied 8 lung cancer patients eligible for pneumonectomy in an academic and in a non-university teaching hospital. Lung function and general health in all patients

was adequate enough to tolerate pneumonectomy[9]. Preoperatively, 2 patients had moderate ($FEV_1$ (% of predicted) and $FEV_1$/FVC of 78/51 and 64/46) chronic obstructive pulmonary disease (COPD) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[10]. Although some patients had an obstructive flow pattern, the CT scans in these patients did not show any evidence for pulmonary emphysema. For this reason the mild obstruction must be interpreted as secondary due to airway obstruction in patients with centrally located carcinomas. A few months before pneumonectomy, 1 patient underwent cardiac surgery (aortic valve prosthetic bio-implant) and 2 other patients underwent induction chemotherapy. Informed consent was obtained from all subjects, and the local ethics committees approved the study.

*Lung function and cardiopulmonary exercise testing*

We performed lung function in all patients before (t = 0) pneumonectomy, directly postoperative (within 2 weeks) (t = 1) and at 3 months (t = 2) after pneumonectomy. Lung function measurements assessed were: vital capacity (VC), forced expiratory volume in 1 second ($FEV_1$) and diffusion capacity for carbon monoxide, corrected for alveolar volume ($D_{LCO\ VA}$).

Furthermore, exercise tests (maximum workload (Wmax); maximum oxygen uptake during exercise ($VO_2$max); ventilation at maximum exercise ($V_E$max)) were done preoperatively (t = 0) and, if possible, also at 3 months postoperatively (t = 2). During maximum incremental exercise test, patients' measurements were recorded after a 3-minute resting period on the bicycle, after which patients started exercising at a constant speed of 60 rpm at 0W during 2 minutes. A ramp protocol based on patient's age, gender and $FEV_1$ followed till patients were exhausted. Recovery period lasted 6 minutes. The Vslope method was used to determine whether the anaerobic threshold was reached.

Lung function and exercise tests were done in accordance with the American Association for Respiratory Care[11] and European Respiratory Society criteria[12] using standard equipment

Vmax 229 and 6200, SensorMedics, Yorba Linda, USA (for the academic centre) and standard equipment Oxycon Beta and Masterlab, Viasys, Bilthoven, the Netherlands (for the non-academic centre).

*Cardiac measurements*

All patients underwent CMR imaging preoperatively (t = 0), within 2 weeks postoperative (t = 1) (or, whenever this was not feasible, as soon as possible after surgery) and at 3 months (t = 2) after pneumonectomy (Figure 1), according to the following protocol.

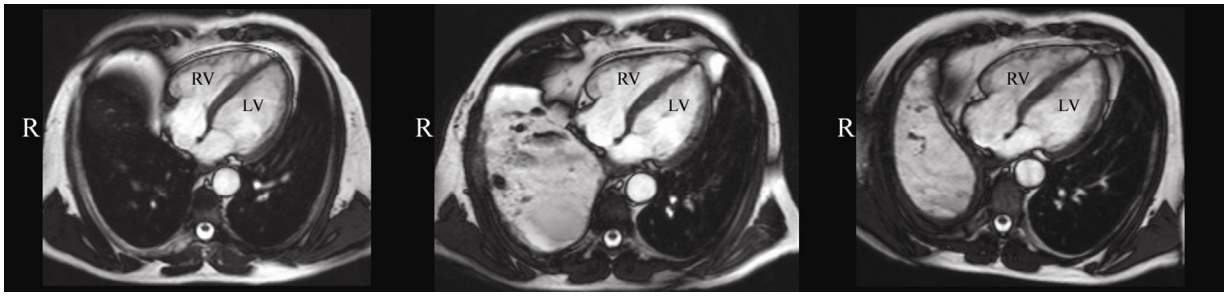


**Figure 1**

*Cardiac MR four chamber images of one patient during each measurement.*
*From left to right: preoperative (t = 0), 2 weeks postoperative (t = 1) and 3 months postoperative (t = 2).*
*R Right side of patient; RV, LV Right and left ventricle*

*Magnetic Resonance Imaging Protocol*[13]

The patients were scanned using a 1.5 T Siemens Sonata whole body system (Siemens Medical Systems, Erlangen, Germany) in the academic centre or the 1.5 T Philips Intera, software release 10.3 ( Philips Medical Systems, Best, the Netherlands) in the non-academic teaching centre. On both systems a phased-array body coil was applied. All image acquisition was prospectively triggered by the R-wave of the electrocardiogram. The subject

was instructed to hold his breath in moderate inspiration during all image acquisitions (thus also during scout imaging for localization of the heart).

Short-axis ventricular imaging

The horizontal long-axis view was determined in a late diastolic frame using a black-blood prepared turbo gradient-echo sequence[13]. Then a breath hold cine-acquisition was performed of this long-axis view. By using the end-diastolic cine frame of this long-axis view, a series of parallel short-axis (SA) image planes was defined starting at the base of the LV and RV, and encompassing the entire LV and RV from base to apex. The most basal image plane was positioned close to the transition of the myocardium to the mitral and tricuspid valve leaflets (at a distance of half the slice thickness). This ensured that also the most basal part of the LV and RV was covered. At every SA plane, a breath hold cine acquisition was then performed (temporal resolution < 40 ms). Slice thickness was 6 mm and gap 4 mm. Thus the slice distance was 10 mm. Heart rate was monitored during the acquisition of the SA images.

Image analysis

The images were processed on a Sun Sparc station using the 'MASS' software package (Dept. of Radiology, Leiden University Medical Center, Leiden, the Netherlands) for the Siemens scanner and on a View Forum (release 3.2) workstation with a dedicated cardiac analysis software package for the Philips. End-diastole was defined as the first temporal frame directly after the R-wave of the ECG. End-systole was defined as the temporal frame at which the image showed the smallest right and left ventricular cavity area, usually 240-320 ms after the R-wave. Epi- and endocardial contours were manually traced, and the papillary muscles were excluded from the RV and LV volume and included with the RV and LV mass as described before[13]. The LV end-diastolic mass was obtained from the volume of the LV muscle tissue including the interventricular septum, the RV end-diastolic mass in a similar way, but excluding the septum. In the mass calculation, the specific weight of muscle tissue was 1.05 g/cm$^3$.

*Statistical analysis*

We used SPSS 13.0 for statistical analysis. Wilcoxon signed rank up tests were used to determine whether differences in measurements regarding lung function, exercise capacity or cardiac function at t = 0, t = 1 and t = 2 were significantly different. Statistical significance was set at $p < 0.05$.

**Results**

In this study, 8 patients (5 males) (4 right-sided pneumonectomies) were included of which 1 was measured in the academic centre and 7 in the non-academic teaching hospital. Mean age was 58 years (± 11.8, ranging from 34-69).

In Table 1 results on preoperative data together with pTNM stages are presented for all patients. One patient underwent pneumonectomy because of a centrally located atypical carcinoid tumour, which was completely resected. The others underwent pneumonectomy for NSCLC.

In one patient that underwent induction chemotherapy, surgical resection was not radical and in this patient a fistula of the right main bronchial stump developed within the first week after surgery, with complicating empyema for which eventually a 'Clagett procedure' (open thoracic cavity) was performed 2,5 months postoperatively. For this reason measurements at three months could not be performed in this patient, due to incapacitating dyspnoea and pain resulting from these complications. The postoperative course of another patient was complicated by paroxysmal atrial fibrillation, for which he received anticoagulation therapy.

*Lung function and cardiopulmonary exercise testing*

Table 2 presents the lung function test results for all measurements. At t = 1, FVC and $FEV_1$ decreased significantly ($p = 0.018$), by 49% and 34% of predicted, respectively, and remained decreased at t = 2 ($p = 0.018$) compared to t = 0. At t = 2, FVC increased again (not significantly), compared to t = 1. No significant changes were found regarding $D_{LCO\ VA}$.

**Table 1 Preoperative perfusion scan results of right and left lung, bronchoscopic view and pTNM stages from all 8 patients**

| | | Perfusion % | | |
|---|---|---|---|---|
| | **R / L *** | **R / L** | **Bronchoscopy** | **pTNM-stage** |
| **1** | L | 64 / 36 | LUL obstructed | $T_2N_0M_0$ |
| **2** | R | - | Apex RLL obstructed | $T_2N_1M_0$ |
| **3** | R | 34 / 66 | No obstruction | $T_2N_0M_0$ |
| **4** | L | 54 / 46 | LLL obstructed | $T_1N_1M_0$ |
| **5** | R | 38 / 62 | RUL obstructed | $T_2N_1M_0$ |
| **6** | L | - | LUL growing into LLL | Atypical carcinoid |
| **7** | R | 52 / 48 | No obstruction | $T_4N_2M_0$ |
| **8** | L | 62 / 38 | Anterior segment LUL obstructed | $T_2N_1M_0$ |

** Right- or left-sided pneumonectomy*

*LLL Left lower lobe; LUL Left upper lobe; RLL Right lower lobe; RUL Right upper lobe*

**Table 2 Preoperative and postoperative (within 2 weeks and at 3 months) lung function test results in all patients (n = 8)**

| **Mean ± SD** | **Preoperative (t = 0)** | **Postoperative (t = 1) *** | **Postoperative (t = 2) *** |
|---|---|---|---|
| **FVC (L)** | 4.0 ± 0.7 | 2.1 ± 0.5 † | 2.4 ± 0.6 † |
| **FVC % predicted** | 105.1 ± 10.2 | 56.0 ± 9.2 † | 61.9 ± 8.3 † |
| **$FEV_1$ (L)** | 2.5 ± 0.4 | 1.5 ± 0.2 † | 1.6 ± 0.3 † |
| **$FEV_1$ % predicted** | 82.1 ± 11.7 | 47.6 ± 6.7 † | 51.1 ± 6.0 † |
| **$FEV_1$/FVC** | 63.0 ± 9.5 | 68.2 ± 12.1 ‡ | 65.5 ± 9.1 |
| **$D_{LCO\ VA}$ (mmol/min/kPa/L)** | 1.21 ± 0.35 | 1.17 ± 0.3 | 1.26 ± 0.35 |
| **$D_{LCO\ VA}$ % predicted** | 85.6 ± 28.0 | 79.7 ± 16.2 | 86.3 ± 23.5 |

****** n = 7 due to postoperative complications in one patient*

*† p = 0.018, compared to t = 0*

*‡ p = 0.028, compared to t = 0*

*$D_{LCO\ VA}$ Diffusion capacity for carbon monoxide, corrected for alveolar volume; $FEV_1$ Forced expiratory volume in 1 second; FVC Forced vital capacity*

**Table 3 Preoperative and postoperative (at 3 months) exercise test results in all patients (n = 8)**

| Mean ± SD | Preoperative (t = 0) | Postoperative (t = 2) * |
|---|---|---|
| **HR max (beats/min)** | 145 ± 18.6 | 130.7 ± 24.2 † |
| **HR max % predicted** | 89.6 ± 10.8 | 79.0 ± 11.2 † |
| **Wmax (W)** | 135 ± 36.8 | 89.8 ± 38.2 † |
| **Wmax % predicted** | 83.9 ± 15.9 | 54.3 ± 21.1 † |
| **$VO_2$ max (ml/min/kg)** | 23.4 ± 2.2 | 17.3 ± 3.3 † |
| **$VO_2$ max % predicted** | 85.9 ± 16.9 | 57.5 ± 16.2 † |
| **$V_E$ max (L/min)** | 72.7 ± 14.0 | 44.0 ± 12.1 † |
| **$V_E$ % predicted** | 79.6 ± 16.1 | 73.3 ± 8.8 |
| **$O_2$-pulse max (ml/beat)** | 11.7 ± 1.4 | 9.8 ± 2.6 † |
| **$O_2$-pulse % predicted** | 88.8 ± 15.8 | 73.0 ± 15.7 † |

** n = 6 due to postoperative complications in one and fear of excessive exercise in another patient*
*† Significantly different ($p < 0.05$) compared to t = 0*
*HR Heart rate; $V_E$ max Ventilation at maximum exercise; $VO_2$ max Maximum oxygen uptake during exercise; Wmax Maximum workload*

Results from the pre- and postoperative maximum exercise tests are presented in Table 3. Wmax and $VO_2$max decreased by 30% and 28% of predicted, respectively. All patients reached their anaerobic threshold. Postoperative exercise tests were interrupted because of dyspnoea in 6 patients and because of exercised induced hypertension (230/128 mmHg) in 1 patient.

*Cardiac measurements*

In Table 4, cardiac function results are presented. No differences were found regarding cardiac output, mass and ejection fraction for both ventricles at either point. At t = 1, heart rate was significantly increased ($p = 0.017$) and stroke volume significantly decreased ($p = 0.036$) compared to t = 0.

**Table 4 Preoperative and postoperative (within 2 weeks and at 3 months) left and right ventricular function in all pneumonectomy patients (n = 8)**

| Mean ± SD | Preoperative (t = 0) | Postoperative (t = 1) | Postoperative (t = 2) * |
|---|---|---|---|
| **HR (bpm)** | 69 ± 6.9 | 83 ± 14.8 † | 75 ± 10.9 |
| **SV (ml)** | 83.5 ± 16.6 | 73.8 ± 15.6 † | 81.1 ± 11.3 |
| **CO (l/min)** | 5.7 ± 1.1 | 5.9 ± 1.4 | 6.1 ± 0.9 |
| **LVEF (%)** | 58.7 ± 5.5 | 59.3 ± 6.0 | 59.8 ± 4.2 |
| **LVEDV (ml)** | 148.3 ± 28.8 | 128.0 ± 27.9 † | 140.1 ± 20.7 |
| **LVEDVI** | 79.1 ± 12.3 | 68.9 ± 14.6 † | 75.9 ± 10.7 |
| **RVEF (%)** | 59.5 ± 5.8 | 56.4 ± 6.2 | 56.9 ± 3.6 |
| **RVEDV (ml)** | 134.4 ± 28.2 | 124.1 ± 26.4 | 138.2 ± 20.9 |
| **RVEDVI** | 71.9 ± 13.6 | 67.0 ± 15.0 | 75.0 ± 13.0 |
| **RVM (g)** | 32.1 ± 10.6 | 31.5 ± 7.1 | 33.3 ± 10.8 |
| **LVM (g)** | 92.4 ± 27.9 | 89.7 ± 29.7 | 83.0 ± 22.0 |

** n = 7 due to postoperative complications in one patient*

*† Significantly different (p < 0.05) compared to t = 0*

*CO Cardiac output; HR Heart rate; LVEDV, RVEDV Left and right ventricular end-diastolic volume; LVEDVI, RVEDVI = LVEDV, RVEDV index = EDV/BSA (body surface area); LVEF, RVEF Left and right ventricular ejection fraction; LVM, RVM Left and right ventricular mass; SV Stroke volume*

At t = 2, both returned to baseline (preoperative) values, although not significantly. Furthermore, at t = 1 LV end-diastolic volume (LVEDV) was significantly decreased (p = 0.036) and this remained significant (p = 0.036) when corrected for body surface area (LVEDVI), compared to t = 0. Mean hematocrit value at t = 1 was normal (0.38 L/L). At t = 2, LVEDV and LVEDVI increased again, almost reaching baseline values. RV volumes and function remained unaltered in the postoperative period.

Figure 2 presents mean results for t = 0, t = 1 and t = 2 for all patients regarding stroke volume and LVEDV. This figure clearly shows that overall LVEDV directly postoperative

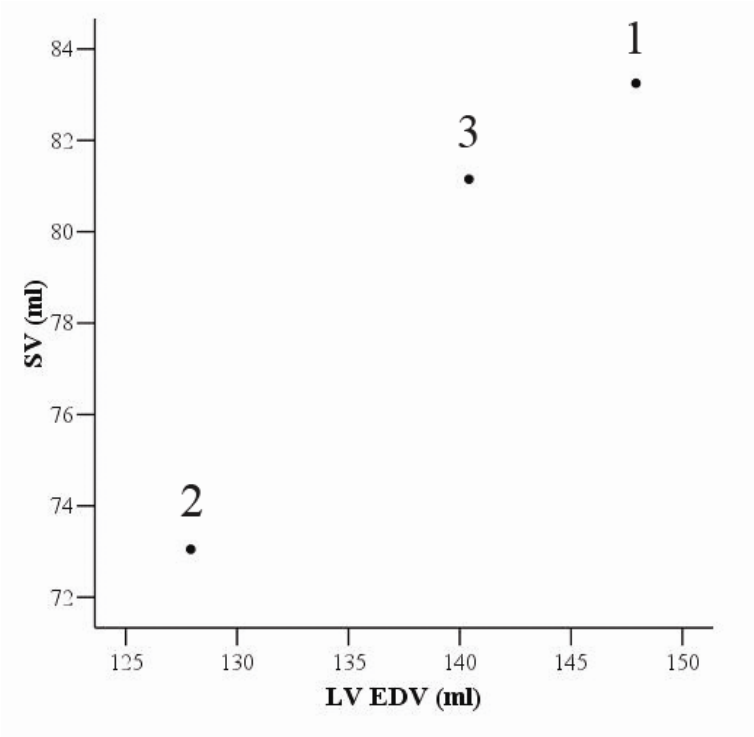


**Figure 2**

*Mean stroke volume (ml) plotted against mean left ventricular end-diastolic volume (ml) for each separate measurement. Results for all patients.*
*1;2 and 3 = Mean preoperative result; mean postoperative result and result at three months postoperatively, respectively.*
*SV Stroke volume; LVEDV Left ventricular end-diastolic volume*

decreased, which was related to a similar decrease in stroke volume. After 3 months, LVEDV and stroke volume were normalised to preoperative values.

**Discussion**

The most important finding of our study was that LVEDV was decreased direct postoperatively, and that this was related to a decrease in stroke volume. Since we did not find signs of RV dysfunction, the underfilling of the LV must be interpreted as a direct consequence of the amputation of the pulmonary vascular bed. Furthermore, our findings

show that the human cardiorespiratory system is capable of adapting in a relatively short period of time. Although the overall cardiac function was depressed directly after the operation, reflected by a decreased stroke volume and LVEDV together with an increased heart rate, these values were normalised three months after surgery.

The changes in pulmonary function and exercise capacity after pneumonectomy we found in our study at t = 2 are generally in agreement with those found in literature[5;14;15]. FVC, $FEV_1$, Wmax and $VO_2$max respectively decreased by 42%, 31%, 30% and 28% of predicted, which is less than would be expected after the removal of an entire lung. Preoperative obstruction of large airways, due to a centrally situated obstructive tumour, can explain this finding (Table 1)[16].

In healthy persons, the RV is capable of handling an increased cardiac output by 3 to 4 fold during exercise, while pulmonary artery pressures increase only mildly[17]. Several studies have previously shown that after pneumonectomy, development of pulmonary hypertension only occurs in patients with emphysematous lung, due to the limited recruitment capacity of the remaining pulmonary vascular bed in the diseased lung[6;18;19]. Since none of our patients showed signs of emphysema on the CT, it is thus not surprising that pneumonectomy in our patients did not lead to signs of RV pressure overload, such as an increased RV end-diastolic volume, decreased RV ejection fraction and signs of septal flattening on the dynamic MR short-axis cines. Thus, RV dysfunction is unlikely the cause of the decrease in stroke volume at t = 1 and underfilling of the LV. Although a decreased vascular filling state, due to a restricted postoperative fluid administration in order to prevent pulmonary edema, could explain lowered stroke volume and decreased LV end-diastolic volume, this is unlikely, since the mean hematocrit values at t = 1 remained normal (0.38 L/L). Therefore, the most likely explanation for the underfilling of the LV is the pulmonary vascular bed itself.

Pneumonectomy leads to a significant reduction of the compliance of the pulmonary vascular bed, directly impairing the filling of the left side of the heart as has been described before[8].

Since we found no significant differences in cardiac structure and function at t = 2, compared to t = 0, and since none of our patients died within the first 90 days after surgery, these results show that the adaptation of the pulmonary vascular bed of the lung and heart have been successfully completed.

Obviously, the findings from our study are from a limited number of patients. However, the findings were consistent in all patients and MRI has proven to be an extremely useful tool for consecutive measurements of cardiac function because its results are accurate as well as reproducible in both normal and abnormal ventricles[20-22]. For this reason we believe our results are an accurate reflection of the hemodynamic adaptation in time after pneumonectomy.

**Conclusion**

The postoperative state of the patient 2 weeks after pneumonectomy is characterized by a decrease of stroke volume together with a decrease of left ventricular end-diastolic volume, without signs of right ventricular dysfunction. Therefore, the reduction in left ventricular end-diastolic volume might be interpreted as a direct consequence of a decreased compliance of the pulmonary vascular bed. Within 3 months, stroke volume is normalised while overall cardiac function remains unaltered in comparison to preoperative values.

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Chapter 7

# Cardiac Function and Position more than 5 years after Pneumonectomy

Sietske A Smulders, Sebastiaan Holverda

Anton Vonk Noordegraaf, Harrie CM van den Bosch

Johannes C Post, J Tim Marcus [1]

Frank WJM Smeenk, Pieter E Postmus

**(Submitted)**

[1] Department of Physics and Medical Technology, VU University Medical Center, Amsterdam

The Netherlands

**Abstract**

*Background:* Pneumonectomy not only reduces the pulmonary vascular bed but also changes the position of the heart and large vessels, which may affect the function of the heart. We investigated long-term effects of pneumonectomy on right and left ventricular (RV and LV) function and whether this function is influenced by the side of pneumonectomy or the migration of the heart to its new position.

*Methods:* In 15 patients who underwent pneumonectomy and survived for more than 5 years we evaluated by dynamic MRI the function of the RV and LV and the position of the heart within the thorax.

*Results:* Long-term effect of pneumonectomy on the position of the heart is characterised by a lateral shift after right-sided pneumonectomy and rotation of the heart after left-sided pneumonectomy. Postoperatively, heart rate was high ($p = 0.006$) and stroke volume was low ($p = 0.001$), compared to the reference values indicating impaired cardiac function. Patients after right-sided pneumonectomy had an abnormal low RV end-diastolic volume of 99 ± 29ml[1] together with a normal LV function. No signs of RV hypertrophy were found. In left-sided pneumonectomy patients RV volumes were normal whereas LV ejection fraction was abnormally low[1].

*Conclusions:* The long-term effects of pneumonectomy on the position of the heart are characterized by a lateral shift in patients after right-sided pneumonectomy and rotation of the heart in patients after left-sided pneumonectomy. Overall, cardiac function in long term survivors after pneumonectomy is compromised which might be explained by the altered position of the heart.

## Introduction

Major lung resection, especially pneumonectomy, decreases ventilatory function and has significant effects on right ventricular (RV) function[2-4]. Immediately after pneumonectomy, the RV dilates and RV ejection fraction decreases[5;6]. Increasing RV afterload, due to rising pulmonary artery pressure and pulmonary vascular resistance occurring after major lung resection, is supposed to be the main cause of this RV dysfunction[5]. However, it is unclear to what extent the early post-pneumonectomy RV dysfunction recovers in the long-term and whether this may still play a role in the exercise limitation of post-pneumonectomy patients.

Pneumonectomy not only changes the pulmonary hemodynamics but also leads to a migration of the heart and large vessels through the thoracic cavity, a process that takes years after the resection. Due to the production of fibrotic tissue in the empty pleural space, intrathoracic pressure changes, with elevation of the diaphragm and overdistension of the remaining lung, the heart and mediastinum shift to the side that was operated on. These changes might induce alterations in cardiac structure and function, which might be different after left-sided pneumonectomy in comparison to right-sided pneumonectomy, and pending on the position of the heart in the thoracic cavity. However, this has not been studied until now, since the altered cardiac position hampers the use of echocardiography in these pneumonectomy patients. For this reason, we used cardiovascular magnetic resonance (CMR) imaging in this study because this technique has the advantage of being independent on the geometric assumptions and acoustic windows that limit echocardiography[7]. The aim of the present study was to measure the effects of right- and left-sided pneumonectomy on the structure and function of the heart, more than 5 years after the operation.

## Methods

We studied 15 consecutive patients presenting for a routine follow up exam in an academic and in a non-university, teaching hospital. At that time, approximately 10 pneumonectomies were done in both hospitals each year. All patients studied underwent pneumonectomy more than five years ago and had a FEV1 above 71% of predicted on the preoperative lung function test. In addition, no signs of emphysema or interstitial lung disease were visible on the preoperative CT scan. No other significant pulmonary or cardiac diseases were present before pneumonectomy, except lung cancer. None of the patients received chemotherapy or radiotherapy prior to surgery. Informed consent was obtained from all subjects, and the local ethics committees approved the study.

*Lung function and cardiopulmonary exercise testing*

We performed lung function (vital capacity (VC) and forced expiratory volume in 1 second ($FEV_1$)) and maximal incremental exercise tests (maximum workload (Wmax), maximum oxygen uptake during exercise ($VO_2$max) and ventilation at maximum exercise ($V_E$max)) in accordance with the American Association for Respiratory Care[8] and European Respiratory Society criteria[9] in all patients. Standard equipment Vmax 229 and 6200, SensorMedics, Yorba Linda, USA (for the academic centre) and standard equipment Oxycon Beta and Masterlab, Viasys, Bilthoven, the Netherlands (for the non-academic centre) were used for all pulmonary function tests. During maximal incremental exercise test, patients' measurements were recorded after a 3-minute resting period on the bicycle, after which patients started exercising at a constant speed of 60 rpm at 0W during 2 minutes. A ramp protocol based on patient's age, gender and $FEV_1$ followed till patients were exhausted. Recovery period lasted 6 minutes. The Vslope method was used to determine whether the anaerobic threshold was reached[10].

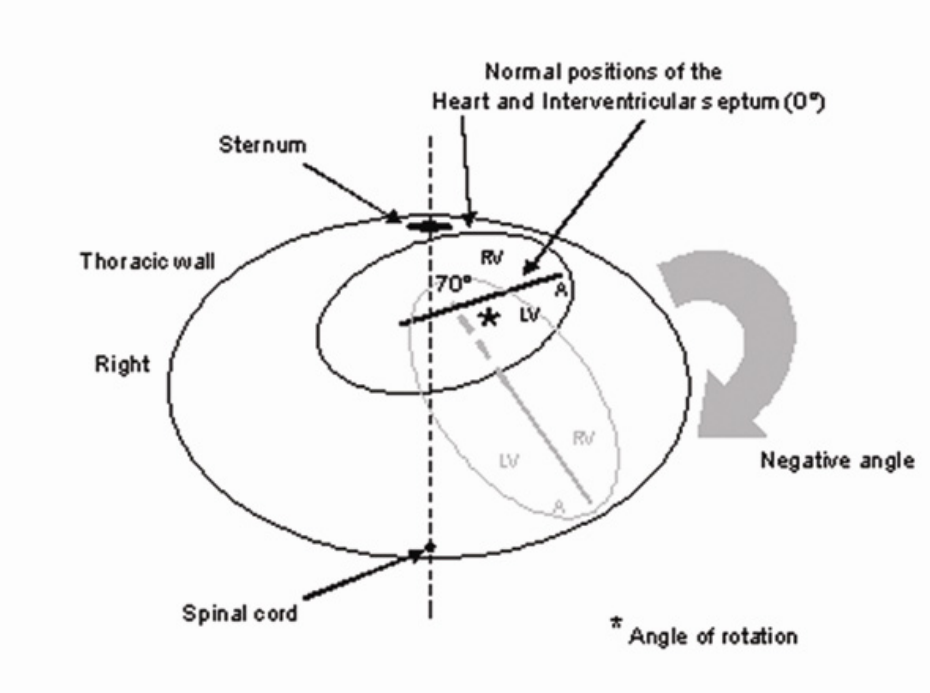


**Figure 1**

*Assessment of the degree of rotation of the heart, by measuring the angle (*) between a normally positioned interventricular septum (set at 0 degrees) and the position of the interventricular septum in the postpneumonectomy heart. Clockwise rotation results in a negative angle and counterclockwise rotation in a positive angle.*
*A Apex of left ventricle; LV, RV Left and Right Ventricle*

*Geometric position of the heart*

Using the four chamber view images according to the method depicted in Figure 1, we established the degree of rotation of the heart in our patients. In normal patients, the angle of the interventricular septum with the anteroposterior line (through the middle of the sternum and the middle of the spinal cord) is approximately 70 degrees. This angle was used as the reference angle, and set at 0 degrees. Clockwise rotation resulted in a negative angle and counterclockwise rotation in a positive angle (Figure 1). By doing this, we tried to establish the differences in degree of rotation of the hearts in our patients, rather than using these angles for mathematical purposes.

*Magnetic Resonance Imaging Protocol*[11]

The patients were scanned using a 1.5 T Siemens Sonata whole body system (Siemens Medical Systems, Erlangen, Germany) in the academic centre or the 1.5 T Philips Intera, software release 10.3 ( Philips Medical Systems, Best, the Netherlands) in the non-academic teaching centre. On both systems a phased-array body coil was applied. All image acquisition was prospectively triggered by the R-wave of the electrocardiogram. The subject was instructed to hold his breath in moderate inspiration during all image acquisitions (thus also during scout imaging for localization of the heart).

Short-axis ventricular imaging

The horizontal long-axis view was determined in a late diastolic frame using a black-blood prepared turbo gradient-echo sequence[11]. Then a breath hold cine-acquisition was performed of this long-axis view. By using the end-diastolic cine frame of this long-axis view, a series of parallel short-axis image planes was defined starting at the base of the left ventricle (LV) and RV, and encompassing the entire LV and RV from base to apex. The most basal image plane was positioned close to the transition of the myocardium to the mitral and tricuspid valve leaflets (at a distance of half the slice thickness). This ensured that also the most basal part of the LV and RV was covered. At every short-axis plane, a breath hold cine acquisition was then performed (temporal resolution < 40 ms). Slice thickness was 6 mm and gap 4 mm. Thus the slice distance was 10 mm. Heart rate was monitored during the acquisition of the short-axis images.

Image analysis

The images were processed on a Sun Sparc station using the 'MASS' software package (Dept. of Radiology, Leiden University Medical Center, Leiden, the Netherlands) for the Siemens scanner and on a View Forum (release 3.2) workstation with a dedicated cardiac analysis software package for the Philips. End-

diastole was defined as the first temporal frame directly after the R-wave of the ECG. End-systole was defined as the temporal frame at which the image showed the smallest right and left ventricular cavity area, usually 240-320 ms after the R-wave. Epi- and endocardial contours were manually traced, and the papillary muscles were excluded from the RV and LV volume and included with the RV and LV mass as described before[11]. The LV end-diastolic mass was obtained from the volume of the LV muscle tissue including the interventricular septum, the RV end-diastolic mass in a similar way, but excluding the septum. In the mass calculation, the specific weight of muscle tissue was 1.05 g/cm$^3$.

*Data analysis*

Results on lung function, exercise tests and cardiac function were compared between patients after left- and right-sided pneumonectomy. Results on RV and LV function in pneumonectomy patients were compared with normal ventricular dimensions for MRI from healthy controls (n = 25). Recently, data from these healthy controls were in part also presented by Vonk-Noordegraaf et al[1]. To our knowledge, this is one of the few recent studies on establishment of these values, addressing both LV and RV structure and function in adults. Other studies that obtained reference values for LV[11-13] and RV[12;13] function by MRI provided only information on the LV (Marcus[11]) or included children (Lorenz[12]) in their study group.

*Statistical analysis*

We used SPSS 13.0 for statistical analysis. Mann Whitney U tests for independent samples were used to determine differences comparing healthy controls with patients and comparing patients after left- or right-sided pneumonectomy regarding cardiac function, lung function and exercise tolerance. Statistical significance was set at $p < 0.05$.

**Table 1 Initial patient characteristics and smoking status**

| | Initial characteristics | | | |
|---|---|---|---|---|
| **Patient [1]** | **M/F [2]** | **Age [3]** | **Survival (months)** | **PY *** |
| **2_I** | F | 53 | 62 | 25 |
| **2_II** | M | 69 | 107 | 40 |
| **2_III** | M | 71 | 91 | 47 |
| **2_IV** | F | 65 | 69 | 45 |
| **2_V** | M | 74 | 96 | 40 |
| **2_VI** | M | 64 | 125 | 44 |
| **2_VII** | M | 71 | 141 | 40 |
| **2_VIII** | F | 64 | 118 | 0 |
| **2_IX** | M | 53 | 77 | 30 |
| **3_I** | M | 67 | 85 | 18 |
| **3_II** | F | 77 | 117 | 60 |
| **3_III** | F | 47 | 191 | 0 |
| **3_IV** | F | 51 | 89 | 30 |
| **3_V** | F | 59 | 92 | 35 |
| **3_VI** | M | 80 | 137 | 50 |

*[1] Patient: Number corresponds to the images and legends from Figures 2 and 3;* ***Figure 2*** *(left-sided pneumonectomy): Top: from left to right numbers I, II and III; Middle: from left to right numbers IV, V and VI; Bottom: from left to right numbers VII, VIII and IX.*
***Figure 3*** *(right-sided pneumonectomy): Top: from left to right numbers I, II and III; Bottom: from left to right numbers IV, V and VI*
*[2] M / F: Male or Female*
*[3] Age (years) at the time of the study*
** Number of pack years smoked before surgery*

**Results**

Table 1 presents initial patient characteristics; 2 never-smoking females underwent pneumonectomy because of a carcinoid tumor and an adenocystic carcinoma, others because of non-small cell lung cancer. Mean age of all patients was 64.3 years (range 47-80), and mean time after pneumonectomy 106.5 months (range 62-191).

Mean age of the healthy controls was significantly lower compared to our patients (Table 2). Preoperatively, mean $FEV_1$ % of predicted, mean Wmax % of predicted and mean $VO_2$max % of predicted were 84.6 (± 14.1), 101.4 (± 42.3) and 86.5 (± 30.4), respectively. In 1 patient, the phrenic nerve was crushed during left-sided pneumonectomy with the surgeons' intention to enhance filling of the postpneumonectomy space. Postoperatively, chest tubes were placed in all patients and connected to a balanced drainage system during the first short postoperative period. The postoperative course in 1 patient that underwent pneumonectomy with partial resection of the pericardium was complicated by the development of insufficiency of the tricuspid valve and in another patient by the development of residual cancer on the bronchial stump for which he underwent a curative re-resection, complicated by hypertension and viral pericarditis which were treated. One patient received medication (nifedipine) for the treatment of systemic hypertension.

*Lung function and cardiopulmonary exercise testing*

Lung function and exercise tests were done more than 5 years after pneumonectomy in all patients except 1, who underwent the exercise test at 28 months after surgery. We found no statistically significant differences regarding lung function or exercise capacity comparing patients after right- or left-sided pneumonectomy. Mean % of predicted FVC and $FEV_1$ were 58.2 (± 14.3) and 49.1 (± 10.6), respectively. All patients reached their anaerobic threshold during the exercise test. Mean $VO_2$max, Wmax and $V_E$max were 15.1 ml/min/kg (± 3.3), 84.1 watt (± 33.3) and 41.6 l/min (± 12.7) respectively, which were 62%, 56% and 77% of predicted. Mean oxygen pulse at maximum exercise was 9.7 ± 3.1 ml/beat, with markedly impaired progression from rest to maximum exercise of 219 ± 76%. Patients after left-sided pneumonectomy tended to have lower $VO_2$max % of predicted (56.5 ± 11.9)

compared to right-sided pneumonectomy patients (70.6 ± 16.5) although this was not significant.

*MRI measurements*

MRI scans were performed in all patients with a mean time interval between the pneumonectomy and the MRI of 101 months (range 60-179) postoperative. Reviewing MRI scan results revealed a myocardial infarction in 1 patient, which had not been diagnosed previously (Figure 2-II).

*Geometric measurements*

Figure 2 (for left-sided pneumonectomy patients) and Figure 3 (for right-sided pneumonectomy patients) present an overview of four chamber views by MRI of all patients who were studied. All patients demonstrated some degree of mediastinal shift, which seemed to be more extensively in case the post-pneumonectomy space was completely obliterated (Figures 2-IV, 2-V, 2-VIII and 3-III). Using the method depicted in Figure 1, we established the degree of rotation of the hearts in our patients. We found that after left- and right-sided pneumonectomy respectively, the mean degree of rotation was 28 (± 62, ranging -96 to 102) and 33 (± 9, ranging 23 to 44) degrees. Resulting from this and from Figures 2 and 3, it is clear that after left-sided pneumonectomy, the heart and vascular structures not only shift into the left hemithorax but also rotate, while the extent of rotation extremely varied between patients. In contrast, rotation of the heart was nearly absent after right-sided pneumonectomy and mostly signs of lateral shifting of the heart and vessels were found in these patients. No correlation was found between the degree of rotation and the LV and RV end-diastolic volumes or LV ejection fraction.

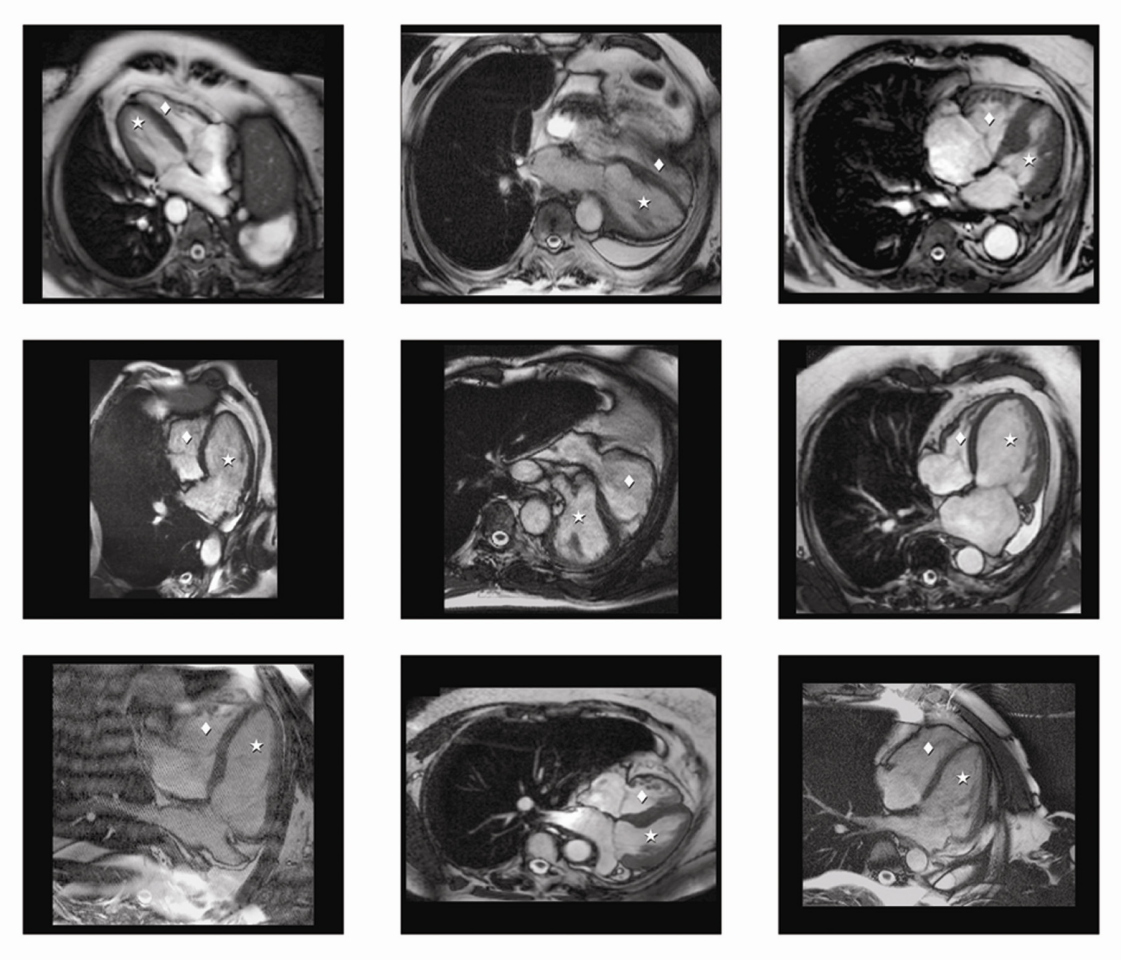

**Figure 2**

*Four chamber views of all patients after left-sided pneumonectomy. Star = LV cavity; Rhomb = RV cavity. Anatomical orientation of the separate figures: top = ventral, bottom = dorsal, right = left side of patient, left = right side of patient.*
*(Top: from left to right figure numbers I, II and III; Middle: from left to right figure numbers IV, V and VI; Bottom: from left to right figure numbers VII, VIII and IX)*

*Cardiac function*

In Table 2 results on RV and LV function are presented, comparing patients with healthy controls and comparing patients after left- and right-sided pneumonectomy. Although cardiac output was normal in all patients, stroke volume was significantly

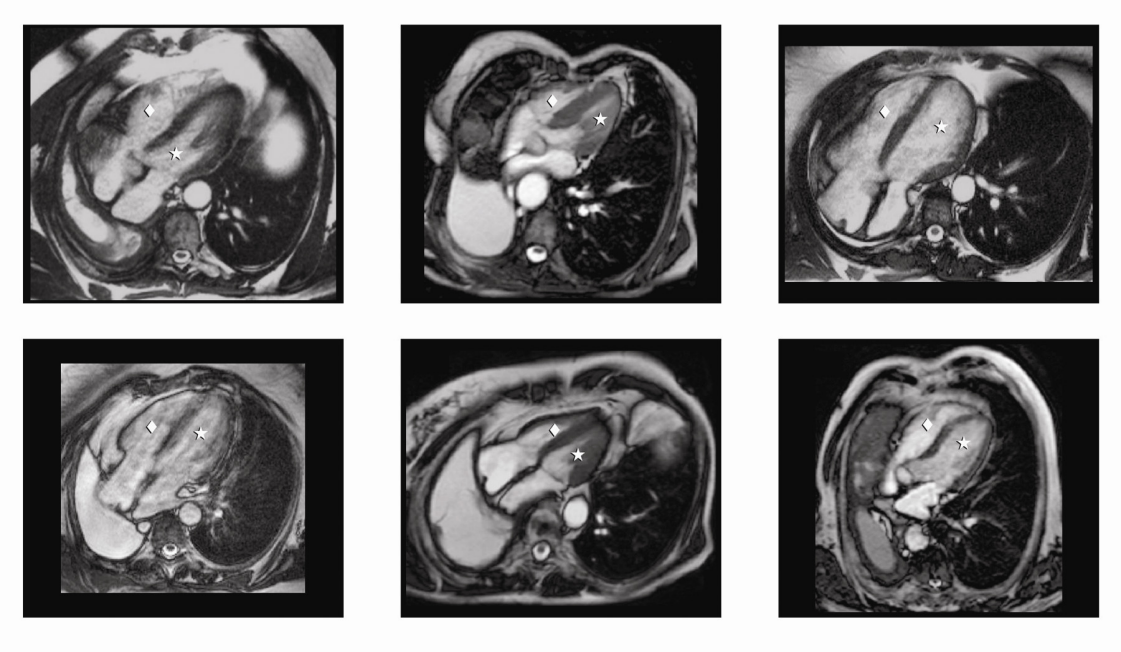

**Figure 3**

*Four chamber views of all patients after right-sided pneumonectomy. Star = LV cavity; Rhomb = RV cavity. Anatomical orientation of the separate figures: top = ventral, bottom = dorsal, right = left side of patient, left = right side of patient.*
*(Top: from left to right figure numbers I, II and III; Bottom: from left to right figure numbers IV, V and VI)*

lower (p = 0.001), compensated by an increased resting heart rate (p = 0.006) compared to healthy controls. No significant difference in stroke volume was observed between the right and left sided pneumonectomy patients.
Patients after left-sided pneumonectomy had an increased LV end-diastolic volume together with a decrease in LV ejection fraction, whereas RV volumes were normal. In contrast, patients after right-sided pneumonectomy had signs of RV hypotrophy together with a decreased RV end-diastolic volume (99 ± 29ml), while LV volume and function were normal.

**Table 2** **Postoperative LV and RV function [1], comparing patients with healthy controls and comparing patients after right- and left-sided pneumonectomy**

| | All n = 15 | Healthy controls n = 25 | p | Right n = 6 | Left n = 9 | p |
|---|---|---|---|---|---|---|
| **Age (yr)** | 64 ± 10 | 43 ± 14 | **.0001** | | | |
| **HR (bpm)** | 80 ± 17 | 65 ± 12 | **.006** | 89 ± 19 | 74 ± 13 | .099 |
| **SV (ml)** | 64 ± 12 | 83 ± 17 | **.001** | 59 ± 14 | 67 ± 10 | .195 |
| **CO (l/min)** | 5.0 ± 0.9 | 5.4 ± 1.5 | .567 | 5.2 ± 1.2 | 4.9 ± 0.8 | .480 |
| **LVEF (%)** | 58 ± 14 | 72 ± 8 | **.001** | 64 ± 11 | 54 ± 15 | .239 |
| **LVEDV (ml)** | 126 ± 67 | 120 ± 18 | .270 | 94 ± 23 | 148 ± 80 | **.025** |
| **LVEDVI** | 64 ± 26 | 61 ± 10 | .645 | 52 ± 9 | 73 ± 31 | .059 |
| **RVEDV (ml)** | 123 ± 39 | 148 ± 32 | **.043** | 99 ± 29 | 139 ± 38 | .059 |
| **RVEDVI** | 64 ± 17 | 75 ± 12 | .061 | 55 ± 14 | 70 ± 16 | .099 |
| **RVM (g)** | 48 ± 24 | 51 ± 20 | .434 | 33 ± 17 | 57 ± 24 | **.018** |
| **LVM (g)** | 120 ± 41 | 148 ± 36 | **.017** | 108 ± 45 | 127 ± 39 | .289 |

[1] *Mean ± standard deviation*

*CO Cardiac output; HR Heart rate; LVEDV, RVEDV Left and right ventricular end-diastolic volume; LVEDVI, RVEDVI Left and right ventricular end-diastolic volume index = EDV/BSA (Body surface area); LVEF Left ventricular ejection fraction; LVM, RVM Left and right ventricular mass; SV Stroke volume*

## Discussion

Our study shows that in a group of long-term survivors after pneumonectomy (> 5 years), considerable intrathoracic anatomical changes occur together with a reduction of stroke volume compensated by an increased heart rate at rest, indicative for a compromised cardiac function. Although we did not measure stroke volume during exercise, the abnormal stroke volume response during exercise in the presence of a normal ventilatory reserve at maximal exercise provide further evidence that cardiovascular limitation contributes to the limited exercise capacity in

these patients. Since we did not find any signs of RV hypertrophy, the decreased stroke volume is unlikely due to increased pulmonary artery pressures (increased afterload). Furthermore, we conclude that based on the differences found between right- and left-sided pneumonectomy patients, the RV underfilling is the primary factor that compromised RV function, whereas LV failure is the primary factor in left-sided pneumonectomy patients.

Previous studies by Biondetti and Suarez have mentioned the finding of more extreme mediastinal shifting in case the post-pneumonectomy space is completely obliterated[14;15]. Although we did not relate the amount of pleural filling with the lung function it is clear from the MRI images that there is variation in the amount and location of pleural filling and both hemidiaphragms influencing the expansion of the remaining lung. Our findings show that mostly rotation of the heart occurs after left-sided pneumonectomy and that there is a huge variability between patients. Factors that determine the extent of rotation are unclear, however it is conceivable that variation in the shape of the thoracic cavity, extent of elevation of the ipsilateral hemidiaphragm and degree of obliteration of the pleural cavity all might influence the final position of the heart. In contrast to this, the alteration of the heart in right-sided pneumonectomy patients is characterized by a lateral shift with only minor rotation of the heart. The extent of the lateral shift seemed to be determined by the degree of obliteration of the pleural space.

Although the group of patients was to small to draw firm conclusions on the effects of right-sided pneumonectomy in comparison to left-sided pneumonectomy on cardiac function, remarkable differences were observed between both groups. First, RV end-diastolic volume and LV mass were extremely low in patients after right-sided pneumonectomy. An explanation for this could be the lateral shift observed in

these patients which possibly impairs RV filling due to external compression of the thoracic wall. Low LV mass could be due to the effect of a chronically reduced stroke volume on the LV wall. Secondly, despite large standard deviations, patients after left-sided pneumonectomy seemed to have a relatively low LV ejection fraction and a significantly increased LV end-diastolic volume, compared to patients after right-sided pneumonectomy. Although we could not find a relation between LV ejection fraction and the degree of rotation of the heart, this does not preclude a causal relationship between cardiac rotation and loss of systolic function. However, the numbers were too small to perform further analysis.

We did not find any signs of RV hypertrophy or RV dilatation in our cohort, making the presence of pulmonary hypertension in our study population very unlikely. In the past few decades, several studies have reported on the effect of pneumonectomy on cardiopulmonary function (measurements ranging from 2-168 months postoperative). In general, these studies agree to the fact that in pneumonectomy patients, pulmonary artery pressure, RV systolic pressure and pulmonary vascular resistance are normal or slightly increased at rest[16-22], and increase during exercise due to the limited recruitment capacity of the pulmonary vascular bed, confirming our findings[2;5;17;18]. Furthermore, Burrows et al. found that RV hypertrophy only occurred in patients with an abnormal remaining lung. Since our patients had no signs of emphysema radiologically, we conclude that the pulmonary vascular bed in the remaining lung was sufficient to prevent the development of increased RV afterload.

**Conclusions**

This study shows that the long-term effects of pneumonectomy on the position of the heart are characterized by a lateral shift after right-sided pneumonectomy, whereas

left-sided pneumonectomy leads to a rotation of the heart. Overall, cardiac function in long term survivors after pneumonectomy is compromised which might be explained by the altered position of the heart.

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Chapter 8.1

# Where is the Heart after Left-Sided Pneumonectomy?

Sietske A Smulders, Harrie CM van den Bosch

Johannes C Post, Anton Vonk Noordegraaf

Pieter E Postmus

**Journal of Thoracic Oncology 2006; 1: 69-70**

**Case Report**

A 64-year old female with a history of pneumonectomy for non-small cell lung cancer 102 months ago, presented without severe complaints of dyspnoea or cough, for a routine follow-up exam at our hospital. Chest X-ray revealed (however somewhat stable for the last few years) extreme shifting of mediastinal structures to the side that was operated on (Figure 1). Exact localisation of the heart was not possible by chest X-ray alone, which is often the case after pneumonectomy. For research purpose (written informed consent obtained), we performed a CT scan (Figure 2). This revealed a very unusual localisation of the heart, where the left ventricular free wall was placed against the left dorsal chest wall. Despite these extreme anatomical changes, she was functioning adequately without severe dyspnoea on exertion. Lung function test showed a FVC and $FEV_1$ of 91% and 79% of predicted, respectively, and she was not ventilatory limited. No overt signs of cardiac dysfunction were observed.

Changes in anatomy of the postpneumonectomy space places these patients at risk of injury to the liver, spleen or heart in case of blind percutaneous needle and/or chest tube insertion[1]. Direct visual guidance with ultrasonography or CT is recommended when placing chest tubes in such patients, in order to prevent serious complications[2].

Presenting case reports like this, we believe, once more shows the need for knowledge on these extreme anatomical changes and the importance of careful localising thoracic structures in postpneumonectomy patients before invasively entering the postpneumonectomy space for any given reason.

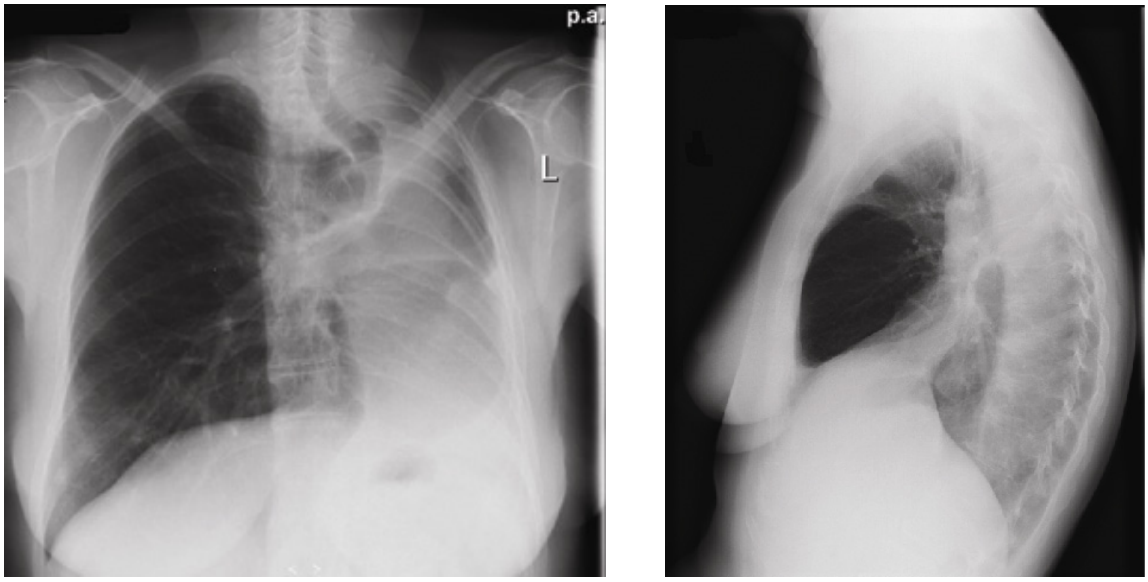


**Figure 1a (left) and 1b (right)**

*The patients' posteroanterior (a) and lateral (b) chest radiographs 102 months following left-sided pneumonectomy demonstrating extreme left-sided mediastinal shifting.*

*L Left side of patient*

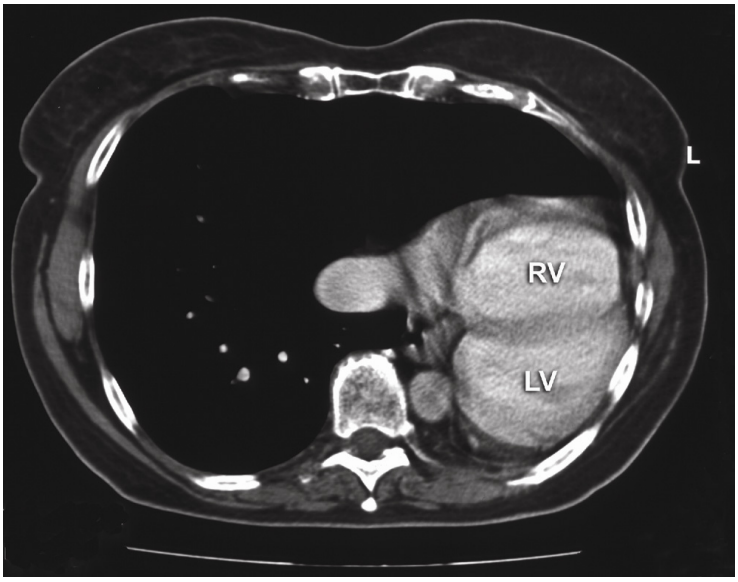


**Figure 2**

*The patients' axial computed tomography image. Notice that the left ventricle is repositioned and placed against the left dorsal chest wall.*

*L Left side of patient; LV, RV Left and right ventricle*

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Chapter 8.2

# Left Ventricular Encasement after Pneumonectomy

Sietske A Smulders, J Tim Marcus

Tji-Joong Gan [1], Tom G Sutedja [1]

Frank WJM Smeenk, Anton Vonk Noordegraaf

**Journal of Thoracic and Cardiovascular Surgery 2006; 132: e23-e24**

[1] Department of Pulmonology, VU University Medical Center Amsterdam

The Netherlands

**Abstract**

We present a case of a left-sided pneumonectomy patient who collapsed while digging. This was caused by the limited space for expansion of the left ventricle hampering its filling, as can be documented by dynamic cardiac MRI imaging.

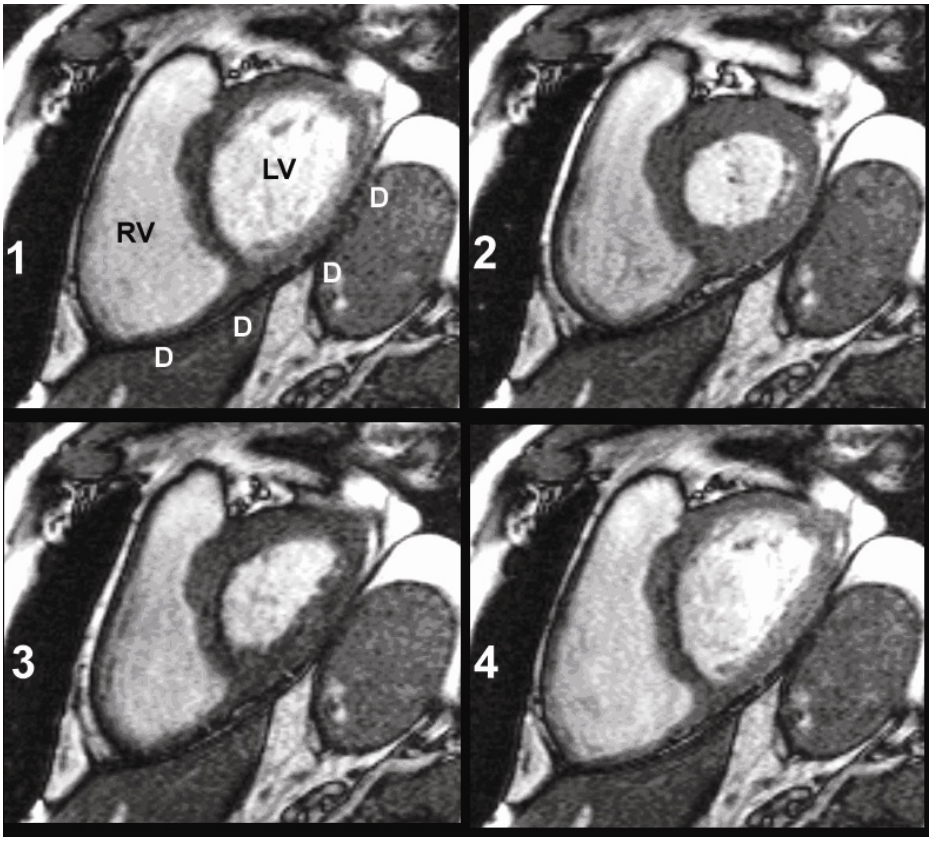


**Figure 1A**

*Ventricular short-axis images. Numbers 1 to 4 are consecutive images during patients' Valsalva manoeuvre. Notice that the left ventricular wall flattening is most clearly seen in '3'.*
*'1' Start of systole at the R wave*
*'2' Midsystole*
*'3' Early diastolic phase*
*'4' Late diastolic phase*
*D Left hemidiaphragm; LV, RV Left and right ventricle*

**Case Report**

A 53 year old male with a history of hypertension and left-sided pneumonectomy 7 years previously was referred to our hospital. He complained about dizziness and had collapsed twice while digging. No other complaints were present, especially no dyspnoea. There were no signs of airway obstruction (FVC 51% and $FEV_1$ 47% of predicted) and CO diffusion capacity was normal (DLCO corrected for alveolar volume 106% of predicted). Maximum exercise test results were normal for a pneumonectomy patient, with Wmax of 62% and $VO_2$max of 77% of predicted. Arterial blood gas analysis showed normoventilation. Echocardiography showed normal right and left ventricular function and slight left ventricular free wall flattening. Finally, dynamic cardiac MRI imaging was performed to study the influence of increasing abdominal pressure on the right and left ventricular (RV and LV) function on a beat per beat basis. During MRI imaging we asked the patient to perform a Valsalva manoeuvre, while short-axis cine images were made (Figure 1A). As is clear from Figure 1A and B (coronal image), the position of the heart in this patient has shifted in the years after his pneumonectomy and the LV free wall was repositioned all the way on top of the paralysed left hemidiaphragm. During Valsalva, intra-abdominal pressure increases and probably hampers LV filling in this patient by a direct transmission of the intra-abdominal pressure to the LV free wall. Note that in the normal thorax the LV free wall is adjacent to the left lung, staying free of contact with the diaphragm. Additionally, we asked the patient to lift both his legs mimicking a digging position and hold his breath for approximately 10 seconds while laying supine in the MRI scanner. The real-time short-axis cine images (Figure 2) showed a progressive LV free wall flattening leading to a decrease of the LV cross-sectional area, as is shown in Figure 2. These changes of the LV cross-sectional area at midventricular level are probably representing the LV volume changes. Thus, the LV end-diastolic volume and stroke volume decreased due to the shifted position of the LV on top of the paralysed hemidiaphragm which seemed to worsen its compliance. LV filling was further deteriorated during breath holding and legs' tilting manoeuvres. In retrospect, it

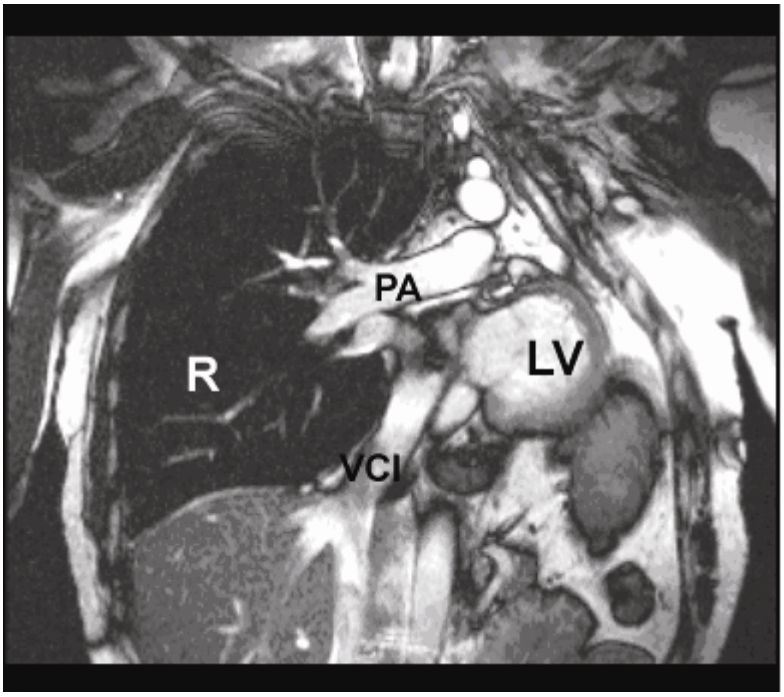


**Figure 1B**

*Coronal image focusing on the inferior vena cava, pulmonary artery and the left ventricle. The left ventricular free wall is positioned against the paralytic elevated left hemidiaphragm.*
*LV Left ventricle; PA Pulmonary artery; R Right lung; VCI Inferior caval vene*

appeared that during pneumonectomy, the phrenic nerve was severed with the surgeons' intention to fill the postpneumonectomy space faster postoperatively, a method that is currently considered controversial[1].

Although we initially proposed surgical plication of the diaphragm as a possible solution, the low frequency of collapse (twice), uncertainty of the outcome of surgery and the assurance of the patient after being informed about the reason of his collapse ultimately were factors not to pursue any surgical solution.

This case report presents an unusual long-term complication of pneumonectomy, which was seen during real-time dynamic cardiac MRI imaging. Therefore, dynamic MRI

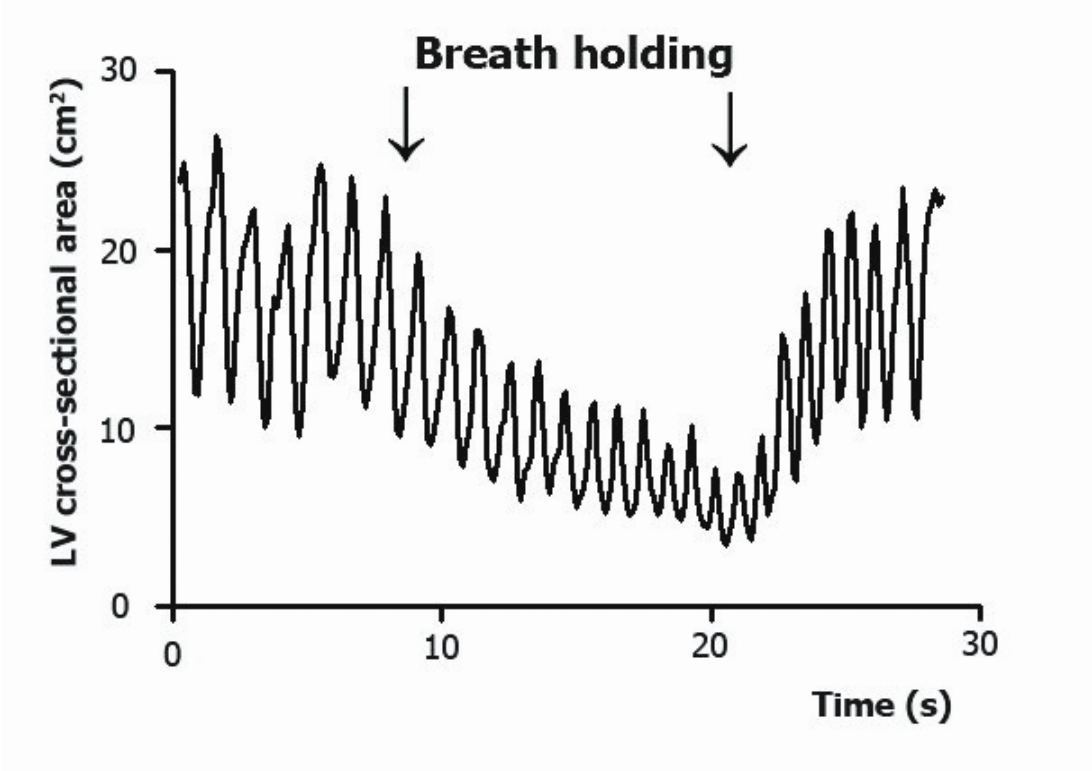


**Figure 2**

*The left ventricular short-axis cross-sectional area (in $cm^2$) at midventricular level, plotted against time (s). After about 8 seconds, the influence of the breath holding manoeuvre with lifting both legs in the supine position is clearly depicted. The LV cross-sectional area comes back to the initial values while breathing normally with both legs stretched and relaxed again.*
*LV Left ventricle*

provides an excellent tool to analyse the complications caused by the relocation of the heart and large vessels in the postpneumonectomy patient.

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Chapter 8.3

# Compression of the Pulmonary Vein after Right-Sided Pneumonectomy

Sietske A Smulders, J Tim Marcus

Sebastiaan Holverda, Marinus A Paul [1]

Pieter E Postmus, Anton Vonk Noordegraaf

**Circulation 2006 May 9; 113 (18): e743-4**

[1] Department of Surgery, VU University Medical Center Amsterdam

The Netherlands

**Abstract**

Pneumonectomy can give rise to extreme mediastinal shifting, especially a few years after the operation. We present a case of such a patient with incapacitating dyspnoea due to compression of the left upper pulmonary vein between the left atrium and descending aorta, which was treated by repositioning of the mediastinum.

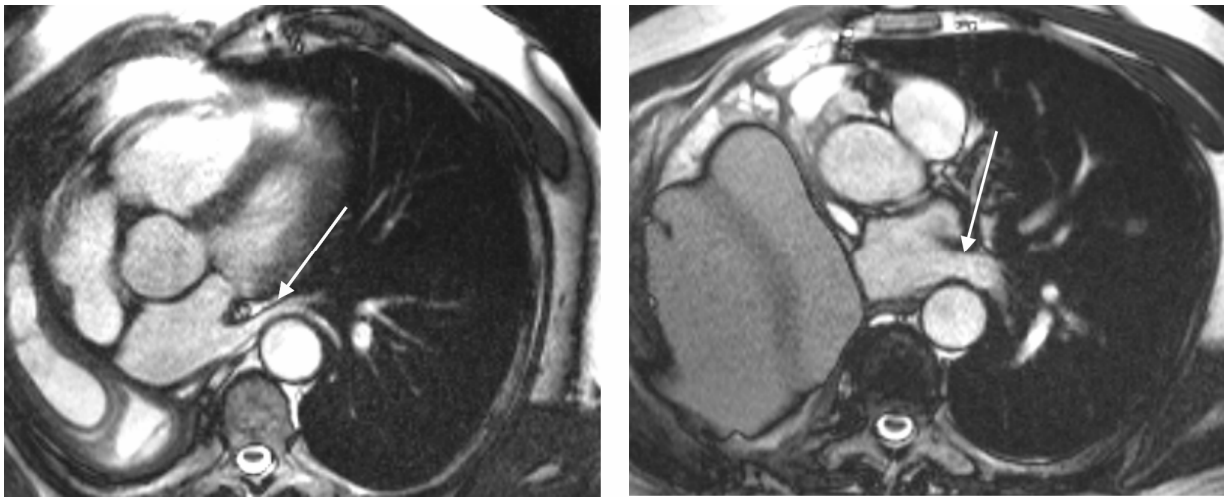


**Figure 1**

*MRI images before (left) and after (right) operation. The obstruction of the pulmonary vein (arrow) is removed by repositioning of the heart. The presented images show the first temporal phase after the ECG-R wave.*

**Case Report**

Six years after right pneumonectomy a 67 year old man developed progressive dyspnoea during exercise. Finally, he was admitted to the hospital due to severe dyspnoea after some exercise. The chest X-ray showed signs of pulmonary edema, improving rapidly after furosemide and oxygen therapy. There were no signs of tumour recurrence or airway obstruction on CT. Pulmonary function tests were not changed compared to the years before ($FEV_1$ 2.1 liter/sec, $DL_{CO}$ 70% of predicted). Cardiopulmonary exercise testing showed a decreased peak work load (44% of predicted), together with a low peak $O_2$ pulse (48% of predicted) and a normal breathing reserve of 30%. Echocardiography showed a normal left ventricular function. For further analysis of the heart and pulmonary vasculature, MRI analysis was performed.

This showed compression of the left upper pulmonary vein between the left atrium and descending aorta (Figure 1, left). Stroke volume was measured by flow velocity quantification and was 40 ml with a cardiac index of 1.8 liter/$m^2$. For this reason, a re-thoracotomy was performed for the repositioning of the heart and placement of 2 silicone prostheses inside the pleural cavity (Figure 1, right). Flow measurement results performed by MRI orthogonal to the left upper pulmonary vein before and after the thoracotomy are presented in Figure 2. Six months after the re-thoracotomy, he had no complaints of shortness of breath and his exercise capacity was 88 % of predicted. Stroke volume and cardiac index at that time were 86 ml and 4 liter/$m^2$, respectively.

This case demonstrates that compression of pulmonary veins, due to shifting of heart and mediastinum to the operated side after pneumonectomy, might result in severe complaints and pulmonary congestion. It improves after re-establishing the normal diameter of these vessels.

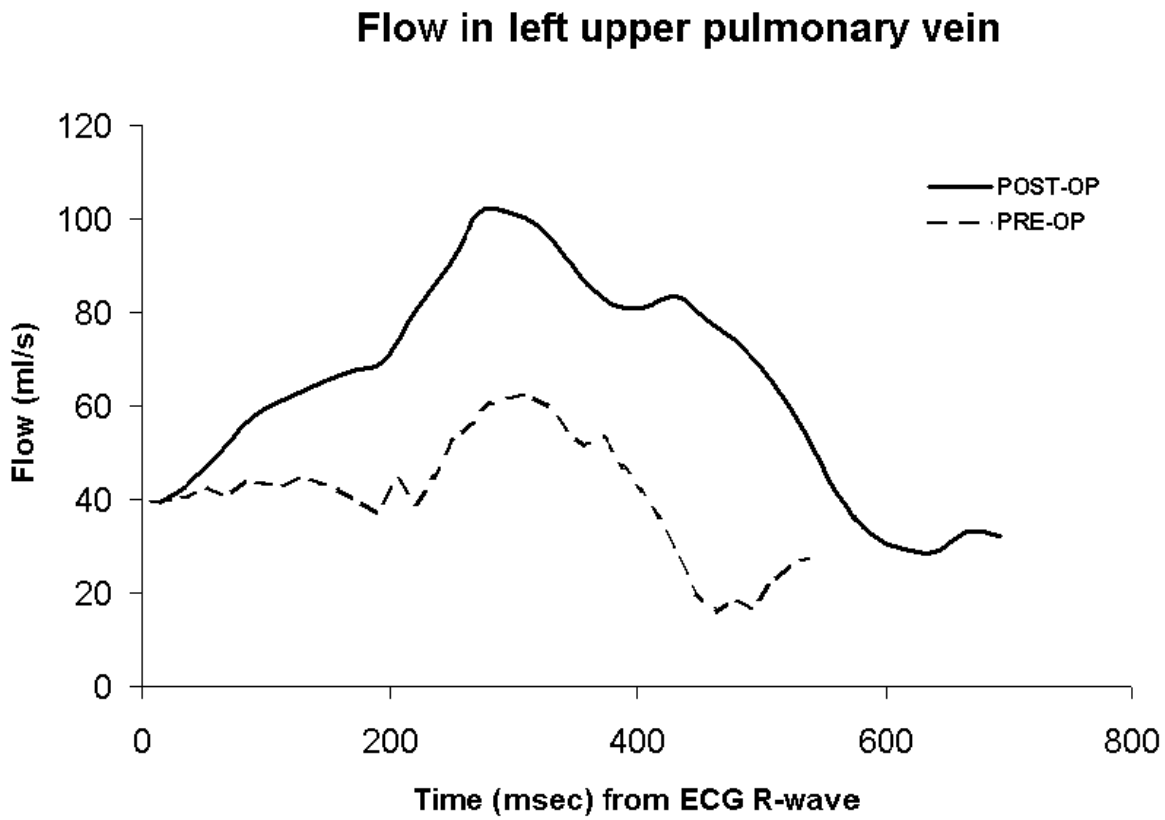



**Figure 2**

*Flow measurement results during one cardiac cycle performed by MRI in the left upper pulmonary vein before (dashed line) and after (black line) thoracotomy. Time (in ms) after the ECG R-wave is on the x-axis and flow through the pulmonary vein (in ml/sec) is on the y-axis. Pre-op: preoperative flow measurement results (dashed line). Post-op: postoperative flow measurement results (black line).*

# Summary

**Summary**

Lung cancer is a disease that is frequently asymptomatic in its early stage, and as a consequence many patients present themselves at a rather late stage of the disease. Despite extensive research efforts in lung cancer patients, mortality rates remain high. In fact, the prognostic most favourable group is the same as several decades ago and consists of patients in whom surgical resection of the tumor is possible. However, the majority of patients present with an unresectable or disseminated tumor. For a small group of these patients, combined modality loco-regional treatment might offer a better prospect. For instance induction chemo-radiotherapy, sometimes followed by surgery, may result in long-term disease free survival. In order to be able to distinguish patients that can be cured by primary surgical resection or combined modality treatment from those who cannot, a number of aspects are important. Several of these (for instance comorbidity, the TNM stage and (predicted) postoperative cardiac and pulmonary function) are described in this thesis. Lung cancer is a disease of the middle aged and older part of the population; these people have to deal with all the consequences of aging and the effects of an unhealthy life-style like smoking. Additional disease may affect the choice of treatment. Another extremely important aspect is adequate staging of the tumor. For this, several imaging modalities *(computed tomography (CT) scanning, magnetic resonance imaging (MRI) and F-18-deoxyglucose positron emission tomography ($^{18}$FDG-PET) scanning*) and invasive tools (*bronchoscopy, transbronchial needle aspiration (TBNA), mediastinoscopy, transoesophageal ultrasound-guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound (EBUS)*) are being used.

In **Part I** of this thesis, several aspects influencing treatment choice in NSCLC patients, like age, comorbidity and the TNM-stage, were investigated.

With the relatively high age many patients will be diagnosed with one or more other serious diseases at the time of lung cancer diagnosis (comorbidity). Since elderly (>70 years) patients are often excluded from clinical trials, little is known about either the best

way to treat elderly patients with comorbidity or the outcome of treatment. In **Chapter 1** the independent prognostic effects of age and comorbidity for patients with NSCLC were evaluated. We found that elderly patients were treated less aggressively. The proportion of patients with localized (stage I and II) NSCLC who underwent surgery decreased from 92% of patients younger than 60 to 9% of those aged 80 or older. Among patients aged 60-79 this proportion also decreased with comorbidity. Among patients with non-localized (stage III and IV) NSCLC the proportion receiving chemotherapy was considerably higher for patients younger than 60 (24%) than those aged 80 or older (2%). The number of comorbid conditions had no significant influence on treatment chosen for patients with non-localized disease. Multivariate survival analyses showed that age, tumour size and treatment were independent prognostic factors for patients with localized disease, and stage of disease and treatment for those with non-localized disease. Comorbidity had no independent prognostic effect.

In **Chapter 2**, we investigated the accuracy of preoperative surgical mediastinal staging procedures in 4 hospitals. Guidelines to perform or to skip mediastinoscopy in patients suspected for malignant lung lesions were adequately followed in all-day clinical practice in approximately two-third of cases in 4 general hospitals. Physicians were especially reluctant to perform mediastinoscopy in patients with peripheral lesions without a preoperative histological diagnosis. Within the 4 hospitals that were investigated, the one with the smallest number of evaluated patients scored the worst percentage of correctly indicated mediastinoscopies, which was significantly different from the other hospitals. We also found that of all mediastinoscopies performed, only 40% were done according to 'gold standards' with regard to sampling of lymph nodes. There was a close relation between the number of mediastinoscopies yearly performed and the percentage of mediastinoscopies performed according to gold standards. Finally, sampling of mediastinal lymph nodes during thoracotomy was done more often and more thorough in the hospitals were most patients were evaluated and operated on. We found that mediastinal lymph node sampling during thoracotomy was done in approximately 50% of

cases, which led to upstaging in 17% of patients. In almost 1 out of every 5 cases, upstaging and surgical intervention could theoretically have been prevented when mediastinoscopy would have been indicated and performed according to gold standards.

In **Chapter 3**, we studied whether the introduction of $^{18}$FDG-PET in our hospital resulted in an improved adherence to surgical mediastinal staging protocols and performance of mediastinoscopy. We found that adherence to guidelines, compared to the results presented in **Chapter 2**, increased significantly ($p = 0.002$). Although we hypothesized that performance of mediastinoscopy would increase because of the awareness of the results from our previous study and the introduction of PET, the opposite appeared to be true. In fact, the number of mediastinoscopies performed according to gold standards decreased (not significantly), from 39% to 27%. Nevertheless, a higher percentage of mediastinoscopies was positive (17.6%) for metastases, compared to our previous study (15.5%). Apparently, the combination of PET and CT can guide the surgeon to possible metastasized mediastinal lymph nodes and therefore increases the number of positive mediastinoscopies.

In **Chapter 4** we studied accuracy and interobserver variation in determining presence of mediastinal lymph node metastases by $^{18}$FDG-PET in NSCLC patients. Two groups of nuclear medicine physicians with different levels of PET experience ('experienced' (n=7) and 'inexperienced' (n=7)) reviewed 30 PET scans of patients with suspected operable NSCLC. They were requested to identify and localise suspicious mediastinal lymph nodes on each scan and to formulate a clinical management advice using standardized algorithms. Results were compared between the 2 groups, between individuals and with expert reading (which was considered the 'gold standard'). We found that 80% of the management recommendations and 68% of N-stage classifications were correct, with moderate and good interobserver agreement (kappa 0.59 and 0.65, respectively). Detection rate (72% versus expert reading) and most common mislocalisations of separate mediastinal lymph node stations were equally distributed between the 2 groups.

Experience with PET translated into a better ability to localise mediastinal lymph node stations (68% versus 51%, respectively), and experienced readers appeared to be more familiar with translating PET readings into clinically useful statements. However in general, even among experienced readers there was obvious room for improvement.

In **Part II** of this thesis, we presented studies regarding postoperative cardiac and pulmonary function, with emphasis on effects in patients after pneumonectomy.
Lung capacity obviously decreases after resection for lung cancer. Several formulas are in use aiming to predict postoperative lung function. In general, these formulas can be divided into two categories. The first category of formulas calculates postoperative FVC and $FEV_1$ by the number of pulmonary segments to be resected. The second category of formulas includes the function of these segments by measuring their actual perfusion preoperatively. In **Chapter 5** we evaluated the long-term validity of 2 formulas frequently used to predict postoperative lung function as well as trends in postoperative lung function and late postoperative exercise capacity in pneumonectomy patients. Postoperative forced vital capacity (FVC) and forced expiratory volume in 1 second ($FEV_1$) according to the 'Kristersson/Olsen formula' (split function of resected lung) and the 'Juhl and Frost formula' (number of segments to be resected) were calculated and compared with observed values measured in the third postoperative year. Calculated values correlated well with observed values, whereas the Kristersson/Olsen formula appeared to be more accurate than the one by Juhl and Frost. When considering trends in $FEV_1$, we found a mean decline of 44 ml/year; only 3 patients (12%) showed a rapid decline of more than 100 ml/year. In 14 patients (44%), postoperative maximal exercise capacity was impaired due to ventilatory limitation.

Besides postoperative lung function we also studied the effects of pneumonectomy on cardiac function. Nowadays, cardiovascular magnetic resonance (CMR) imaging offers a unique possibility to study the cardiac function in an altered geometric position of the heart. CMR not only is accurate and reproducible in normal as well as abnormal

ventricles, but also free of ionising radiation and independent of the geometric assumptions and acoustic windows that limit echocardiography. Therefore, we studied short- and long-term effects of pneumonectomy on cardiac function by MRI.

In **Chapter 6**, the short-term effects of pneumonectomy on cardiac function were studied. We found that shortly after the operation, heart rate increased and stroke volume decreased, both significantly, indicating depressed cardiac function. Furthermore, left ventricular end-diastolic volume was significantly decreased and this was related to the decrease in stroke volume. Since we did not find any signs of right ventricular dysfunction, the underfilling of the left ventricle must be interpreted as a direct consequence of a decreased compliance of the pulmonary vascular bed. Eventually however, at 3 months postoperatively, these values normalised indicating that initial adaptation of the heart had been successfully completed.

In **Chapter 7**, the long-term effects of pneumonectomy on cardiac function, exercise limitation and geometric position of the heart were studied in 15 patients more than 5 years postoperatively. Large deviations of the normal position of the heart within the thorax were observed in patients after right-sided pneumonectomy whereas torsion of the heart was predominantly seen after left-sided pneumonectomy. There were findings indicative for compromised cardiac function, such as an increased heart rate and decreased stroke volume at rest, and these findings together with an abnormal stroke volume response during exercise provided further evidence that cardiovascular limitation contributed to the limited exercise capacity in our patients. As an explanation, we found in the right-sided pneumonectomy patients an underfilling of the right ventricle most probable due to thoracic wall compression, whereas in the left-sided pneumonectomy patients left ventricle dysfunction was frequently present. We did not find any signs of right ventricular enlargement or hypertrophy, making the presence of pulmonary hypertension unlikely. Based on these findings, we concluded that the impaired cardiac function can be explained by the altered position of the heart.

In **Chapter 8** three unusual features in patients after pneumonectomy were presented. The first described patient was asymptomatic despite a replacement of the heart to the dorsal side of the thorax after pneumonectomy. The left ventricular free wall was positioned against the left dorsal chest wall (**Chapter 8.1**), placing this patient at risk of injury (or worse) in case of blind percutaneous needle and/or chest tube insertion. Secondly (**Chapter 8.2**), a case of a pneumonectomy patient who had the tendency to collapse while bending due to compression of the left ventricular free wall against the paralytic left hemidiaphragm, causing a sever diastolic filling disorder in case the intraabdominal and intrathoracic pressure increased.
Finally (**Chapter 8.3**), a pneumonectomy patient experiencing dyspnoea due to compression of the pulmonary vein between the left atrium and descending aorta, which was treated by repositioning of the mediastinum.

# Samenvatting

**Samenvatting**

Door het ontbreken van vroege symptomen presenteren patiënten met niet-kleincellig longkanker (NKL) zich vaak pas in een laat stadium van de ziekte. Ondanks uitgebreid wetenschappelijk onderzoek de afgelopen decennia blijft het aantal patiënten wat jaarlijks overlijdt hoog en bestaat de groep patiënten met de meest gunstige prognose nog altijd uit patiënten waarbij chirurgische resectie de aangewezen methode van behandeling is. Helaas presenteert de meerderheid van de patiënten zich met een irresectabel of gedissemineerd stadium. Slechts een klein deel van deze groep kan na inductie chemo-radiotherapie alsnog curatief geopereerd worden. Om de groep patiënten die genezen kunnen worden door primair chirurgische resectie, al dan niet voorafgegaan door chemo- en/of radiotherapie, te kunnen onderscheiden van de groep waarin geen curatieve therapie meer mogelijk is, zijn een aantal aspecten van belang. Ten eerste is longkanker in het algemeen een ziekte die voorkomt op middelbare en oudere leeftijd, waar factoren als leefstijl (rookstatus) en co-morbiditeit een rol gaan spelen. Daarnaast is adequate stadiering van de tumor van groot belang. Hiertoe worden verschillende beeldvormende (*computer tomografie (CT) scan, magnetische resonantie (MR) scan en F-18-deoxyglucose positron emissie tomografie ($^{18}$FDG-PET) scan*) en invasieve technieken (*bronchoscopie, transbronchiale naaldaspiratie (TBNA), mediastinoscopie, transoesofageale echogeleide fijne naaldaspiratie (EUS-FNA) en endobronchiale echografie (EBUS)*) gebruikt.

In **Deel I** van dit proefschrift komen aspecten aan bod die invloed hebben op de therapiekeuze bij patiënten met NKL, zoals onder andere leeftijd, co-morbiditeit en het TNM stadium waarin de ziekte zich bevindt bij eerste presentatie.
Een hogere leeftijd ten tijde van de diagnose longkanker zal bij veel patiënten gepaard gaan met het hebben van meerdere (ernstige) aandoeningen (co-morbiditeit). Omdat oudere (> 70 jaar) patiënten vaak worden buitengesloten van wetenschappelijk onderzoek, is er enerzijds weinig bekend over de beste manier om longkanker bij

ouderen met co-morbiditeit te behandelen en anderzijds over de resultaten van de behandeling. In **Hoofdstuk 1** worden de onafhankelijke prognostische effecten van leeftijd en co-morbiditeit bij patiënten met NKL onderzocht. Het blijkt dat ouderen met longkanker minder agressief worden behandeld dan jongere patiënten. Het percentage patiënten met gelokaliseerde stadia NKL (stadium I of II) die worden geopereerd neemt af van 92% bij patiënten jonger dan 60 naar 9% bij patiënten ouder dan 80 jaar. Binnen de leeftijdsgroep 60-79 jaar neemt dit percentage ook af naarmate co-morbiditeit toeneemt. Jongere patiënten (< 60 jaar) met gevorderde stadia (III en IV) worden vaker (24%) behandeld met chemotherapie dan patiënten van 80 en ouder (2%). Het aantal ziektes dat een patiënt heeft buiten longkanker heeft geen significante invloed op de therapiekeuze bij patiënten met gevorderde ziekte. Multivariate analyse laat zien dat leeftijd, grootte van de tumor en therapiekeuze onafhankelijke prognostische factoren zijn voor patiënten met gelokaliseerde ziekte, terwijl het stadium en de therapiekeuze dat zijn voor patiënten met gevorderde ziekte. Co-morbiditeit alleen heeft geen onafhankelijk effect op prognose.

In **Hoofdstuk 2** hebben we onderzocht in hoeverre preoperatieve mediastinale stadieringsmethoden accuraat worden toegepast in 4 perifere ziekenhuizen. Het blijkt dat richtlijnen met betrekking tot het al dan niet uitvoeren van een mediastinoscopie bij patiënten die verdacht worden van longkanker in 2/3 van de gevallen correct worden gevolgd. Vooral in geval van een verdachte perifere nodus waarvan geen histologische diagnose verkregen kan worden, zijn longartsen terughoudend in het laten uitvoeren van een mediastinoscopie. Binnen de 4 onderzochte klinieken blijkt het ziekenhuis waar het minst aantal patiënten wordt geëvalueerd het significant slechter te doen dan de rest. Van alle uitgevoerde mediastinoscopieën, wordt 40% volgens ‘gouden standaard’ uitgevoerd (adequate sampling van lymfklierstations Naruke 4 rechts, 4 links en 7). Er is een relatie tussen het aantal uitgevoerde mediastinoscopieën in een ziekenhuis en het percentage dat volgens de gouden standaard wordt verricht. Ook wordt sampling van

mediastinale lymfklieren gedurende thoracotomie vaker en nauwkeuriger gedaan naarmate er in een ziekenhuis meer patiënten worden behandeld.
In het algemeen wordt mediastinale lymfkliersampling tijdens thoracotomie in 50% van de gevallen verricht, wat uiteindelijk resulteert in 17% van de patiënten waarbij postoperatief mediastinale lymfkliermetastasen worden geconstateerd. Theoretisch had 1 op de 5 patiënten een thoracotomie bespaard kunnen blijven indien richtlijnen met betrekking tot het indiceren en uitvoeren van een mediastinoscopie volgens gouden standaard uitgevoerd waren.

In **Hoofdstuk 3** analyseren we of de introductie van de FDG-PET scan in ons ziekenhuis geresulteerd heeft in een verbetering van het volgen van bestaande richtlijnen met betrekking tot mediastinale stadiering en de uitvoering van mediastinoscopie bij patiënten met NKL, ten opzichte van **Hoofdstuk 2** (voor de introductie van PET). Richtlijnen worden significant beter gevolgd ($p = 0.002$) dan voorheen. Terwijl we verwachten dat het aantal mediastinoscopieën dat volgens gouden standaard uitgevoerd wordt zou zijn toegenomen, gezien de resultaten van Hoofdstuk 2 en de introductie van de PET scan, is het tegenovergestelde waar. Het percentage mediastinoscopieën dat wordt uitgevoerd volgens gouden standaard neemt af (niet significant) van 39% (Hoofdstuk 2) naar 27%, echter het percentage mediastinoscopieën met een positief resultaat neemt daarentegen toe (niet significant) naar 17.6% ten opzichte van 15.5% in het vorige onderzoek. Blijkbaar kan de combinatie van PET en CT de chirurg exacter vertellen waar hij moet biopteren tijdens mediastinoscopie, zodat het percentage positieve klieren toeneemt.

In **Hoofdstuk 4** beoordelen we de accuratesse en interobserver variatie van nucleair geneeskundigen ten aanzien van de detectie en het correct lokaliseren van mediastinale lymfkliermetastasen op een $^{18}$FDG-PET scan bij patiënten met NKL. Twee groepen nucleair geneeskundigen met verschillend niveau van ervaring met betrekking tot beoordelen van PET ('ervaren' (n = 7) en 'beginner' (n = 7)) beoordelen ieder

afzonderlijk 30 PET scans van patiënten met mogelijk operabel NKL. Er wordt hen gevraagd om iedere verdachte hot spot op PET te identificeren en te lokaliseren, en om een advies te formuleren met betrekking tot het verdere beleid (bv mediastinoscopie, thoracotomie), gebruik makende van standaard algoritmen. Resultaten worden vergeleken tussen de beide groepen, tussen individuen en met experts (wordt beschouwd als zijnde de 'gouden standaard'). In totaal is 80% van de beleidsadviezen en 68% van de 'N-stadium' classificaties correct, met een gemiddeld tot goede interobserver overeenkomst (kappa 0.59 en 0.65, respectievelijk). Detectiepercentage (72% vergeleken met beoordeling door experts) en meest voorkomende fouten in lokalisatie van aparte mediastinale lymfklierstations zijn eerlijk verdeeld tussen de beide groepen. Ervaring met PET resulteert in het beter kunnen lokaliseren van verdachte mediastinale lymfklierstations (68% versus 51%, respectievelijk) en het adequater kunnen interpreteren van de resultaten van PET naar klinisch bruikbare informatie. In het algemeen echter blijft er ruimte voor verbetering bestaan, zelfs in de groep van ervaren PET beoordelaars.

In **Deel II** van dit proefschrift presenteren we studies over cardiale en pulmonale functie bij patiënten die geopereerd werden voor NKL, in het speciaal bij patiënten na pneumonectomie.
Na resectie van een (deel van) de long neemt de longfunctie af. Er zijn verschillende formules die de postoperatieve longfunctie van patiënten na een resectie proberen te voorspellen. Deze formules worden verdeeld in 2 categorieën. De eerste categorie formules berekent de postoperatieve functie van het resterende longweefsel door het aantal longsegmenten wat verwijderd gaat worden te tellen en zo het percentage te berekenen van het aantal segmenten dat overblijft. Een andere categorie formules neemt in deze berekening de daadwerkelijke functie van deze segmenten mee, die bepaald wordt met behulp van de ventilatie-perfusiescan. In **Hoofdstuk 5** bepalen we de validiteit van 2 van dit soort formules voor de voorspelling van postoperatieve longfunctie

op lange termijn, alsmede de trend in postoperatieve longfunctie en de mate van inspanningstolerantie bij patiënten na pneumonectomie.
Postoperatieve 'geforceerde vitale capaciteit' (FVC) en 1 seconde capaciteit ($FEV_1$) worden berekend volgens de formule van 'Kristersson/Olsen' (perfusie van verwijderde segmenten) en de formule van 'Juhl en Frost' (aantal segmenten wat verwijderd wordt) en vergeleken met daadwerkelijk gemeten postoperatieve waarden 3 jaar na pneumonectomie. Berekende waarden komen goed overeen met de gemeten waarden, maar de formule van 'Kristersson/Olsen' is beter in het voorspellen van postoperatieve functie dan de formule van 'Juhl en Frost'. Met betrekking tot de jaarlijkse trend in longfunctie bij patiënten na pneumonectomie, vinden we dat er een gemiddelde jaarlijkse afname is van $FEV_1$ van 44 ml/jaar; slechts 3 patiënten (12%) hebben een versnelde achteruitgang van 100 ml/jaar. Postoperatieve inspanningstolerantie is afgenomen bij 14 patiënten (44%) ten gevolge van ventilatoire beperking.

Naast postoperatieve longfunctie bestuderen we ook de effecten van pneumonectomie op cardiale functie. Cardiovasculaire MRI geeft een unieke mogelijkheid om de functie van het hart te bestuderen in geval van veranderde anatomische verhoudingen. Het geeft nauwkeurige en reproduceerbare resultaten voor zowel normale als pathologische ventrikels, maakt daarbij geen gebruik van radioactieve straling en doet geen anatomische aannames zoals echocardiografie. Daarom onderzoeken we korte- en lange termijn effecten van pneumonectomie op de functie van het hart middels MRI.
In **Hoofdstuk 6** worden de korte termijn effecten van pneumonectomie op de functie van het hart onderzocht. Direct na de operatie (2 weken) neemt het slagvolume af terwijl de hartfrequentie toeneemt, beiden significant, wat duidt op afgenomen hartfunctie. Verder is het linker ventrikel eind-diastolisch volume direct postoperatief significant afgenomen. Deze afname is direct gerelateerd aan het afgenomen slagvolume. Omdat we geen tekenen van rechter ventrikel dysfunctioneren vinden, moet de verminderde vulling van de linker ventrikel dan ook geïnterpreteerd worden als zijnde direct veroorzaakt door verminderde compliantie van het pulmonale vaatbed. Drie maanden na

de operatie zijn deze waarden weer genormaliseerd dus het lijkt erop dat de initiële aanpassing van het hart aan de nieuwe situatie postpneumonectomie dan voltooid is.
In **Hoofdstuk 7** bestuderen we de lange termijn effecten van pneumonectomie op de functie van hart en longen en anatomische positie van het hart binnen de thorax bij 15 patiënten meer dan 5 jaar na de operatie. Er wordt in het algemeen een forse horizontale verschuiving naar de aangedane zijde gezien van het hart binnen de thorax terwijl torsie van het hart om zijn eigen as alleen gezien wordt bij patiënten na linkszijdige pneumonectomie. We vinden aanwijzingen voor verminderde hartfunctie, zoals verminderd slagvolume en toegenomen hartfrequentie. Deze bevindingen tezamen met het feit dat we een abnormale toename vinden van het slagvolume tijdens inspanning duiden erop dat het verminderd cardiovasculair functioneren bijdraagt aan gedaalde inspanningscapaciteit in onze patiënten. Bij rechtszijdige pneumonectomie patiënten wordt een ondervulling gevonden van de rechter ventrikel, waarschijnlijk ten gevolge van druk door de thoraxwand op de ventrikel, en bij linkszijdige pneumonectomie patiënten constateerden we met name een verminderde linker ventrikelfunctie. Er is postoperatief geen rechter ventrikel dilatatie of hypertrofie dus het bestaan van pulmonale hypertensie is onwaarschijnlijk. Gebaseerd op deze bevindingen concluderen we dat de verminderde hartfunctie bij patiënten 5 jaar na pneumonectomie het gevolg kan zijn van de veranderde postoperatieve positie van het hart in de thorax.

In **Hoofdstuk 8** worden drie zeldzame situaties beschreven bij patiënten na pneumonectomie.
Ten eerste (**Hoofdstuk 8.1**) een patiënt met ernstige anatomische veranderingen een paar jaar na de operatie, waarbij de linker ventrikel helemaal tegen de dorsale zijde van de linker thoraxhelft gepositioneerd is. Hierdoor loopt deze patiënt ernstig gevaar in geval invasieve diagnostiek van de post-pneumonectomieholte noodzakelijk zou zijn en dit gebeurt zonder begeleiding van beeldvormende technieken.
Ten tweede (**Hoofdstuk 8.2**) een casus van een pneumonectomie patiënt die de neiging had te collaberen tijdens bukken ten gevolge van een diastolische dysfunctie van de

linker ventrikel. Dit trad op doordat de vrije wand van de ventrikel tegen het linker hemidiafragma aan lag zodat bij bukken (verhogen intrathoracale- en intra-abdominale druk) dit aanleiding gaf tot afplatting van de vrije wand en vermindering van de linker ventrikel preload.

Als laatste (**Hoofdstuk 8.3**) een patient die een aantal jaar na pneumonectomie last kreeg van dyspnoe ten gevolge van compressie van een grote vena pulmonalis tussen het linker atrium en de aorta descendens. Dit werd succesvol behandeld door chirurgische repositie van het mediastinum.

# General Discussion

# Future Considerations

# and Conclusions

**General Discussion and Future Considerations**

Overall, the presence of serious comorbidity in NSCLC patients is high, especially in the elderly. Because elderly patients (> 70 years) are often excluded from clinical trials, little is known about the best ways to treat them and about the outcome of such treatment. With the rising mean age, more people will be older with more comorbid conditions at the time of lung cancer diagnosis. Therefore, more studies on this subject are needed. Especially because we found in **Chapter 1** that elderly patients are treated less aggressively than younger patients, while the choice of treatment was not influenced by the presence of comorbidity, but mainly by age. Furthermore, comorbidity had negligible influence on survival of NSCLC patients, despite the less aggressive treatment in case of comorbidity. So, we question whether this less aggressive treatment in the elderly is always justified. In recently published Dutch guidelines it is recommended that patients of 70-80 (and even > 80) years old eligible for resection, should be evaluated like younger patients, with special attention to comorbidity and overall condition, and that surgical resection should not be denied on age only[1]. We agree on this, however, it is known that pneumonectomy (especially right-sided) in patients more than 80 years old is associated with significantly more complications and worse survival[2-4], compared to younger patients. Therefore we believe this procedure should probably be refrained from in these particular patients and one should consider (radical) radiotherapy as an alternative, if eligible. Besides this, being also responsible for elderly patients with lung cancer, we believe one should keep in mind that in everyday practice resectability is not primarily determined by the *number* of comorbid conditions but by the *impact* of comorbidity, such as pulmonary and cardiac function.

In every new NSCLC patient, one of the first problems a pulmonary physician has to solve is assigning the disease to the correct TNM stage, because this has major impact on the choice of treatment. Recently, EUS-FNA and EBUS were introduced for invasive

lung cancer staging and without doubt, these modalities will become more available and probably change current NSCLC staging guidelines in the near future.
Nowadays however, mediastinoscopy still is the overall gold standard and remains the most available and frequently used tool for invasive staging. So, how come that in daily practice only 40% of 'gold standard' mediastinoscopies is actually done according to gold standards and sampling of mediastinal lymph nodes during thoracotomy is done in only 50% of all patients (**Chapter 2**)? After confronting surgeons with these results they mentioned that often 'no mediastinal lymph nodes were found', 'it was not possible to biopsy that particular lymph node' or 'fear of complications existed'. Apparently "normal" daily practice differs from published data obtained in large academic centers. A reason for this could be the retrospective data gathering. Perhaps, in case data would have been collected prospectively and surgeons had to work according to a fixed protocol, like in other prospective studies, overall results would have been better. Secondly, because quality of care relates to the number of procedures performed in a hospital[5-7]. Therefore, it might be recommended to perform these procedures according to a fixed protocol and only in those centres where one has sufficient experience. Unfortunately however, perhaps due to the limited number of patients in our study, we have not been able to show that this non-adherence to guidelines in fact also had a negative effect on clinical outcome or survival in these patients (data therefore not presented in this thesis). Nevertheless, we believe that one should always make the maximum effort to adhere to existing guidelines, because only then it will be possible to adequately monitor these aspects of care and to find out whether problems in these areas are present and if so, how they need to be approached.

In the past few years, a lot of studies have been published on the utility of FDG-PET scanning in the conventional work-up of patients with possible curable NSCLC. In a review from 2003, Silvestri et al. recommended PET to evaluate the mediastinum in all patients who are candidates for surgery[8]. In a more recent review by Detterbeck et al.[9] there appears to be only a minor role for PET imaging in patients with peripheral cT1

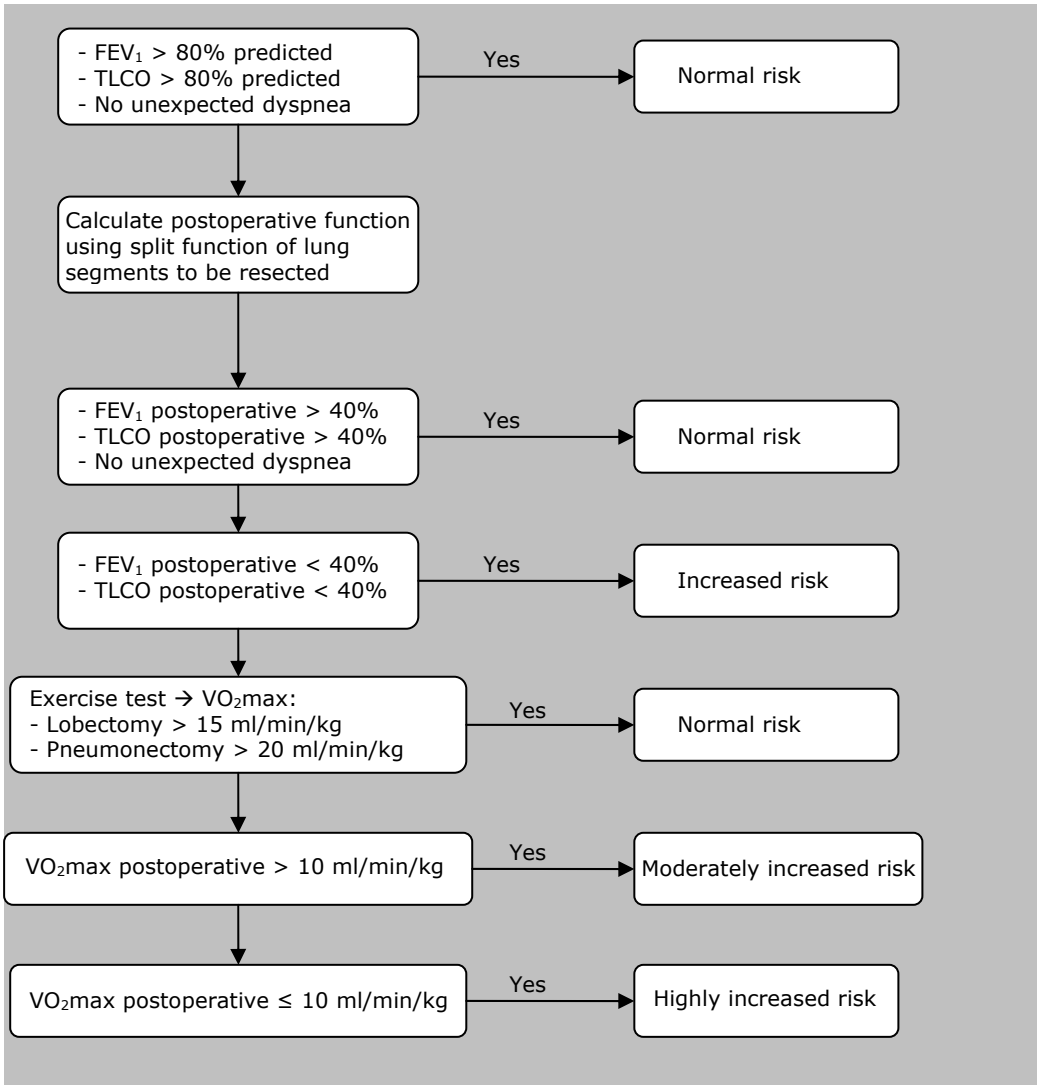
tumours because evidence indicates that the incidence of finding either unsuspected distant or mediastinal metastases on PET in this particular group of patients is quite low. In patients with evidence of mediastinal lymph node enlargement on CT, mediastinoscopy (or other invasive biopsy) is likely to be indicated regardless of the PET findings in the mediastinum[10]. Furthermore, especially in certain subgroups of patients (those with tumours adjacent to the mediastinum, adenocarcinomas, or N1 nodal involvement), physicians seem to argue whether or not mediastinoscopy is needed in case of a negative PET result, according to Detterbeck.

Obviously, the first few months (even years) after a new and promising diagnostic tool becomes available, recommendations considering its use and applicability can still change, like we have seen with PET. Therefore, when implementing such a tool, we believe we can say that physicians are almost obliged to do this according to current literature and guidelines. Because, only in that case, results of this implementation can be adequately monitored, problems will become more clear and with that, probably also the possible solutions.

In **Chapter 3**, we tried to monitor the implementation of FDG-PET in our hospital. We hypothesized that its' introduction would result in an improved staging process and better selection of patients for surgical resection. This appeared to be true, however, there was obvious room for further improvement. Certainly, PET-CT will help to improve the yield of PET and CT reading in the future. We found that the proportion of tumour positive invasive staging procedures increases with PET, which has recently been suggested in literature[11;12]. The yield of whole-body PET pertains to typing the primary pulmonary lesion (benign / malignant) and to identify and localise distant and mediastinal lymph node metastases. Since the mediastinal areas covered by mediastinoscopy, EUS-FNA, TBNA and EBUS are largely complementary, proper localisation of possible malignant nodes is important to assign patients to the appropriate procedure.

While studying accuracy in PET readings by experienced and inexperienced nuclear medicine physicians, we had anticipated differences between these two groups, however

this was not the case. While realizing that it takes practice to reach an expert level, apparently even inexperienced observers can achieve credible levels of performance. Previously, it has been questioned whether people always improve their judgements with experience[13]. Because without adequate feedback, how do you really know that what you think is true, is actually true? In **Chapter 4** we discussed the importance of education with structured databases in a skills' lab setting because the guarantee of validity might not be the experience itself! Therefore we suggested the need for higher levels of feedback from expert observers in such educational settings.




**Algorithm** *for preoperative evaluation of surgical risk, adapted from v Meerbeeck et al.*[14]

In NSCLC patients eligible for resection, postoperative pulmonary and cardiac function should preoperatively be calculated in order to predict postoperative lung function. Operating on a patient while leaving him a respiratory cripple after the resection with obviously very poor quality of life is unacceptable. In recently published Dutch guidelines, the algorithm on the previous page is recommended for evaluation of operative risk and prediction of possible outcome for patients with NSCLC, eligible for surgical resection[15]. Prediction of postoperative lung function in pneumonectomy patients is done more accurately by formulas using the split function of lung segments that are going to be resected, compared to formulas just counting the number of segments (**Chapter 5**). Trends in postoperative lung function have been extensively studied. Pneumonectomy in adults produces overdistention of the remaining lung rather than compensatory lung growth[16-18]. In the majority of studies done in children however, compensatory growth appears to be present.

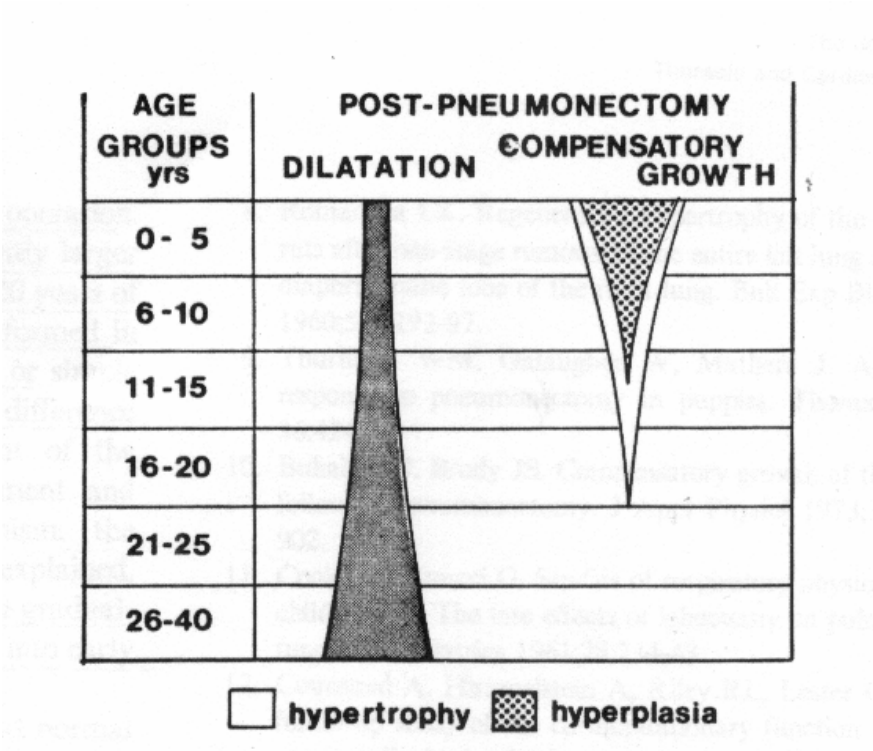



**Figure** *presenting the adaptive mechanism related to the age at operation, adapted from Laros et al.*[17]

Laros et al. showed (see figure) that the adaptive mechanism related to the age at operation[17]. Compensatory growth, hyperplasia (shaded area) with a gradual shift to simple hypertrophy (open area), occurs in the age groups 0-20 years, after which dilatation becomes the most important mechanism. As such, post-operative measured lung volumes might be somewhat better than the preoperative calculations predicted. However, one should keep in mind that the amount of functioning tissue is not increasing and the only "reserve-capacity" is therefore improvement by recruitment, enhanced by dilatation of less used areas. Despite these adaptive mechanisms, pneumonectomy has serious implications on exercise capacity in long term survivors, possibly also due to the presence of COPD preoperatively.

Cardiac MRI can be considered the gold standard for the assessment of cardiac structure and function. Pneumonectomy influences cardiac structure and function, especially of the right ventricle. The first few days after pneumonectomy, the right ventricle increases its preload (right ventricular end-diastolic volume) supposedly due to increased afterload[19;20]. In **Chapter 6** we found that 2 weeks after surgery, no signs of right ventricular enlargement were found but increased heart rate and decreased stroke volume in stead. Furthermore, left ventricular filling was impaired, and this was related to the decreased stroke volume. Since there were no signs of right ventricular dysfunction, the underfilling of the left ventricle must be interpreted as a direct consequence of a decreased compliance of the remaining pulmonary vascular bed. We hypothesize that adaptation by decreasing stroke volume is a mechanism by which the heart aims to prevent further increase in afterload and possibly right ventricular failure (like in case of massive pulmonary embolism). This might also explain why we did not find right ventricular hypertrophy in long term survivors after pneumonectomy (**Chapter 7**). However, in the long term, this chronically state of underfilling might again result in worsening of left ventricular function (ejection fraction) with dilatation and decreased wall mass, like we found in our patients 5 years after pneumonectomy.

The fact that we did not find any signs of RV hypertrophy in our studies in pneumonectomy patients could indicate that even in patients with some pulmonary hypertension a not too large reduction of the vascular bed (segmentectomy or even lobectomie) might be safe, because recently it was shown that RV hypertrophy is an early sign of adaptation of the RV to intermittent pressure overload in COPD patients[21]. Whether pneumonectomy will be possible in combination with already existing mild pulmonary hypertension is questionable.

Due to the fact that long term survivors after pneumonectomy are relatively hard to find, the number of patients in both studies was relatively small. Therefore, larger prospective studies are needed to validate our results and to determine the effects of left-sided pneumonectomy in comparison to right-sided pneumonectomy. While studying left- and right-sided pneumonectomy patients by dynamic MRI, we found remarkable differences between both groups. After left-sided pneumonectomy, in contrast to right sided-pneumonectomy, the heart not only shifts but also rotates with large individual differences. It is not inconceivable that the postoperatively impaired cardiac function is in part due to these differences. However, if this is really the case remains unclear because our patient groups were too small to draw firm conclusions. These extreme anatomical changes after pneumonectomy may result in unusual features, described in **Chapter 8**. MRI provides an excellent tool to analyse the complications caused by the repositioning of the heart and great vessels in the postpneumonectomy patient. These patients illustrate in an impressive way how important cardiac MRI is as a diagnostic tool in patients with unexplained shortness of breath after pneumonectomy. Circulatory problems are potentially a cause of this complaint and therefore cardiac evaluation needs to be incorporated into the diagnostic approach of these patients.

**Conclusions**

This thesis evaluated several aspects influencing treatment choice in NSCLC patients and studied postoperative cardiac and pulmonary function in pneumonectomy patients. Several conclusions originated from this thesis.

*Chapter 1 Effect of Comorbidity on the Treatment and Prognosis of Elderly patients with NSCLC*

* Elderly patients were treated less aggressively than younger patients.
* Age had more influence on the choice of treatment than comorbidity did.
* Age, stage of disease and treatment were independent prognostic factors for patients with localised disease, and stage of disease and treatment for those with non-localized disease. Comorbidity had no independent prognostic effect.

*Chapter 2 Surgical Mediastinal Staging in Daily Practice*

* In clinical practice, accuracy of preoperative mediastinal staging procedures and sampling of mediastinal lymph nodes is not as adequate as one should hope for.
* Mediastinoscopy was done according to gold standards in 40% of cases.
* There is probably a direct relationship between the number of mediastinoscopies performed and quality.
* Adequate mediastinal staging can result in less futile thoracotomies.

*Chapter 3 Influence of Introduction of PET on Adherence to Mediastinal Staging Protocols and Performance of Mediastinoscopy*

* After introduction of PET, adherence to mediastinal staging procedures increased significantly ($p = 0.002$).
* The combination of PET and CT can guide the surgeon to possible metastasized mediastinal lymph nodes and therefore increases the number of positive mediastinoscopies.

* Monitoring of these aspects of care, especially after the introduction of new diagnostic tools like for instance, FDG-PET scanning, is important firstly, to see whether problems regarding its' implementation are present and secondly to find out how improvement can be achieved, if necessary.

*Chapter 4 Accuracy and Interobserver Variation in Determining Presence of Mediastinal Lymph node Metastases by $^{18}$FDG-PET in patients with NSCLC*

* Clinical experience with PET increases observers' ability to read and interpret results from PET adequately compared to expert observers. However, there is obvious room for improvement because overall performance of experienced observers was only slightly better than that of inexperienced observers.
* Optimal performance is not acquired by experience alone but requires higher levels of feed-back from expert observers.

*Chapter 5 Actual and Predicted Postoperative Changes in Lung Function after Pneumonectomy*

* In patients surviving for more than 2 years after pneumonectomy, the formula that calculates the split function of lung segments that will be removed is a better predictor of postoperative lung function than the formula that only counts the number of lung segments.
* The annual decline in $FEV_1$ in long-term survivors after pneumonectomy, if quitted from smoking, is almost the same as in healthy non-COPD patients, while Wmax and $VO_2$max in these patients are both decreased by approximately 30%.

*Chapter 6 Underfilling of the Left Ventricle is the primary cause of a Low Stroke Volume after Pneumonectomy*

* Shortly after pneumonectomy the right ventricle adapts to the new situation of increased pulmonary blood flow through one lung by increasing heart rate and

decreasing its stroke volume together with, and related to, a decrease of left ventricular end-diastolic volume.

* Since no signs of right ventricular enlargement or hypertrophy at 2 weeks or 3 months after surgery were found, underfilling of the left ventricle must be due to decreased compliance of the pulmonary vascular bed.
* Three months after pneumonectomy no signs of hemodynamical impairment are found and cardiac adaptation to the new situation seems complete.

*Chapter 7 Cardiac Function and Position more than 5 years after Pneumonectomy*

* Cardiac function 5 years after pneumonectomy is impaired (increased heart rate and decreased stroke volume) which might be explained by the altered position of the heart.
* Long term effect of pneumonectomy on the position of the heart is characterised by a lateral shift after right-sided pneumonectomy and rotation of the heart to a variable degree after left-sided pneumonectomy.
* No signs of right ventricular hypertrophy were found.

*Chapter 8 Unusual Features after Pneumonectomy*

* Extreme shifting and torsion of the heart and great vessels can occur after pneumonectomy.
* Careful localisation of intrathoracic structures before invasively entering the postpneumonectomy space is extremely important in order to prevent serious complications.
* MRI provides an excellent tool to analyse the complications caused by the replacement of the heart and large vessels in the postpneumonectomy patient.

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# Dankwoord

## Dankwoord

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**Curriculum Vitae**

Sietske Anke Smulders werd op 29 mei 1975 geboren te Tilburg. Na haar eindexamen Atheneum B in 1993 aan het Titus Brandsma Lyceum te Oss ging zij geneeskunde studeren aan de Universiteit van Maastricht. Onder leiding van Dr. FWJM Smeenk en RM Schipper deed zij tijdens haar co-schappen een wetenschappelijke stage op de afdeling longziekten van het Catharina ziekenhuis te Eindhoven. In augustus 2000 haalde zij haar artsexamen en per september begon zij haar loopbaan als AGNIO longziekten in het inmiddels vertrouwde Eindhovense.

Haar promotieonderzoek begon in januari 2002 op de researchafdeling longziekten van het Catharina ziekenhuis te Eindhoven, onder leiding van Dr. FWJM Smeenk (Catharina ziekenhuis te Eindhoven), Dr. A Vonk Noordegraaf en Prof.dr. PE Postmus (Vrije Universiteit te Amsterdam). De resultaten daarvan staan beschreven in dit proefschrift.

Met 5 jaar klinische en wetenschappelijk ervaring begon zij per september 2005 haar vooropleiding interne geneeskunde in het Bosch Medisch Centrum, lokatie GZG, te ’s-Hertogenbosch (opleider Dr. P Netten). Hierna zal zij haar opleiding tot longarts afronden in het Catharina ziekenhuis te Eindhoven.

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