Assessment of Preoperative Condition and Postoperative Outcome in Nonsmall Cell Lung Cancer Surgery

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Aan mijn ouders

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CHAPTER 1

General introduction

Özcan Birim

INTRODUCTION

Active smoking is by far the most important causative agent in the development of lung cancer [1, 2], accounting for approximately 90% of lung cancer cases. Lung cancer has increased in incidence throughout the twentieth century and is now the most commonly diagnosed cancer worldwide. Whereas the incidence in men is decreasing, the incidence in women has increased progressively since 1980 and has stabilized in the last few years. In the Netherlands, lung cancer is the leading cause of cancer mortality in men and the second cause of death in women after breast cancer [3]. In 1997 in the Netherlands, approximately 8,800 people were diagnosed with lung cancer and 8,650 patients died from the disease [4]. There is a general trend worldwide of an increasing lung cancer incidence of the elderly population together with an increase in patients with serious comorbidity as a consequence of an increased life expectancy.

Based on histology, lung cancer is divided into small cell lung cancer and nonsmall cell lung cancer (NSCLC). Nonsmall cell lung cancer represents 85% of all primary lung tumors. At presentation the majority of patients will have advanced disease making a cure unlikely. However, in those diagnosed with early-stage disease, a cure (usually surgical resection) is achievable. If patients do not receive any specific treatment, median survival is 9 months and maximum survival is 3 years [5].

HISTOLOGICAL CLASSIFICATION

The WHO classification of NSCLC is based on four histological subtypes: adenocarcinoma (including bronchoalveolar cell carcinoma), adenosquamous cell carcinoma, squamous cell carcinoma, and large cell carcinoma.

Adenocarcinomas account for approximately 31% of all lung cancers [6]. Adenocarcinomas are typically peripheral tumors with a diameter of less than 4 cm, only 4% of which cavitate [7]. Fifty-one percent show hilar or mediastinal lymphadenopathy on the chest radiograph at diagnosis [8]. On CT imaging adenocarcinomas may be characterized by either a localized ground glass opacity with a slow doubling time (> 1 year) or a solid mass with a more rapid doubling time (< 1 year) [9].

Bronchoalveolar cell carcinomas, a subtype of adenocarcinoma, comprises 2% to 10% of all lung cancers [6]. In 41% of the cases it presents as a solitary pulmonary nodule, in 36% there is multicentric or diffuse disease, and in 22% it presents as an area of non-resolving consolidation [10]. Hilar and mediastinal

lymphadenopathy is uncommon [11].

Adenosquamous cell carcinoma represents 2% of all lung cancers [6]. It usually presents as a solitary peripheral nodule, approximately 1 to 3 cm in size and 13% cavitate. These tumors are intimately related to parenchymal scars or fibrosis in 50% [12].

Thirty percent of all lung cancers are in the squamous cell group [6]. Typically, these are centrally located and often larger than 4 cm in diameter. Cavitation is seen in up to 82% [7]. Due to their central location segmental lobar collapse is common.

Large cell carcinomas are poorly differentiated tumors that do not possess the typical appearance of small cell cancer. They account for 9% of all lung cancers [6]. They typically present as large peripheral masses. They often grow rapidly and metastasize early to the mediastinum and brain [13].

STAGING

The purpose of staging is to determine the extent of disease and determine prognosis in order to select patients who will benefit from surgery or other treatment modalities. Traditional staging modalities include complete medical history, physical examination, routine laboratory tests, pulmonary function tests, and non-invasive staging techniques, such as chest radiography, computed tomography (CT), bone scan, magnetic resonance imaging (MRI) and positron emission tomography (PET). If these tests do not suggest the presence of metastatic disease or unresectable local disease, then further invasive staging procedures including bronchoscopy, mediastinoscopy and video-assisted thoracoscopic surgery (VATS) may be necessary.

The most widely used scheme for the classification of the anatomical extent of NSCLC is described according to the T-primary tumor, N-regional lymph nodes, M-distant metastases (TNM) classification and stage group according to the International System for Staging Lung Cancer [14].

TNM classification

The TNM classification is an anatomical basis for unifying staging, which was initiated already in 1946. Since its original proposal it has been modified, but the principles remain the same. The American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer (UICC) approved the most recent revision of the TNM classification based on pathological findings in 1997 [14]. Properties of the current T, N, and M descriptors are shown in Table 1.

The T component of the classification describes the extent of the primary tumor

both in terms of size and local invasion.

The N component describes regional lymph node involvement. The regional lymph node classification described by Mountain and Dresler [15] is shown diagramatically in Figure 1 and anatomical definitions are given in Table 2. Nodes contained within the mediastinal pleural envelope are numbered 1 to 9. Nodes contained within the hilus or lungs are numbered 10 to 14. Mediastinal nodes may be described as ipsilateral or contralateral according to the location of the primary tumor. Midline prevascular and retrotracheal nodes are considered ipsilateral. On CT and MR imaging the nodal classification is based on the presence of mediastinal nodes greater than 1 cm in short-axis diameter.

The M component describes the presence or absence of distant metastases. In this regard, a number of specific points about the classification system are worthy of further comment. Firstly, satellite tumor nodules in the primary tumor lobe are classified as T4 while ipsilateral metastases in the non-primary lobe are considered M1 disease. A malignant pleural or pericardial effusion is also considered T4 disease.

Clinical staging (cTNM) is based on all investigations prior to the initiation of therapy. This includes invasive procedures directed at the primary tumor (bronchoscopic or needle biopsy) and investigations aimed at electing the nodal stage (mediastinoscopy or video assisted thoracoscopic surgery). The surgical-pathological staging (pTNM) is based on histological analysis of the resection specimen. It is intuitive that prognosis is more accurately predicted by the surgical-pathological stage than the clinical stage. Clinical staging turns out to be understaged in a considerable number of patients when surgical data become available for these patients [14].

The International System for Staging Lung Cancer

The International System for Staging Lung Cancer attempts to group together patients with similar prognosis and treatment options. Various combinations of T, N, and M define different clinical or surgical-pathological stages (IA-IV) (Table 3) characterized by different survival characteristics.

Nonsmall cell lung cancer staging

Combinations of TNM subtypes are grouped into different clinical or surgical-pathological stages of NSCLC according to prognosis (Table 3) [14]. Surgical-pathological staging is a more accurate predictor of prognosis than the clinical staging.

Recent modifications in 1997 resulted in the subdivision of stages I and II into A and B subgroups based on the size of the primary tumor, reclassification of T3N0M0 tumors as stage IIB, and reclassification of ipsilateral pulmonary metastases as described earlier [14].

Stage I tumors are confined to the lung, without evidence of parietal pleural invasion or invasion of the main bronchi within 2 cm of the carina, and with no evidence of lymph node metastases or extrathoracic metastases. Stage I is subdivided based on the size of the primary tumor into stage IA (size ≤ 3cm, T1N0M0), which has the best prognosis, and stage IB (size > 3cm, T2N0M0).

Stage IIA is limited to patients with T1 primary tumors who have intrapulmonary or ipsilateral hilar lymph node metastases (T1N1M0). Stage IIB includes patients with large tumors confined to the lung with localised hilar lymph node involvement (T2N1M0) as well as those with no lymph node involvement with circumscribed but potentially respectable extrapleural extension into chest wall, diaphragm or mediastinum (T3N0M0).

Stage IIIA tumors include four TNM subgroups as listed in Table 3. In essence this group comprises patients with T3 tumors and ipsilateral hilar lymph nodes or those with T1-3 tumors and N2 nodes. In contrast with stages I and II, the tumor cannot be completely resected using simple lobectomy or pneumonectomy. However patients with IIIA disease may benefit from lobectomy or pneumonectomy with mediastinal lymph node dissection often in combination with preoperative chemotherapy. Stage IIIB includes all patients with T4 tumors or those with N3 lymphadenopathy but without evidence of extrathoracic metastases. In this group conventional surgery is not considered an option.

The stage IV group of patients includes all those presenting with extrathoracic metastasic disease in whom prognosis is poor and palliative therapy is appropriate.

The important distinction with regard to staging is thus between those stages that are likely to be operable (including stage I, II, and some patients with stage IIIA disease) and those with stage IIIB and IV disease in whom palliative treatment is appropriate.

Table 1. TNM descriptors

Primary tumor (T)	
Tx	Primary tumor can not be assessed or tumor proven by the presence of malignant cells in sputum or in bronchial washing but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus[a] (i.e. not in the main bronchus)
T2	Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension Involves main bronchus, 2 cm or more distal to the carina Invades the visceral pleura Associated with atelectases or obstructive pneumonitis that extends 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 the superior sulcus tumors), diaphragm, mediastinal pleura or parietal pericardium; or tumor in the main bronchus less than 2 cm from the carina but without involvement of the carina; or associated atelectases or obstructive pneumonitis of the entire lung
T4	Tumor of any size that directly invades any of the following: mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, or carina; or tumor with a malignant pleural or pericardial effusion[b] or with satellite tumor nodules within the ipsilateral primary tumor lobe of the lung
Regional lymph nodes (N)	
Nx	Regional lymph nodes can not be assessed
N0	No regional lymph node metastases
N1	Metastases to ipsilateral peribronchial and/or ipsilateral hilar and intrapulmonary lymph nodes involved by direct extension of the primary tumor
N2	Metastases to the ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastases to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
Distant metastases (M)	
Mx	Presence of distant metastases can not be assessed
M0	No distant metastases
M1	Distant metastases present[c]. Specify sites

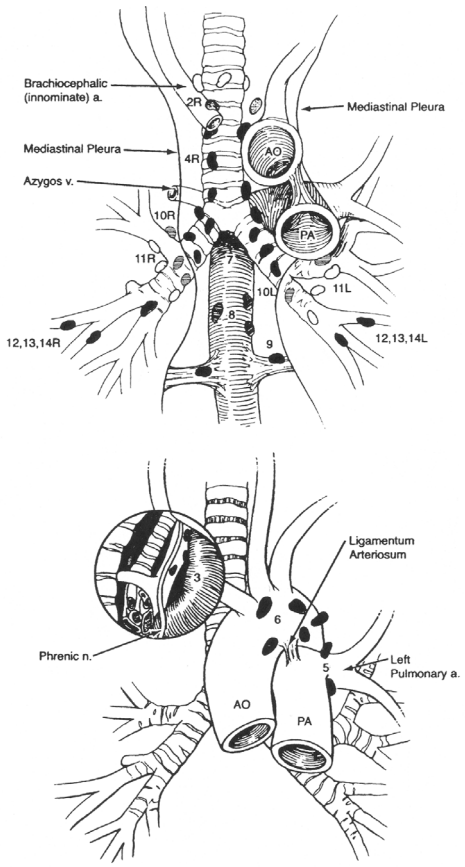
[a] T1: The uncommon superficial tumor of any size with its invasive component limited to the main bronchus is classified as T1

[b] T4: Most pleural effusions associated with lung cancer are caused by tumor. There are however, a few patients in whom cytopathologic examination of pleural fluid (on more than one specimen) is negative for tumor, the fluid is non-bloody, and is not an exudate. In such cases in which these elements and clinical judgement dictate that the effusion is not related to the tumor, the patients should be staged T1, T2 or T3, excluding effusion as a staging element

[c] M1: Seperate metastatic tumor nodule(s) in the ipsilateral nonprimary tumor lobe(s) of the lung also are classified M1

From Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111(6): 1710-1717

Figure 1. Regional lymph node stations for nonsmall cell lung cancer



Superior mediastinal nodes

1	Highest mediastinal
2	Upper paratracheal
3	Pre-vascular and retrotracheal
4	Lower paratracheal (including azygos nodes)

N_2 = single digit, ipsilateral
N_3 = single digit, contralateral or supraclavicular

Aortic nodes

5	Subaortic (A-P window)
6	Para-aortic (ascending aorta or phrenic)

Inferior mediastinal nodes

7	Subcarinal
8	Paraesophageal (below carina)
9	Pulmonary ligament

N_1 nodes

10	Hilar
11	Interlobar
12	Lobar
13	Segmental
14	Subsegmental

From Mountain CF. Staging classification of lung cancer. A critical evaluation. Clinics in chest medicine 2002; 23: 103-121

Table 2. Lymph node map definitions

N2 nodes - All N2 nodes lie within the mediastinal pleural envelope

1 Highest mediastinal nodes: Nodes lying above a horizontal line at the upper rim of the brachiocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline

2 Upper paratracheal nodes: Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes

3 Prevascular and retrotracheal nodes: Prevascular and retrotracheal nodes may be designated 3A and 3P; midline nodes may be considered to be ipsilateral

4 Lower paratracheal nodes: The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope; the lower paratracheal nodes on the left lie to the left of midline of the trachea between a horizontal line drawn tangential to the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope

5 Subaortic (aorto-pulmonary window) nodes: Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope

6 Para-aortic nodes: Nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate artery, beneath a line tangential to the upper margin of the aortic arch

7 Subcarinal nodes: Nodes lying caudal to the carina of the trachea, but not associated with the lower lobe bronchi or arteries within the lung

8 Paraesophageal nodes: Nodes lying adjacent to the wall of the oesophagus and to the left or right of the midline excluding subcarinal nodes

9 Pulmonary ligament nodes: Nodes lying within the pulmonary ligament, including those in the posterior wall and lower part of the pulmonary vein

N1 nodes - All N1 nodes lie distal to the mediastinal pleural reflection and within the visceral pleura

10 Hilar nodes: The proximal lobar nodes, distal to the mediastinal pleural reflection and the nodes adjacent to the bronchus intermedius on the right; radiographically the hilar shadow may be created by enlargement of both hilar and interlobar nodes

11 Interlobar nodes: Nodes between the lobar bronchi

12 Lobar nodes: Nodes adjacent to the distal lobar bronchi

13 Segmental nodes: Nodes adjacent to the segmental bronchi

14 Subsegmental nodes: Nodes around the subsegmental bronchi

From Mountain CF and Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997; 111: 1718-1723

Table 3. TNM subsets according to stage

Stage	TNM subset
0	Carcinoma in situ
IA	T1 N0 M0
IB	T2 N0 M0
IIA	T1 N1 M0
IIB	T2 N1 M0
	T3 N0 M0
IIIA	T3 N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
IIIB	T4 N0 M0
	T4 N1 M0
	T4 N2 M0
	T1 N3 M0
	T2 N3 M0
	T3 N3 M0
	T4 N3 M0
IV	Any T Any N M1

From Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111: 1710-1717

NON-INVASIVE IMAGING IN NONSMALL CELL LUNG CANCER STAGING

The major issue in the staging of NSCLC is the question of operability as surgical resection offers the best chance of cure and long-term survival. Chest radiography and spiral CT of the chest and upper abdomen are nowadays the most commonly used modalities in the initial evaluation of patients with suspected or documented NSCLC. The upper abdomen is routinely included in CT imaging, as the adrenal glands and liver are one of the most common sites of extrathoracic metastases, occurring in 3% to 6% of NSCLC patients [16]. Refinements in staging based on imaging findings have enabled clinical staging to more accurately reflect the surgical-pathological stage and therefore more accurately predict prognosis. Newer generations multislice CT and particularly PET promise to further increase the accuracy of staging and therefore to reduce the number of invasive staging

procedures and inappropriate thoracotomies. Some of the limitations of conventional CT and MRI and potential benefits of PET are outlined below.

Computed tomography

Computed tomography is currently the standard radiologic imaging study for patients with suspected or diagnosed NSCLC. Computed tomography provides information about tumor size and invasion but difficulties commonly arise in the evaluation of mediastinal and chest wall invasion of the primary tumor. Although fulfillment of CT criteria relating to the mediastinum (contact with the mediastinum of less than 3 cm, contact with the aorta of less than 90 degrees and the presence of a fat stripe between the mass and the mediastinum) are predictive of resectability in 97% of cases [17], inoperability can not be inferred by their absence, 50% still being operable. Similarly the sensitivity and specificity of CT for chest wall invasion is reported to range from 38% to 87% and 40% to 90%, respectively [18].

Of greatest value in evaluating NSCLC, CT assesses the mediastinal lymph nodes for the possible presence of metastatic disease. The most widely accepted criterion for malignant involvement of lymph nodes is a short-axis diameter of more than 1cm. However, the reliability of CT on the use of size criteria to discriminate normal from metastatic lymph nodes is an important limitation leading to a low sensitivity (range, 41% to 67%) and specificity (range, 79% to 86%) [19-21]. Clearly, in patients with NSCLC, large nodes may be reactive, particularly in patients with pneumonia, and small nodes may contain micrometastatic disease. Even when CT is combined with invasive techniques, such as mediastinoscopy and anterior mediastinotomy, up to 14% of patients undergoing thoracotomy may have unsuspected N2 disease [22].

Computed tomography of the upper abdomen detects approximately 75% of abdominal metastases but its specificity in the adrenal glands is limited by the high prevalence of benign adrenal lesions.

Magnetic resonance imaging

Like CT, MRI is an anatomic imaging modality. Magnetic resonance imaging of pulmonary lesions and mediastinal lymph nodes has been disappointing and has a very limited role in the evaluation of NSCLC. It may allow better anatomic evaluation of the lung apices, thoracic inlet, chest wall, or diaphragm due to its ability to provide saggital, coronal, and oblique images. Experience evaluating MRI in the detection of mediastinal lymph nodes in patients with NSCLC is minimal. Two reports [23, 24] suggest that the use of contrast enhancement may improve the accuracy of MRI in the evaluation of mediastinal lymph nodes. However, most

centers continue to rely on CT scanning as the non-invasive anatomic study of choice for the potential mediastinal spread of lung cancer, mostly due to the high costs of MRI. With the exception of special instances, such as determining the presence of vertebral or vascular invasion, MRI is not indicated for the routine workup of NSCLC patients.

Positron emission tomography

Positron emission tomography is a physiologic imaging technique that exploits the differences in glucose metabolism between normal and neoplastic cells [25]. Following intravenous administration of the radiopharmaceutical 2-[18F]-fluoro-2-deoxy-D-glucose (FDG), a D-glucose analogue labelled with fluorine-18, neoplastic cells absorb and retain FDG, with the relative uptake correlating with tumor aggressiveness and growth rates [26]. Positron emission tomography is thus a metabolic imaging technique based on the function of a tissue rather than on its anatomy. False-negative results can occur in hyperglycemia, which interferes with tissue uptake (and is therefore a contraindication for the use of FDG), microscopic tumor deposits [27], and biologically indolent neoplasms such as bronchoalveolar cell carcinoma. False positive scans may occur in the context of inflammation, infection, hyperplasia, sarcoid and antracotic nodes [28, 29]. Positron emission tomography scans may be limited to the chest or extended to include the whole body to assess for distant metastases.

Positron emission tomography promises to be a useful adjunct to CT, being superior to CT in the evaluation of nodal metastases with a sensitivity ranging from 67% to 100% and specificity ranging from 81% to 100% [29-32]. The incorporation of PET into imaging algorithms alters the CT nodal staging in 21% of presurgical patients [33]. The high negative predictive value of FDG PET (range, 93% to 95%) may enable a reduction in the frequency of invasive mediastinoscopy. However, with a positive predictive value of only 74% [27] due to positive results in inflammatory disease, many authors recommend biopsy confirmation by mediastinoscopy of positive PET results. Positron emission tomography is an accurate imaging technique to detect metastatic disease unrecognized by conventional imaging or to downstage patients disease by interpreting false-positive findings on conventional imaging correctly negative [34-36]. However, PET has limitations in detecting brain metastases because of high glucose uptake of the surrounding normal brain tissue [36, 37]. The main limitation of PET is its poor spatial resolution making primary tumour (T) staging impossible and difficulties are reported on differentiating hilar from mediastinal lymph nodes.

TREATMENT

The choice of treatment for NSCLC depends on extent of disease as reflected by tumor stage, comorbidity, and performance status. Complete resection of the primary tumor and involved lymph nodes remains the most effective mode of treatment. Patients with stage I and II disease are generally eligible for surgery. Survival after limited resection (e.g. wedge resection and segmentectomy) versus lobectomy and pneumonectomy has been analyzed in several studies. The recurrence rate is higher for limited resections [38, 39], and survival decreases [38]. In general, lobectomy must be considered the surgical procedure of choice for stage I disease, but limited resection may be considered in patients with a decreased pulmonary reserve.

The best treatment for patients with more advanced disease (stage IIIA and IIIB) is still being evaluated and is a matter for debate because surgery alone results in only moderate survival rates [40, 41]. Controversy exists whether neoadjuvant chemotherapy followed by surgery or non-surgical treatment in these patients can substantially alter the course of the disease. Locoregional radiotherapy has been the traditional approach in patients with advanced disease, as it represents a useful palliative tool and has resulted occasionally in long-term survival [42]. However, The American Society of Clinical Oncology recommends chemotherapy combined with radiotherapy in patients with a good performance status [43-45]. Patients with stage IV disease show a significant improvement of quality of life when treated with chemotherapy, but until now only with minimal survival benefit [43, 46].

SURVIVAL

Lung cancer has a poor prognosis, only 10-15% of patients with diagnosed NSCLC survive 5 years or longer. Sadly in a recent survey of improvements in cancer survival [47] lung cancer showed only a 0.2% reduction in the number of deaths avoided between 1981 and 1990. This compares poorly with other cancers such as breast (11% reduction) and melanoma (32% reduction).

Prognosis is dependent on the anatomical staging and histological classification of the tumor as well as clinical factors. Patients with surgical-pathological stage IA have the best prognosis with a 5-year survival of 67% [14] (Table 4; Fig. 2). Stage IB patients have a 5-year survival of 57%. Stage IIA patients have a 55% 5-year survival, similar to those with stage IB tumors. Stage IIB NSCLC patients have a 5-year survival of approximately 38%. Patients with advanced stage NSCLC are generally not considered operable, and prognosis is poor. Patients with surgical-pathological

stage IIIA disease have a 5-year survival rate ranging from 23% to 25%, whereas patients with clinical stage IIIA disease have a 5-year survival rate ranging from 9% to 13%. Survival in patients with clinical stage IIIB ranges from 3% to 7%. Stage IV patients do have the worst prognosis, only 1% being alive after 5 years.

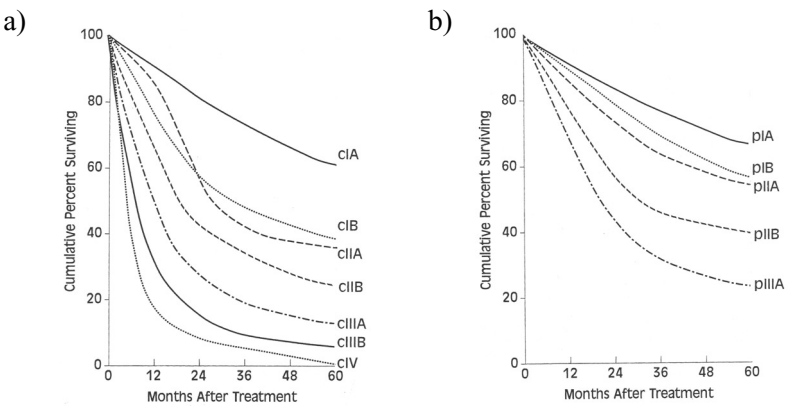
Table 4. Stage grouping and 5-year survival

Stage	TNM subset	5-year survival (%)	
		cTNM	pTNM
0	Carcinoma in situ		
IA	T1 N0 M0	61	67
IB	T2 N0 M0	38	57
IIA	T1 N1 M0	34	55
IIB	T2 N1 M0	24	39
	T3 N0 M0	22	38
IIIA	T1-3 N2 M0	13	23
	T3 N1 M0	9	25
IIIB	T4 N0-3 M0	7	
	T1-4 N3 M0	3	
IV	Any T Any N M1	1	

cTNM = clinical TNM stage pTNM = pathological TNM stage

From Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997; 111: 1710-1717

Figure 2. Survival curves for patients with nonsmall cell lung cancer according to a) clinical stage and b) pathological stage



From Mountain CF. Staging classification of lung cancer. A critical evaluation. Clinics in chest medicine 2002; 23: 103-121

AIMS OF THE THESIS

Nonsmall cell lung cancer (NSCLC) has increased in incidence in the Western world in the twentieth century, and its incidence in elderly patients is increasing together with an increase in patients with serious comorbidity. It is important to know what the prognostic factors for poor outcome are to select patients for the best treatment, give patients the most accurate information necessary to make the best decision, and inform patients about estimated survival after surgery. Although a lot of research is performed to identify risk factors for poor outcome, the prognostic effect of several factors is still unclear. Clinical staging of patients is important to decide whether patients can undergo curative surgery or should be offered radiotherapy or chemotherapy, or both. Therefore, new non-invasive diagnostic tools are of interest for the clinical staging of NSCLC.

To gain insight in the currently reported possible risk factors for poor outcome in NSCLC surgery, clinical factors, tumor-related factors, and treatment-related factors are reviewed in **Chapter 2.**

The pathological TNM stage is the most important prognostic factor for survival following pulmonary resection. Therefore, it is of utmost importance to know whether patients have positive mediastinal lymph nodes, indicating non-resectability. The sensitivity and specificity of CT scan in detecting mediastinal lymph nodes are not outstanding. To evaluate the accuracy of both CT imaging as well as FDG PET imaging in detecting mediastinal lymph node metastases in NSCLC, a meta-analysis comparing these two non-invasive imaging modalities is described in **Chapter 3** and the contributions of FDG PET to improvement of clinical staging of NSCLC patients is discussed in **Chapter 4.**

Currently, there is no accepted scoring system that can be used in order to stratify patients according to risk of complications and survival following NSCLC surgery. The Charlson comorbidity index is a weighted index of nineteen conditions found to significantly influence survival in cancer patients and given a score based on the relative mortality risk. This index has been validated in patients with head and neck cancer and dialysis patients. The validation of this comorbidity index in NSCLC surgery is described in **Chapter 5 and Chapter 6.**

Due to the increase of NSCLC incidence in the elderly as a consequence of increased life expectancy, and the relatively higher incidence of comorbidity in this patient population, the incidence of high-risk patients also increases. **Chapter 7** describes the mortality and morbidity of patients older than 70 years undergoing pulmonary resection for primary NSCLC, and compares the long-term survival of this patient population with the survival of the general population older than 70 years.

Tumor size is highly prognostic for survival. As a result stage I was subdivided into IA (tumor size ≤ 3 cm, T1N0M0), and IB (tumor size > 3 cm, T2N0M0) in the current staging system in 1997. However, controversy concerning the relation between tumor size and patient prognosis persists, and the appropriate cut-off value for tumor size to classify T1 and T2 disease continues to be debated. Recurrence rate is thought to be the lowest in stage IA NSCLC patients. Patients within this stage do not always die as a result of their tumor. **Chapter 8** evaluates prognostic factors for survival in pathological stage IA NSCLC with special emphasis on tumor size, and assesses tumor recurrence rate by actual and actuarial analysis.

Surgical resection is usually regarded as the treatment of choice in patients with stage I and II NSCLC. However, some patients with early-stage NSCLC do not receive surgical treatment because they either refuse surgery or have severe associated comorbidity. Careful selection of candidates suitable for surgical resection is the key issue for optimal treatment, and due to improvement in surgical techniques and postoperative care, patients with severe comorbid disease might nowadays do better after surgery than after other treatments. In order to compare the survival of those patients who received surgical resection and those who did not, and identify those patients who will benefit from surgery, in **Chapter 9** the incidence of comorbidity and long-term survival of patients receiving surgical treatment and non-surgical treatment is evaluated.

Survival is not only dependent on tumor stage but also on many other factors, such as comorbidity and type of resection. Several scoring systems have previously been used in order to stratify patients according to risk of survival following NSCLC surgery. However, these models are developed in other patient populations and thus are not specific for NSCLC surgery patients and do not include tumor-related and treatment-related risk factors. In addition, these models do not estimate the long-term survival of individual patients after surgical resection. In order to provide surgeons and patients with better quality information on risk assessment and postoperative survival, we developed a prognostic model with a preoperative and postoperative mode that can be used in daily practice to estimate long-term survival of individual patients, which is presented in **Chapter 10.**

In **Chapter 11,** the general discussion, the results of this thesis are briefly discussed and future perspectives are outlined. Finally, in **Chapter 12,** a summary is given of the results and conclusions of the previous chapters followed by a Dutch version of the summary.

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CHAPTER 2

Prognostic factors in nonsmall cell lung cancer surgery

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ABSTRACT

Background: Complete surgical resection of primary tumors remains the treatment with the greatest likelihood for survival in early-stage nonsmall cell lung cancer (NSCLC). Although TNM stage is the most important prognostic parameter in NSCLC, additional parameters are required to explain the large variability in postoperative outcome. The present review aims at providing an overview of the currently known prognostic markers for postoperative outcome.

Methods: We performed an electronic literature search on the MEDLINE database to identify relevant studies describing the risk factors in NSCLC surgery. The references reported in all the identified studies were used for completion of the literature search.

Results: Poor pulmonary function, cardiovascular disease, male gender, advanced age, TNM stage, non-squamous cell histology, pneumonectomy, low hospital volume and little experience of the surgeon were identified as risk factors for postoperative outcome. However, with the exception of TNM stage and extent of resection, the literature demonstrates conflicting results on the prognostic power of most factors. The role of molecular biological factors, neoadjuvant treatment and adjuvant treatment is not well investigated yet.

Conclusions: The advantage of knowing about the existence of comorbidity and prognostic risk factors may provide the clinician with the ability to identify poor prognostic patients and establish the most appropriate treatment strategy. The assessment of prognostic factors remains an area of active investigation and a promising field of research in optimising therapy of NSCLC patients.

INTRODUCTION

Because of the relatively high incidence of postoperative complications, the hospital mortality, as well as disappointing long-term survival after surgical resection of nonsmall cell lung cancer (NSCLC), the appropriate selection of patients with NSCLC for pulmonary resection is a continuing challenge. It has been demonstrated that postoperative complications are associated with the extent of resection and the pre-existing comorbidity [1, 2]. The occurrence of severe comorbidity is increasing owing to the rise of lung cancer incidence among the elderly as a consequence of improved life expectancy. Therefore, the decision on how to treat patients should not be based on tumor stage only, but also on comorbidity and performance status. As a result, it is important to be informed about the risk factors and how they affect postoperative morbidity, mortality, and long-term survival. Over the last decades, several studies have studied the impact of various factors on the early and late outcome. The prognostic factors can be categorized into clinical factors, tumor-related factors, and treatment-related factors [3]. The purpose of this review is to provide an overview of the currently known prognostic markers for hospital mortality, morbidity, and long-term survival.

CLINICAL FACTORS

Pulmonary function

As tobacco use is associated with both chronic obstructive pulmonary disease (COPD) and NSCLC, the prevalence of COPD in patients with NSCLC is high [4]. Underlying pulmonary disease consistently has been shown to be an important predictor of postoperative morbidity and hospital mortality. However, pulmonary function tests are not uniformly assessed, and as a consequence, not uniformly reported. The most valuable parameters reported for evaluation of pulmonary function are the absolute spirometric parameters such as forced expiratory volume in 1 second (FEV_1), pulmonary diffusion capacity for carbon monoxide (DLco), and maximum oxygen consumption during exercise testing (VO_2max). Adjustments for age, sex, and height can be made with the percentage of the predicted values.

The prognostic value of a reduced preoperative FEV_1 is controversial. Some reports showed FEV_1 to have impact on postoperative morbidity and survival [5-9], whereas others found no correlation [1-3, 10, 11]. This difference could be attributed to the retrospective nature of most of the latter studies in which patients were largely selected for operation on the basis of a sufficient FEV_1. In such a highly selected group, the predictive value of FEV_1 is substantially reduced.

The DLco reflects the adequacy of gas change affected by both ventilation and perfusion and is a predictor of both morbidity and hospital mortality. Ferguson and associates [12, 13] and others [14, 15] identified DLco as an important factor associated with operative mortality not only from pulmonary complications but also from all other causes. A comparison between the use of percentage of the DLco, FEV_1, and VO_2max predicted revealed that the percentage of DLco predicted was the best predictor of pulmonary complications after pulmonary resection [12].

Preoperative exercise testing with measurement of the VO_2max has been advocated to assess cardiopulmonary reserve and demand postoperatively, and has also been found to predict outcome [7, 16]. Bolliger and colleagues [17] reported that VO_2max expressed in absolute values was highly predictive, but the VO_2max expressed as a percentage of predicted ($VO_2max\%$) was even more sensitive.

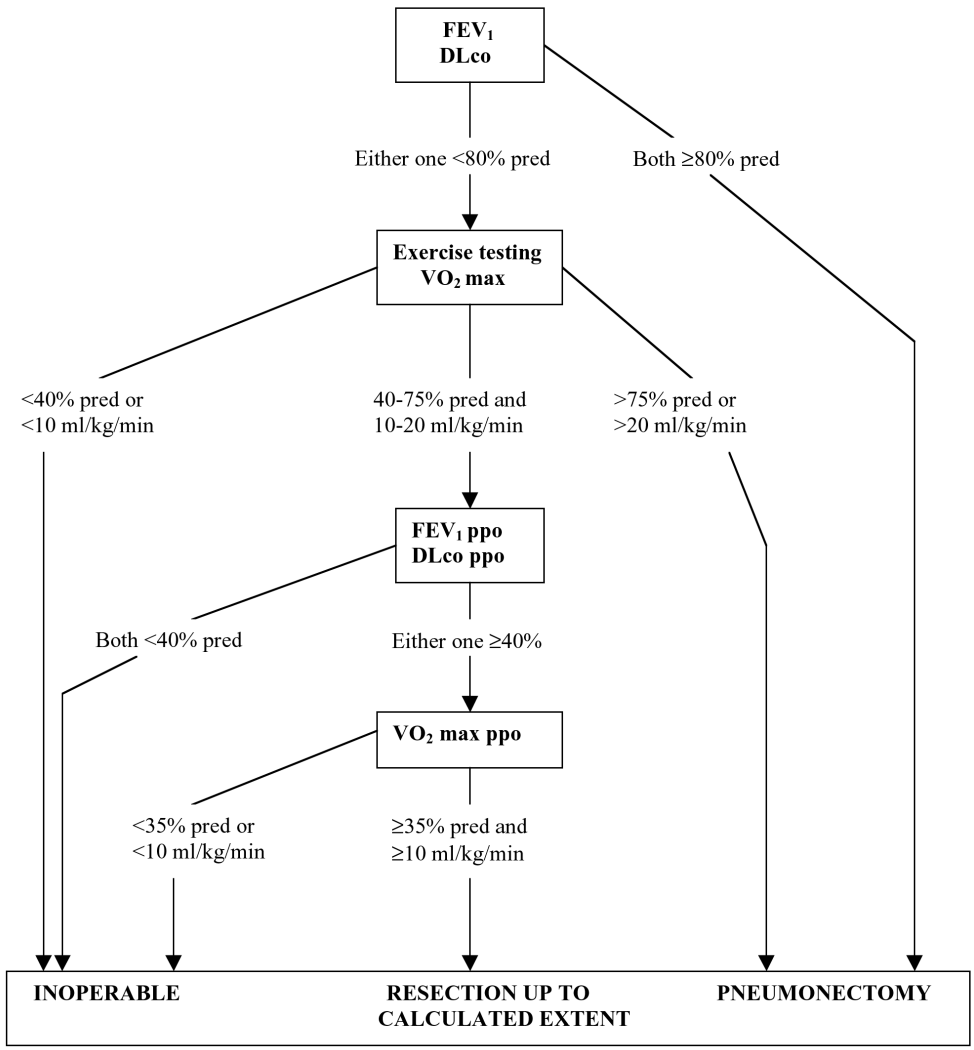
Recent descriptions of simpler, older tests of gas exchange and oxygen consumption such as the 6-minute walk test or stair-climbing test of three flights of stairs without rest warrant renewed consideration [7, 18]. During exercise, oxygen consumption, carbon dioxide production, and cardiac output increase, and the level of augmentation reflect how well the cardiopulmonary system interacts to deliver oxygen to the tissue. Several investigators reported a high predictive value of stair-climbing in assessing cardiopulmonary morbidity after pulmonary resection

[7, 18, 19]. These tests can be easily repeated during the preoperative period to evaluate the improvement of pulmonary function after rehabilitation or physiotherapy and are highly cost-effective, familiar to patients, and widely applicable. Moreover, it has been reported that during stair-climbing higher VO_2max values are yielded than during cycle ergometry [20].

The most predictive pulmonary function test is currently the estimation of the absolute postoperative spirometry value and percentage of predicted postoperative spirometry value [12, 21]. The calculation is usually performed by multiplying the raw observed preoperative spirometry value with the percentage of lung parenchyma remaining after resection, or by performing a lung perfusion scan, by which the relative contribution of the left and right lung to the total ventilation can be estimated.

Appropriate preoperative evaluation of pulmonary function may prevent postoperative complications. Therefore, it is recommended to perform at least an FEV_1 and DLco test in the preoperative evaluation of patients with NSCLC. Patients with an FEV_1 and DLco of 80% of predicted or more can safely undergo pneumonectomy. If one of them is less than 80%, other tests such as exercise tolerance tests (stair-climbing test or 6-minute walk test) or split function tests (predicted postoperative FEV_1 and DLco) are necessary. A pulmonary function approach to the selection of patients for pulmonary resection adapted from Bolliger and Perruchoud [17] is summarized in the algorithm in Figure 1.

Figure 1. Preoperative assessment of pulmonary function



FEV_1 = forced expiratory volume in 1 second
DLco = diffusion capacity of the lung for carbon monoxide
VO_2max = maximum oxygen consumption during exercise
ppo = predicted postoperative
From Bolliger CT and Perruchoud AP. Functional evaluation of the lung resection candidate. Eur Resp J 1998; 11: 198-212

Cardiovascular disease

In patients with NSCLC the likelihood of having cardiovascular disease is significant, given the association of both disorders with tobacco use. Cardiovascular disease repeatedly has been found to be a prognostic risk factor for postoperative morbidity and survival [11, 22-24]. In one study, a decrease in 5-year survival from 56% to 36% is reported among patients with cardiovascular comorbidity [22].

Patients with an increased cardiovascular risk should be referred for cardiovascular evaluation prior to pulmonary resection [25]. Those with a history of coronary artery disease or coronary artery bypass graft surgery should undergo an exercise stress test to evaluate cardiac function. In patients whose coronary disease warrants revascularization therapy, coronary revascularization should precede pulmonary resection [25-27]. It is still a matter of debate whether coronary artery bypass graft surgery and pulmonary resection should take place in a one-stage combined procedure or a two-stage procedure [26, 27]. If cardiac surgery is performed first followed by pulmonary resection at a later date, the tumor resection is delayed, there is a longer overall stay in the hospital, there is double the preoperative stress and postoperative pain, and there is the morbidity and additional cost of two operations [28, 29]. Furthermore, exposure to the immunosuppressive effects of cardiopulmonary bypass may have a deleterious effect on tumor growth and dissemination. When both operations are performed simultaneously, thus avoiding a second procedure, concern exists regarding the adverse effects of systematic heparinization and cardiopulmonary bypass [30, 31]. Another concern is related to the limited exposure that median sternotomy offers for left lower lobectomy and for lymphadenectomy in the posterior mediastinum. A solution to the adverse effects of heparinization and dissemination of neoplasmatic cells by extracorporeal circulation is to perform off-pump coronary artery bypass graft surgery in patients with suitable coronary anatomy [26].

Age

Advanced age has been identified as a negative prognostic factor for hospital mortality as well as long-term survival [3, 10, 32-35]. However, elderly patients generally have a shorter life expectancy than younger patients, regardless of the presence of NSCLC. The relationship between operative mortality and age, however, was addressed in several series and it was shown that acceptable operative mortality rates can be achieved in elderly patients ranging from 3% to 7% compared with 4% to 5% in younger patients [1, 2, 8, 36, 37]. The most likely reason for this is the substantial improvement in perioperative and postoperative medical care during the last decades.

Age is an issue of utmost importance, because 50% of all lung cancer cases occur in patients over 65 years of age. In Western Europe, even a quarter of the population is aged over 70 years. One of the striking features of the elderly population is its heterogeneity. While many individuals remain quite healthy with advancing age, others develop worsening and functional impairments. Janssen-Heijnen and coworkers [38] investigated the influence of age on treatment choice in 3,864 lung cancer patients and concluded that age alone appeared to be a more important factor in treatment choice than comorbidity. This may be explained by the fact that many physicians are reluctant to operate on elderly patients, and in their decision comorbidity appears to play a minor role.

As with increasing age comorbidity increases, age is confounded by other factors such as cardiovascular function and pulmonary function [38]. Therefore, presently advanced age should not be the only reason to withhold surgical therapy.

Gender

Different studies have yielded conflicting outcomes regarding the influence of gender on survival. Jazieh and associates [3] did not find a different outcome in their series in contrast to other studies of comparable design that found an impaired survival for men in comparison with women (5-year survival, 32% versus 65%) [39-42].

Differences exist among men and women with NSCLC. Women have a higher expected life time than males regardless of the presence of NSCLC, a relatively lower incidence of cardiovascular disease, a superior pulmonary function, less aggressive smoking habits, tend to be diagnosed at an earlier stage, have a higher incidence of adenocarcinoma, and need less extensive surgical procedures (fewer pneumonectomies), which all might contribute to a superior survival [41, 43, 44]. Once women have developed NSCLC, they experience a survival benefit that is not accounted solely by a longer life expectancy or imbalance of other prognostic factors. Genetic, metabolic, and hormonal factors (oestrogen signalling) might all be important to the way women react to carcinogens and develop NSCLC [45-47]. The oestrogen metabolite 2-methoxy-oestradiol was shown to inhibit angiogenesis to suppress tumor growth [48] and induce apoptosis in human lung cancer cells in vitro [49], which could favour the long-term outcome in women.

The impact of gender on survival needs to be clarified in light of the increase of NSCLC incidence in women and decrease in incidence in men in the last decades [50].

Comorbidity scoring scales

Currently, no widespread and well-proven or accepted scoring system for risk assessment in NSCLC surgery exists. Comorbidity scoring scales that attempt to quantify comorbidity and thereby allow objective evaluation of the impact of selected factors on outcome are the Charlson comorbidity index (CCI) [51] and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [52]. Both scales are well defined and validated and have been used in clinical studies with reliable results [1, 2, 53, 54].

The CCI, developed in 1987 by Charlson and colleagues [51], is an index of 19 conditions found to significantly influence outcome in breast cancer patients and given a weighted score based on the relative mortality risk (Table 1). In two recently published studies we found a CCI score of 3 or more to be a predictive value for major postoperative complications [1, 2]. This index is easy to use and could have widespread applicability.

The CIRS, developed in 1968 by Linn and colleagues [55], grades the severity of 13 organ systems from 0 (no problem) through 4 (extremely severe impairment). This scale has been revised to reflect the common problems of the elderly and was rearranged as CIRS-G (Table 2) [52]. Firat and colleagues [56] reported CIRS-G as prognosticator for impaired survival. Using the comorbidity scoring scale in stage I surgically treated patients, the presence of a CIRS-G score of 4 in at least 1 of 14 categories resulted in a 5-year overall survival of 15% versus 65% when it was not present.

Although these two scoring systems for risk assessment are validated in NSCLC surgery, they are not specific for NSCLC patients. Therefore, a specific scoring system for NSCLC surgery patients, including type of resection and TNM tumor stage, might further improve specific risk assessment.

Table 1. Charlson comorbidity index

Comorbidity	Weighted score
Myocardial infarction	1
Congestive heart failure	1
Chronic pulmonary disease	1
Peptic ulcer disease	1
Peripheral vascular disease	1
Mild liver disease	1
Cerebrovascular disease	1
Connective tissue disease	1
Diabetes	1
Dementia	1
Hemiplegia	2
Moderate to severe renal disease	2
Diabetes with end organ damage	2
Any prior tumor (within 5 years of diagnosis)[a]	2
Leukemia	2
Lymphoma	2
Moderate to severe liver disease	3
Metastatic solid tumor	6
AIDS (not only HIV positive)	6

[a] Except basal cell skin carcinoma AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

Table 2. Cumulative illness rating scale for geriatrics

Scored organ system	
Heart	
Vascular	
Haematopoietic	
Respiratory	
Eyes, ears, nose, throat	
Upper gastrointestinal	
Lower gastrointestinal	
Liver	
Renal	
Genitourinary	
Musculoskeletal/integument	
Neurologic	
Endocrine/metabolic and breast	
Psychiatric	
Rating strategy	
No problem	0
Mild: does not interfere with normal activity; prognosis excellent	1
Moderate: interferes with normal activity; treatment necessary	2
Severe: disabling impairment; urgent treatment necessary; prognosis poor	3
Extremely severe: life-threatening; prognosis grave	4

TUMOR-RELATED FACTORS

TNM stage

For NSCLC, the concept of curability has been linked to resectability. The tumor-node-metastasis (TNM) staging system seeks to group patients with similar expected outcome based on potential for surgical treatment. The surgical-pathological TNM stage has been consistently found to be the most powerful predictive tool in prognostic assessment of survival in patients with NSCLC [3, 57-60].

Tumor (T) stage has been described as a prognostic factor in many series [37, 40, 61-63]. Several investigators have demonstrated that tumor size (greater versus smaller than 3 cm) is highly prognostic for survival [64]. Consequently, stage I was subdivided into IA (3 cm or less, T1N0M0) and IB (more than 3 cm, T2N0M0) in the current staging system in 1997 [57]. In a recently published study on pathological stage IA NSCLC patients, we even showed an inferior survival for tumors 21 to 30 mm in diameter compared with tumors 0 to 20 mm in diameter (5-year survival, 51% versus 69%, $p = 0.038$) [65], which was also reported by others [66]. Therefore, controversy regarding the relation between tumor size and patient prognosis persists and the appropriate cut-off point for tumor size to classify T1 and T2 disease continues to be debated.

The TNM revision of 1997 [57] defines the nodal tumor involvement as an important prognostic factor for long-term survival in surgically treated patients. Martini and associates [67] proposed the number of involved lymph nodes in the hilar region (N1) to be a significant prognostic factor. This was supported by others who also reported a superior survival in favour of patients with single-station N1 disease compared with patients with multiple-station N1 disease [61]. Five-year survival in patients with multiple-station N1 disease is even reported to be not different from that of patients with single-station mediastinal lymph node (N2) involvement [61]. In addition, another study has described a prognostic significance of involvement of main bronchial nodes (location 10, N1 disease) similar to that of single-station N2 disease [68].

Mediastinal lymph node disease (N2 disease), as in the cases of incomplete resection, is a powerful negative prognostic factor. Patients with N2 metastases without metastases in N1 nodes are described as having “skip metastases” [69]. Skip metastases to mediastinal lymph nodes account for 25% to 40% of resected N2 disease [70]. Several authors found an improved survival in patients with isolated N2 disease relative to those with both positive N1 and N2 disease [69, 70]. Despite the fact that lymph node metastases has been described as important predictor of poor prognosis, debate persists regarding the exact boundary between N1 and N2 disease.

Not unexpectedly, distant metastases or separate metastatic tumor nodules in an ipsilateral nonprimary tumor lobe of the lung (M1-disease), is the most prognostic factor for long-term survival [57]. After clinical assessment, surgically treated patients do not have M1-disease. However, some patients do have unforeseen M1-disease and consequently a poor prognosis.

As a result, accurate preoperative clinical assessment of the TNM stage is of utmost importance to determine the extent of disease in order to select patients who will benefit from surgery or other treatment modalities.

Histology

Histopathological cell type of NSCLC correlates with tumor behaviour and prognosis. With regard to the histological parameters, some authors did not find prognostic implications of a histological subtype [3, 61]. However, several studies have shown an improved survival for squamous cell histology over non-squamous cell histology [37, 56, 71]. Lung Cancer Study Group trials in 1,121 surgically treated patients showed superior postoperative outcome for patients with squamous cell carcinoma over non-squamous histology in all TN categories and for survival in all but stage III disease [71]. The 5-year survival data comparing adenocarcinoma versus squamous cell histology were 55% versus 65%. Komaki and associates [72] also found squamous cell histology prognostic for improved outcome in patients with pathologically staged N1 NSCLC. The authors looked at levels of apoptosis and mitosis in their population and found a direct correlation with incidence of metastasis for adenocarcinoma and large cell carcinoma.

The prognostic significance of histological cell type is by itself unclear, but it is of note that where the cell type was shown to have an effect, this has been consistently in favour of the squamous cell type.

Molecular biological factors

Many molecular biological factors have been shown to have independent prognostic significance, and might play a future role in more precise individual prognostication. Currently, these factors are not routinely applied in clinical practice. A detailed discussion of each factor is therefore beyond the scope of this review. However, excellent reviews are available [73-76]. These factors are briefly summarized as (1) clinical chemistry and serum tumor markers, (2) markers of tumor proliferation, (3) markers of cellular adhesion, and (4) other molecular biological factors, including regulators of cellular growth (e.g., ras oncogene or protein, erb-b2 retinoblastoma, and epidermal growth factor receptor), regulators of the metastatic cascade (e.g., tissue polypeptide antigen and cathepsin), and regulators of apoptosis (p53 and bcl-2).

TREATMENT-RELATED FACTORS

Type of resection

It is widely recognized that the risk of significant postoperative complications and hospital mortality increases with increasing extent of resection [77]. Despite tremendous advances in operative techniques and perioperative and postoperative medical care, pneumonectomy has the highest complication and mortality rate of all elective pulmonary resections [8, 77, 78]. Although operative morbidity and mortality seem to have declined, it is unclear whether pneumonectomy has become really safer over time. Mortality rates reported for pneumonectomy ranges from 6% to 12% in comparison with lesser resections ranging from 1% to 7% [8, 32, 79, 80]. Right-sided pneumonectomy is associated with an even higher mortality rate than left-sided pneumonectomy [32, 81-83]. The average mortality rate associated with left-sided pneumonectomy is approximately 4% to 6%, with reported values ranging between 11% and 37% for right-sided pneumonectomy [32, 83]. There are multiple possible reasons for this substantial difference. One suggested reason is that patients undergoing right-sided pneumonectomy are more likely to experience bronchopleural fistulas [10, 84] and post-pneumonectomy pulmonary edema [85], which in turn increase mortality.

Lung-sparing procedures, such as wedge resections and segmental resections, are sometimes performed in patients with impaired pulmonary function at the risk of increased locoregional recurrences in comparison with pneumonectomy or lobectomy [86]. In a trial by the Lung Cancer Study Group among 247 stage IA patients eligible for analysis, recurrence rate was 75% higher among those undergoing limited resection compared with lobectomy ($p = 0.02$) [86]. This was primarily due to a 3-fold increase in the local recurrence rate. In addition, no significant difference was seen in perioperative morbidity and mortality. Therefore, lobectomy still must be considered the surgical procedure of choice for patients with peripheral T1 N0 NSCLC and limited resections must be avoided when possible.

An important circumstance of prognostic importance is that of incomplete resection, either with gross disease remaining or with positive microscopic resection margins, in which adjuvant therapy is usually recommended. Even when adjuvant therapy is provided, patients with microscopically involved margins have an impaired survival compared with patients with a complete resection.

The risk of morbidity and mortality has to be carefully balanced with the risk of cancer recurrence and long-term survival after surgery. Despite lobectomy still being the surgical treatment of choice for eligible patients with early-stage NSCLC, lung-sparing procedures remain good treatment options in patients with associated

comorbidity and significant impaired pulmonary function. This is particularly true in elderly patients where general life expectancy is shorter than that of their younger counterparts. Long-term survival in this population becomes less relevant than mid-term survival and quality of life. It is a matter of debate and further investigation whether the preferable surgical approach for small sized NSCLC is lobectomy or smaller resections. So far, standard lobectomy and systematic lymph node dissection is still the recommended standard of care.

Neoadjuvant chemotherapy

The poor long-term prognosis for the majority of patients with locally advanced unresectable NSCLC (stage IIIA or IIIB) has prompted intensive efforts to develop combined modality treatments that will improve survival. In order to improve control of localized disease and eradicate micrometastases, multimodality treatment has been developed: (chemo)radiation and surgery aiming at the local disease, and chemotherapy targeting the distant micrometastases. The administration of neoadjuvant chemotherapy may offer several potential advantages, such as delivery of chemotherapy through an intact vasculature, early treatment of distant micrometastases, and cytoreduction of local tumor burden with increase in resectability rates. However, potential disadvantages of neoadjuvant therapy, such as perioperative complications, toxicity, and as a consequence delay in secondary therapy, exist.

Clinical trials of neoadjuvant therapy have consistently demonstrated improved survival of the neoadjuvant patient arm [87-89]. Roth randomised 60 patients to receive either six cycles of perioperative chemotherapy (n = 28) or surgery alone (n = 32) [88]. Following three cycles of preoperative chemotherapy, 35% of patients had a major clinical response. Patients in the neoadjuvant chemotherapy group had an estimated median survival of 64 months compared with 11 months for patients who had surgery alone ($p = 0.008$). With additional follow-up (median 81 months), 32% of patients were alive in the neoadjuvant chemotherapy group versus 16% in the surgery alone group ($p = 0.06$) [89]. Depierre conducted a randomised clinical trial comparing neoadjuvant chemotherapy to surgery alone in patients with stages IB to IIIA NSCLC [87]. An improvement of median survival of 11 months (37 months versus 26 months, $p = 0.15$), a decrease in distant metastases ($p = 0.009$), and a significantly prolonged disease-free survival ($p = 0.033$) was noted favouring the neoadjuvant arm.

Thus, neoadjuvant chemotherapy is useful for downstaging disease and improving the rate of complete resection and survival. Unresolved issues with neoadjuvant therapy remain, including the question whether radiation therapy

should be used and in what dose and schedule, as well as identifying the optimal chemotherapy regimen. Ongoing and planned neoadjuvant trials assessing newer agents and combinations in stage IIIA and IIIB disease as well as in resectable early-stage disease will further define the role of chemotherapy followed by surgery.

Adjuvant chemotherapy and radiotherapy

Although patients with stage I and II NSCLC may undergo resection with curative intent, many relapse and eventually die of their disease. These patients most likely had cancer cells left behind, either locally or at distant sites, which redeveloped into clinical disease. Adjuvant therapy is applied after surgical resection in an effort to eradicate residual disease and to prevent recurrence.

Even though recurrence rate has been reported to decrease in patients who received adjuvant radiotherapy [90], no survival advantage was conferred among patients who had undergone surgical resection for early-stage NSCLC [90, 91]. The postoperative radiation therapy (PORT) meta-analysis [91] reported even an adverse affect of adjuvant radiation which was greatest for patients with stage I/II, N0-N1 disease, whereas for those patients with stage III N2 disease there was no clear evidence of detrimental effect. Therefore, to date routine adjuvant radiation therapy is not recommended for early-stage NSCLC.

Relapses at distant sites play a major role in the recurrence of NSCLC after complete resection. Adjuvant chemotherapy, a systematic form of treatment, might have an impact on distant recurrence and as a consequence long-term survival. Randomised trials have demonstrated controversial outcomes in terms of a survival benefit from the use of adjuvant chemotherapy. The outcome of these studies may vary, in part, due to the type of chemotherapy used. Old studies that employed alkylating agents were associated with a negative effect on survival with a decrease of 5% after 5 years [92]. Cisplatin-containing regimens were associated with a 4% to 5% improvement in survival at five years [92, 93]. However, others did not find a survival benefit [94]. At the 2004 Annual Meeting of the American Society of Clinical Oncology (ASCO), the US CALGB trial [95] and Canadian JBR-10 trial [96] were positive with an improved survival rate of 12% at 4 years and 15% at 5 years, respectively. However, these reports are not yet reported as full papers, and the patient population was highly selected with many patients being excluded because of comorbidity. In addition, the risk of toxicity after chemotherapy is not low, which can result in an increase in postoperative mortality rate and a decrease in patient's quality of life. Therefore, the use of adjuvant chemotherapy in NSCLC remains controversial and needs further research to identify the optimal target

population and the most appropriate chemotherapy regimen.

Hospital volume and experience of the surgeon

The impact of both hospital volume and surgeon specialty has been discussed extensively and is important for operative success. While several different surgical specialists perform pulmonary resection for cancer, many believe that this procedure is best performed by board-certified cardiothoracic and noncardiac thoracic surgeons. Training programs for cardiothoracic and noncardiac thoracic surgeons require each resident to complete a specified amount of major thoracic operations, whereas training programs for general surgeons do not necessitate this. The majority of general surgeons perform lung cancer operations occasionally. This contrasts to cardiothoracic and noncardiac thoracic surgeons where the number of cases per surgeon is importantly higher. Some investigators observed an increase in morbidity and mortality rate following pulmonary resection undertaken by general surgeons in comparison with cardiothoracic surgeons and noncardiac thoracic surgeons [97, 98].

In lung cancer surgery, hospital volume is associated with operative mortality as well as late survival [99, 100]. In one study, postoperative complication rates were twice as high at hospitals with the lowest volume compared with those with the highest volume [99]. Another observation was that patients treated at higher volume hospitals were 25% more likely to be alive at 5 years compared with patients at very low volume hospitals.

Certain hospitals provide postoperative care in Intensive Care Units staffed by full-time intensivists, a process of care shown to decrease mortality and length of stay [101]. Further work is necessary to understand the mechanisms underlying differences in performance across hospitals in lung cancer care.

SUMMARY AND CONCLUSION

Identifying prognostic factors in operated early-stage NSCLC patients has been the focus of many investigations in order to improve outcome. Despite tremendous advances in perioperative and postoperative care, morbidity and mortality after pulmonary resection remain relatively high. Because of the heterogeneity of this disease and the variation in the surgical interventions and expertise, as well as the patient characteristics, the importance of prognostic factors varies from one study to another. With the exception of pathological TNM stage and extent of resection, the literature demonstrates conflicting results on the prognostic power of most factors. A summary of the studies assessing prognostic factors for early postoperative morbidity, mortality, and late survival is given in Table 3 and Table 4.

The advantage of knowing about the existence of comorbidity and prognostic risk factors may provide the clinician with the ability to identify poor prognostic patients and establish the most appropriate treatment strategy. In previous published studies, we identified the CCI as an independent predictor of postoperative outcome. However, this comorbidity index is developed in another patient population and thus may be suboptimal for application in NSCLC surgery patients. In addition, this index does not include several other prognostic factors in NSCLC surgery patients, such as gender, age, extent of resection, and stage. Presently, there is no accepted prognostic model that is specific for NSCLC patients. Therefore, a prognostic model for hospital mortality as well as long-term survival in which the predictive factors in NSCLC surgery patients are incorporated may further improve specific risk assessment.

In high-risk candidates for lung surgery, treatment strategy should be made in each centre by a local interdisciplinary conference involving the (cardio) thoracic surgeon, the pneumonologist, the medical oncologist, and the radiation-oncologist. The assessment of prognostic factors remains an area of active investigation and a promising field of research in optimising therapy of NSCLC patients.

Table 3. Recently published risk factors for morbidity and hospital mortality following surgical resection for nonsmall cell lung cancer

Factor	Reference number																	Sum
	1	2	5	6	8	10	11	14	18	24	28	32	33	35	79	80	82	
Type of resection				X	X			X		X	X	X		X	X		X	9
Age						X	X	X		X	X	X	X	X		X		9
FEV_1			X	X	X						X		X			X	X	7
Cardiovascular disease							X	X	X	X					X			5
Gender					X						X		X					3
Charlson comorbidity index	X	X																2
Hypertension											X				X			2
Comorbidity indices				X														1
Pulmonary disease				X														1
Bronchopleural fistula						X												1
Hematologic disease										X								1
Bronchial stump reinforcement										X								1
Low preoperative hemoglobin										X								1
Preoperative chemotherapy				X														1
Stair climbing test									X									1
Pathological stage							X											1
DLco								X										1
ASA															X			1
VC																	X	1

FEV_1 = forced expiratory volume in 1 second
DLco = diffusion capacity of the lung for carbon monoxide
ASA = American society of anaesthesiology physical status
VC = vital capacity

Table 4. Recently published risk factors for long-term survival following surgical resection for nonsmall cell lung cancer

Factor	Reference number													Sum
	2	3	9	10	28	40	42	56	59	60	62	63	80	
Pathological stage	X	X	X	X	X	X	X		X	X	X	X	X	12
Histology		X		X				X	X				X	5
Age		X	X	X		X	X							5
FEV_1			X		X		X						X	4
Gender						X	X							2
Smoking	X							X						2
Type of resection						X							X	2
Incomplete resection										X				1
Bronchopleural fistula				X										1
COPD	X													1
KPS								X						1
CIRS-G								X						1
Lymphatic vessel invasion											X			1
Low preoperative hemoglobin		X												1
Creatinine level					X									1
Hypertension					X									1
MPBE									X					1

FEV_1 = forced expiratory volume in 1 second

COPD = chronic obstructive pulmonary disease

KPS = karnofsky performance score

CIRS-G = cumulative illness rating scale for geriatrics

MPBE = microscopic proximal bronchial extension

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CHAPTER 3

Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer

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ABSTRACT

A systematic review was undertaken to select studies that compared the accuracy of 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography with computed tomographic imaging in detecting mediastinal lymph node metastases in patients with nonsmall cell lung cancer. Two authors selected relevant articles according to predefined criteria. With a meta-analytic method, summary receiver operating characteristic curves were constructed. The point on the receiver operating characteristic curve with equal sensitivity and specificity for 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography was Q*= 0.90 (95% confidence interval, 0.86 to 0.95). For computed tomography it was 0.70 (95% confidence interval, 0.65 to 0.75). The difference was highly significant ($p < 0.0001$). We conclude that 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography is more accurate than computed tomography in detecting mediastinal lymph node metastases.

INTRODUCTION

Lung cancer is the most common cause of death by malignancy in industrialized countries. Approximately only 15% of patients can be cured to enjoy long-term survival. The optimal management of patients with nonsmall cell lung cancer (NSCLC) depends on the accuracy of appropriate staging strategies. In this regard, chest radiography and computed tomographic (CT) images are frequently performed on patients with suspected lung cancer. These diagnostic modalities provide anatomic and morphologic information and are non-invasive, but they are limited in distinguishing between benign and malignant abnormalities. The likelihood of surgical cure of primary NSCLC is strongly dependent on the local extent of the cancer, particularly whether or not the mediastinal lymph nodes are involved with cancer or whether extrathoracic metastases are present [1]. Therefore, diagnostic evaluation of mediastinal lymph nodes should be accurate. Patients with metastases to the mediastinal lymph nodes have an average 5-year survival rate of approximately 23% as compared with a survival rate of 50% when there is no mediastinal involvement [1]. Dales and colleagues [2] found an overall accuracy of 79% of chest CT imaging in detecting mediastinal metastases. Presently, the most accurate method for staging the mediastinal lymph nodes is mediastinoscopy, an invasive procedure that has a sensitivity of approximately 90% for malignant disease [3, 4].

In the last decade, attention has focused on positron emission tomography (PET), a new noninvasive imaging modality using 2-[18F]-fluoro-2-deoxy-D-glucose (FDG); this method has demonstrated increased glucose metabolism in malignant cells and pulmonary malignancies [5]. The principal mechanism for which it is based was an observation made in 1930. Warburg [6] observed that cancer cells are characterised by higher glycolitic rate than normal cells. The glucose analogue FDG undergoes membrane transport and phosphorylation by hexokinase and is trapped intracellularly. Therefore, intracellular FDG concentration reflects intracellular glucose metabolism and permits differentiation between benign and malignant tissue. The FDG PET imaging is performed in the fasting state to minimize competitive inhibition of FDG uptake by glucose. Several studies have addressed the diagnostic accuracy of FDG PET for detecting mediastinal lymph node metastases, but most studies have enrolled a small numbers of patients. The purpose of this study is to perform a meta-analysis to estimate the diagnostic accuracy of FDG PET versus CT imaging on detecting mediastinal lymph node metastases in patients with NSCLC.

MATERIAL AND METHODS

Study identification

We attempted to identify all studies that examined functional imaging with FDG PET and CT scanning for diagnosis of mediastinal lymph node metastases in patients with NSCLC. Articles were identified by an electronic search on MEDLINE using specific keywords (ie, positron emission tomography, computed tomography, FDG, lung cancer, staging). The references reported in all the identified studies were used for completion of the literature search. When authors reported on the same patient population in several publications, only the most recent or complete study was included in the analysis. Articles by the same author or research group were identified for analysis only when it was obvious that different patient populations had been used. The search ended in January 2003. The following items were searched for in each of these series: number of patients, mean age, design of the study, reference standard, sensitivity and specificity of FDG PET and CT scan.

Study eligibility

Two investigators (ÖB, APK) independently evaluated potential English language studies for inclusion and subsequently resolved disagreements by discussion. To be eligible for this analysis, reports had to have primary NSCLC cases only, have enrolled at least 15 patients, have evaluated the correlation of FDG PET and mediastinal lymph node metastases, have evaluated the correlation of CT imaging and mediastinal lymph node metastases, have presented sufficient data to allow calculation of sensitivity and specificity for malignancy, and had to have been published as a full article in the English language peer-reviewed literature. Abstracts were excluded from this analysis because of insufficient data to evaluate the methodological quality and to allow the calculation of sensitivity and specificity.

Study quality

We designed criteria to assess the quality of the different studies. The trial quality was assessed according to the information provided in the publication. Each trial was read and scored independently by two investigators (ÖB, APK) and disagreements were subsequently resolved by discussion. To identify high-quality studies, we selected criteria for methodological quality from a checklist for reporting diagnostic accuracy studies proposed by the STARD (Standards for reporting of Diagnostic Accuracy) group [7]. The STARD checklist consists of 25 items. We selected eight general quality criteria covering eight dimensions: (1) description of the study

population, (2) cohort assembly, and (3) study design, (4) a clear description of CT technique, (5) a clear description of FDG PET technique, (6) a technical quality of the reference standard, (7) a clear definition of cut-off levels, and (8) interpretation of both FDG PET and CT scans independent of each other and without knowledge of histology. A value between 0 and 2 was attributed to each dimension (2= adequate and complete description or prospective design, 1= partial or not optimal description or retrospective design, 0= not performed or not mentioned), giving a maximum possible score of 16.

Statistical analysis

The raw data were summarized according to a method described previously by Irwig and associates [8]. For each study, sensitivity, specificity and diagnostic odds ratios (DOR) were calculated from the 2x2 tables of true-positive, true-negative, false-positive, and false-negative results. The DOR is a simple statistic to express the discriminative power of a test. It is defined as the ratio of sensitivity/(1-sensitivity) over (1-specificity)/specificity. In simpler terms, the DOR is the odds of a positive test result if mediastinal lymph nodes are involved with cancer, divided by the odds of a positive test result if mediastinal lymph nodes are free from cancer. A DOR greater than 1 indicates that a test has discriminative power, which increases with the magnitude of the DOR. To prevent division by 0 when calculating the DOR, the conventional correction by adding 0.5 to each cell in the 2x2 tables was applied [9]. The DOR was analyzed using a random effect meta-analysis model for the logarithm of the DOR, leading to an overall estimate of the DOR and a corresponding 95% confidence interval (95% CI), taking possible heterogeneity between studies into account [10]. Sensitivity and specificity were analyzed in an analogous way, using the logit transformation.

The models contained study as random factor and did not contain fixed factors, except for a constant. These analyses were carried out with SAS proc mixed as described by van Houwelingen and colleagues [10].

To quantitatively summarize the diagnostic test performance of FDG PET and CT imaging, we also used a meta-analytic method to construct summary receiver operating characteristic (ROC) curves [11, 12]. Receiver operating characteristic curves illustrate the trade-off between sensitivity and specificity as the threshold for defining a positive test varies from most stringent to least stringent. Construction of a summary ROC curve involves calculation of the sum and the difference of the logit transforms of the true-positive and false-positive rates for each study [8]. Our method assumes that each individual study represents a unique point on a common ROC curve. To construct the common ROC curves, we applied the equally weighted

least squares method described by Moses and colleagues [11]. We defined the maximum joint sensitivity and specificity as the intersection point of the ROC curve and the diagonal line that runs from the top left corner to the bottom right corner of the ROC diagram. This point Q*, at which sensitivity and specificity are equal, is a global measure of test accuracy, similar to the area under the ROC curve. The maximum joint sensitivity and specificity of a perfect test is 1.0, and a maximum joint sensitivity and specificity of a test that has no discriminative ability is 0.5, meaning that probability of correctly identifying disease would be 50%. We calculated Q* and its corresponding standard error by the method described by Moses and colleagues [11]. A larger value of Q* means that the ROC curve tends to be positioned more towards the left upper corner and the better is the test [13, 14]. The analysis was carried out with SPSS.

To assess publication bias, funnel plots were made accompanied by the linear regression test on symmetry [15].

RESULTS

Study identification and eligibility

Our search identified 49 potentially relevant studies. We excluded 26 studies after scanning their abstracts, including 12 studies written in another language other than English, five studies that evaluated small cell lung cancer, eight review articles, and one study that evaluated not only NSCLC. Twenty-three potentially eligible studies were subsequently appraised. Of these, we excluded six studies because the same patient population as another more recently published article was used [16], because only the accuracy of FDG PET was evaluated [17], because only patients with stage I NSCLC on CT imaging were included [18], because only patients with probable N1-disease were included [19], because there was insufficient data reported to allow the calculation of sensitivity and specificity [20], or because only the number of mediastinal nodal stations examined were reported and not the number of patients [21]. The remaining 17 studies were published between 1994 and 2001 [22-38].

Study description

The main characteristics of the 17 eligible studies are outlined in Table 1. The total number of patients included was 833, ranging from 18 to 102 patients by report. There were no data reported on age in 11 studies. The sex distribution was only reported in three studies. Five studies evaluated the role of whole-body FDG PET and CT imaging in the staging of NSCLC (pulmonary nodules, lymph node metastases, and distant metastases) [25, 33-36], three studies assessed the role of FDG PET and CT imaging on detecting pulmonary nodules and mediastinal metastases [22, 27, 32], three studies evaluated lymph node metastases [30, 37, 38], and six trials only assessed mediastinal lymph node staging of NSCLC [23, 24, 26, 28, 29, 31]. The patients included in the studies were found operable on CT scan findings if mediastinal lymph nodes were ≤ 10 mm in diameter. If mediastinal lymph nodes were larger, patients underwent mediastinoscopy prior to surgery. All patients underwent FDG PET imaging. Histology was confirmed by mediastinoscopy or thoracotomy, or both. Thirty-two patients (in two studies, respectively in 1 and 31 patients [23, 35]) were followed up with CT scan. Lymph nodes were recorded as pathologic if there was a substantial growth in size. Studies did not report which and how many patients underwent mediastinoscopy on FDG PET findings before thoracotomy. Only six studies [30, 31, 33, 35, 38] described a differentiation between N2 and N3 disease. Two studies [30, 37] reported results by using lymph nodes as the unit of analysis and differentiated between single versus multiple nodes. The results of the remaining studies were reported by using the patient as the unit of analysis.

Table 1. Studies comparing 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography in mediastinal lymph node staging of nonsmall cell lung cancer

Reference, Year	Patients (% Male)	Mean Age (Range)	Design	Reference Standard[a]	Modality	True-Positive	False-Negative	False-Positive	True-Negative	Sensitivity (%)	Specificity (%)	P value	Diagnostic OR
Scott et al. (1994) [22]	25		Retrospective	1,2	PET	2	1	3	19	67	86		12.7
					CT	1	2	2	20	33	91		5.0
Wahl et al. (1994) [23]	23[b] (74)	64 (42-84)	Prospective	1,3	PET	9	2	3	13	82	81	< 0.05	19.5
					CT	7	4	9	7	64	44		1.4
Chin et al. (1995) [24]	30 (63)	61 (46-76)	Prospective	1,2	PET	7	2	4	17	78	81	0.004	14.9
					CT	5	4	3	18	56	86		7.5
Valk et al. (1995) [25]	74[c]		Prospective	1,2	PET	20	4	3	49	83	94	< 0.01	76.5
					CT	15	9	14	38	63	73		4.5
Scott et al. (1996) [26]	27	64 (40-85)	Prospective	1,2	PET	9	0	0	18	100	100	0.031	703.0
					CT	6	3	3	15	67	83		10.0
Sazon et al. (1996) [27]	32		Prospective	1	PET	16	0	0	16	100	100		1089.0
					CT	13	3	7	9	81	56		5.6
Sasaki et al. (1996) [28]	29	65 (46-82)	Prospective	1	PET	13	4	1	53	76	98	< 0.05	155.2
					CT	11	6	7	47	65	87		12.3
Vansteenkiste et al. (1997) [29]	50	65 (40-83)	Prospective	1,2	PET	10	5	1	34	67	97	0.004	65.6
					CT	10	5	13	22	67	63		3.4
Steinert et al. (1997) [30]	47[d]		Prospective	1,2	PET	25	3	1	83	89	99	0.0066	801.0
					CT	16	12	5	79	57	94		20.8
Guhlmann et al. (1997) [31]	32		Retrospective	1,2	PET	13	2	0	17	87	100	< 0.02	189.0
					CT	8	7	3	14	53	82		5.3
Hagberg et al. (1997) [32]	18		Retrospective	1,2	PET	6	3	0	9	67	100		35.3
					CT	5	4	0	9	56	100		23.2
Bury et al. (1997) [33]	66		Prospective	1,2	PET	12	2	0	52	86	100		525.0
					CT	11	3	8	44	79	85		20.2
Saunders et al. (1999) [34]	84		Prospective	1,2	PET	12	5	2	65	71	97		78.0
					CT	3	12	7	62	20	90		2.2
Marom et al. (1999) [35]	78		Prospective	1,3	PET	40	4	3	31	91	91	< 0.001	103.3
					CT	26	18	4	30	59	88		10.8
Pieterman et al. (2000) [36]	102		Prospective	1,2	PET	29	3	10	60	91	86	< 0.001	58.0
					CT	24	8	24	46	75	66		5.8
Gupta et al. (2000) [37]	54[c]		Prospective	1,2	PET	51	2	8	107	96	93		318.8
					CT	36	17	36	79	68	65		1.0
Poncelet et al. (2001) [38]	62	65 (45-83)	Prospective	1,2	PET	6	3	8	44	67	85	0.08	11.5
					CT	5	4	17	36	33	91		5.0

[a] 1 = thoracotomy, 2 = mediastinoscopy, 3 = imaging follow up with computed tomography
[b] 27 mediastinal sides were evaluated; [c] 76 mediastinal sides were evaluated; [d] 112 lymph nodes were evaluated
[c] 168 lymph nodes were evaluated; PET = positron emission tomography; CT = computed tomography
OR = odds ratio

Methodological quality assessment

The results of the methodological quality assessment for each study are given in Table 2. The overall quality score ranged from 10 to 16 (mean, 14.1). The most poorly described item was the description of the study population. This was particularly caused by the different primary objectives of the studies, of which most did not only evaluate mediastinal lymph node metastases. These trials reported the total study population, but did not report the study population for whom evaluation of mediastinal lymph node metastases was done. No correlation was found between the year of publication and the quality scores.

Table 2. Methodological quality score

Reference, Year	Quality score
Scott et al. (1994) [22]	10
Wahl et al. (1994) [23]	16
Chin et al. (1995) [24]	16
Valk et al. (1995) [25]	13
Scott et al. (1996) [26]	14
Sazon et al. (1996) [27]	13
Sasaki et al. (1996) [28]	16
Vansteenkiste et al. (1997) [29]	16
Steinert et al. (1997) [30]	14
Guhlmann et al. (1997) [31]	13
Hagberg et al. (1997) [32]	13
Bury et al. (1997) [33]	14
Saunders et al. (1999) [34]	14
Marom et al. (1999) [35]	13
Pieterman et al. (2000) [36]	14
Gupta et al. (2000) [37]	14
Poncelet et al. (2001) [38]	16

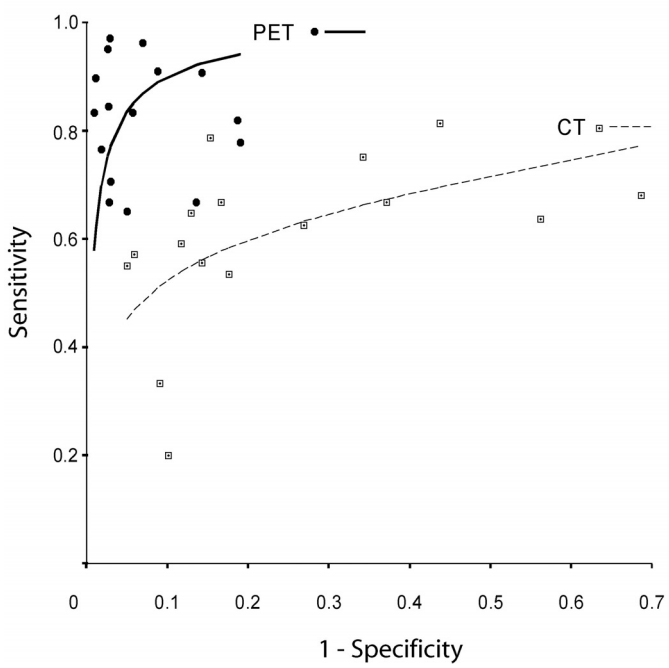
Diagnostic accuracy and meta-analysis

The sensitivity of FDG PET for detecting mediastinal lymph node metastases ranged from 66% to 100%. The estimate of the overall sensitivity was 83% (95% confidence interval, 77 to 87). Specificity ranged from 81% to 100%, with an overall estimated specificity of 92% (95% confidence interval, 89 to 95). The sensitivity and specificity of CT scan for detecting mediastinal lymph node metastases ranged from 20% to 81% and 44% to 100%, respectively. The overall estimates were 59% (95% confidence interval, 50 to 67) and 78% (95% confidence interval, 70 to 84),

respectively. No statistically significant heterogeneity in sensitivity or specificity was detected for both methods. All 17 studies reported a better accuracy of FDG PET when compared with CT imaging in detecting mediastinal lymph node metastases, of which the results of 10 trials were considered as statistically significant ($0.001 \leq p < 0.05$). Table 1 shows accuracy results expressed in terms of DOR. The DOR ranged from 1.0 to 23.2 for CT imaging, and from 11.5 to 1089.0 for FDG PET. In all studies the DOR was higher for FDG PET than for CT imaging. The overall estimate of the DOR was 5.4 (95% confidence interval, 3.3 to 8.8) for CT imaging and 76.4 (95% confidence interval, 41.2 to 141.7) for FDG PET. For both methods, there was no statistically significant heterogeneity found in the DOR.

The summary ROC curves for the compared diagnostic modalities are shown in Figure 1. The point on the ROC curve with equal sensitivity and specificity for CT imaging was $Q^* = 0.70$ (95% confidence interval, 0.65 to 0.75) and for FDG PET it was 0.90 (95% confidence interval, 0.86 to 0.95). The difference was highly significant ($p < 0.0001$). Funnel plots and linear regression tests on the symmetry of them did not show evidence of publication bias.

Figure 1. Summary receiver operating characteristic curves for 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography and computed tomography scan on detecting mediastinal lymph nodes in patients with nonsmall cell lung cancer



COMMENT

The correct identification of the extent of disease in NSCLC is a difficult problem for the clinician. Distinguishing between intrapulmonary involvement and mediastinal lymph node involvement is an important part of the process, deciding whether thoracotomy should be performed. Patients without metastatic lymph nodes (N0 disease) or with only intrapulmonary or hilar nodes (N1) are generally considered operable. Those with ipsilateral (N2) or contralateral (N3) metastatic mediastinal lymph nodes have locally advanced disease and are usually not considered for primary surgical treatment. The current noninvasive methods have significant limitations for evaluating the mediastinum and potential extrathoracic metastases. Metastases may be found in 21% of nodes considered normal by imaging criteria [39], and up to 40% of enlarged nodes in some series are not cancerous [2, 40]. In contrast to CT imaging, which is primarily dependent on anatomic imaging features, FDG PET is mainly dependent on the metabolic characteristics of a tissue for assistance in the diagnosis of disease. Because biochemical changes in a tumor will occur before morphological changes, FDG PET has the potential to monitor the progression of disease before anatomical changes are apparent on conventional imaging techniques. However, because inflammatory cells such as activated macrophages also avidly take up FDG [41], false-positive findings have been reported in active lung diseases such as granulomas, aspergillomas, active tuberculosis and abscesses [16, 18].

This meta-analysis, which pooled all the studies we found evaluating and comparing the diagnostic accuracy of FDG PET and CT imaging on detecting mediastinal lymph node metastases, showed that FDG PET was more accurate than CT imaging. The high negative predictive value of FDG PET for mediastinal lymph node metastases can be used as an advantage in the approach to patients with NSCLC, because the necessity of invasive procedures can be questioned in a patient with negative findings on FDG PET. However, even with optimal current technology, FDG PET fails to identify microscopic N2 disease. Therefore, nowadays mediastinoscopy is still warranted in some FDG PET negative patients with certain clinical factors, such as size and location of the tumor, which can be predictive for mediastinal lymph node metastases. A lower positive predictive value of FDG PET, mostly due to inflammatory processes, means that patients in whom mediastinal metastases are found on FDG PET will need to undergo a cervical mediastinoscopy as part of the work-up for NSCLC, to be sure that no single patient with N0 or N1 disease is denied the chance of cure by direct surgical resection based on a false-positive FDG PET.

Dwamena and colleagues [42] stated in their meta-analysis that they found a high accuracy of FDG PET versus CT imaging. However this meta-analysis also included

studies evaluating CT scanning only and studies evaluating N1 lymph nodes. Because N1 disease is generally considered operable for treatment decision it is more essential to know whether FDG PET is more accurate to detect N2 or N3 lymph node disease.

In addition to the higher accuracy of FDG PET in detecting mediastinal lymph nodes, it is also accurate in detecting metastatic disease and residual disease after induction therapy. Studies comparing the ability to detect metastases within the liver and adrenal gland demonstrated that FDG PET has a higher sensitivity and specificity than CT scans [43, 44], and it has been found to be superior to bone scinctigraphy [45, 46]. Conventional imaging techniques do not provide tumor-specific information. For example, it is difficult to distinguish residual disease from necrosis or fibrotic tissue after induction therapy. The FDG PET has been proven to be more accurate than CT scans in monitoring tumor response to chemotherapy or irradiation [47-49].

The main drawback of FDG PET is the limited ability for precise anatomic localization. Therefore, correlation between the FDG PET images and a recent CT scan of the chest is needed for precise localization of mediastinal lymph nodes. Image registration and image fusion have been used for combining anatomic information from CT scans and metabolic information from FDG PET images [50, 51]. However, computerized fusion of the two types of images currently seemed to be only marginally more beneficial than simple visual correlation of the FDG PET scan and CT imaging in terms pinpointing metastases in lymph nodes. Whether the benefit of computerized fusion of FDG PET and CT imaging will progress has yet to be proven in further investigation.

Policy-level decisions regarding dissemination of FDG PET must consider not only diagnostic accuracy but also clinical outcome and costs. The high cost is one of the reasons limiting its widespread utilization. Gambhir and coworkers [52] developed a cost to benefit model that demonstrated a significant cost savings by including FDG PET imaging in the staging of lung cancer. They found that a conservative strategy of using chest CT imaging plus FDG PET imaging showed potential cost savings of $1,154 per patient without a loss of life expectancy. This strategy would involve taking biopsy specimens from all positive findings with either CT scan or FDG PET imaging that may indicate nonresectability malignancy so that 100% of surgical candidates are identified definitively. The major cost savings of FDG PET is mainly the result of a patient with unresectable disease who is not undergoing an unnecessary surgery [53].

We attempted to identify all studies that examined functional imaging with FDG PET and CT scans for diagnosis of mediastinal lymph node metastases in patients with NSCLC, and we attempted to prevent biases. However all potential biases can not be prevented. This review was restricted to articles published in English, because other languages such as Japanese or French were not accessible for the readers. This

selection could favor the positive studies, as positive studies are often published in English, whereas negative studies, if at all published, tend to be reported in native languages [54].

Another possible source of confusion is the use of the same cohort of patients in different publications. It may be difficult to avoid the same patients being included more than once in the meta-analysis, although publications in which this seems to be the case have to be excluded. We included two publications by Scott and coworkers [22, 26] on different cohorts.

For most studies, the patient was the unit of analysis. For two studies [30, 37], the results were reported by using lymph nodes as the unit of analysis. Analysis of individual lymph nodes can be a source of bias. In these studies, observations are not statistically independent (ie, if a given patient has one positive lymph node, then that patient is more likely to have other positive lymph nodes). In addition, it is important to note that the clinically relevant unit of analysis is the patient, and treatment decisions depend on the presence or absence of lymph node involvement rather than the number of involved nodes.

The fact that mainly operable patients were included in all studies could be a source of work-up bias. In addition, doctors sometimes rely more on the results of the FDG PET scan compared with the CT scan, resulting in more mediastinoscopies performed in patients with a positive FDG PET scan. In all of our studies, no information was given on which and how many patients underwent mediastinoscopy based on FDG PET results before thoracotomy.

The techniques and specialists' reviews that were used to detect mediastinal lymph node metastases may also be potential sources of bias, as nowadays FDG PET scan technology is disseminated to centers with less experience.

In conclusion, our meta-analysis indicates that FDG PET is more accurate than CT imaging for the detection of mediastinal lymph node metastases in patients with NSCLC. However, the main drawback of FDG PET is the limited ability for precise anatomic localization. Therefore, correlation between the FDG PET images and a recent CT scan is needed for precise localization of mediastinal lymph nodes. Nowadays, the FDG PET image is not yet able to replace the CT scan as a staging procedure, but it does provide essential additional information. Advances in FDG PET technology, including the refinements of computerized fusion of FDG PET and CT scan, may overcome the limitations in the future. As more accurate staging should lead to more appropriate therapy, FDG PET may lead to improvements in both patient quality of life and in savings of healthcare costs.

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CHAPTER 4

Relearning the lesson from the past - are we making progress?

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LETTER

We extend our appreciation to Dr. Detterbeck for his comments on and interest in our recent investigation using meta-analysis and summary receiver operating characteristic curves to compare the reliability of positron emission tomographic (PET) and computed tomographic (CT) imaging for mediastinal staging of nonsmall cell lung cancer (NSCLC) [1]. Nowadays, among oncologists and thoracic surgeons, CT scanning is still considered the "gold standard" for non-invasive nodal staging despite the low accuracy of CT scan. In our meta-analysis, however, we demonstrated that the accuracy of PET for detecting mediastinal lymph node metastases was significantly higher in comparison with CT.

In addition to the high accuracy of detecting mediastinal lymph nodes, PET scan improves non-invasive clinical staging by detecting unexpected extrathoracic metastases without any evidence of metastases after conventional imaging, thus avoiding futile mediastinoscopy and eventually thoracotomy [2, 3].

In the work-up of staging for NSCLC and considering a thoracotomy, a cervical mediastinoscopy is still considered the "gold standard", providing a high positive and negative predictive value. Currently, almost all national and international associations recommend a staging mediastinoscopy in patients with lymph nodes of more than 1 cm in short-axis diameter on the pre-therapeutic CT scan. However, have we forgotten that mediastinoscopy remains an invasive procedure, that accuracy of a mediastinoscopy is surgeon dependent, and maybe most important, that mediastinoscopy is not without morbidity and mortality [4, 5]?

Therefore, the question, "Can PET reduce the need for mediastinoscopy…?" is relevant to clinical practice. So, we are now questioning the use of mediastinoscopy once a PET scan is performed. To eliminate mediastinoscopy, PET should be at least as accurate as mediastinoscopy. However, presently it is not. Although PET does not eliminate mediastinoscopy, PET does reduce the need for mediastinoscopy.

The low positive predictive value of PET due to FDG uptake in inflammatory lymph nodes makes cytologic or histologic confirmation necessary in case of a positive mediastinum, being a known pitfall. With the high negative predictive value, a negative mediastinum on PET can lead directly to thoracotomy, without further invasive preoperative staging. This implementation should be done with caution in case of patients with centrally located tumors, in case of positive central hilar N1-disease, and in case of bronchoalveolar cell carcinoma, due to the higher false-negative rate in these circumstances [6]. We realize that some occasional patient with a false-negative mediastinal PET will proceed to straightforward thoracotomy. In these cases, however, "minimal N2 disease" is found, where a

reasonable prognosis after surgical resection can be expected in comparison with patients with preoperative confirmed N2 disease [7]. An additional advantage of PET over mediastinoscopy is that PET can indicate suspected lymph nodes in stations not amenable to mediastinoscopy (e.g. para-oesophageal or infraclavicular).

Staging of the mediastinum by PET is definitely better than staging by CT alone, and therefore PET has a definite role in non-invasive mediastinal staging independent of the availability and expertise in mediastinoscopy. In our view, PET scan is able to reduce the need for mediastinoscopy and reduce the number of unnecessary thoracotomies. A clinician must always seek for an accurate preoperative staging with minimal need for invasive procedures. The use of PET needs further validation in outcome studies. These studies should examine, in a randomized design, whether PET actually improves NSCLC management, by e.g. decreasing the number of unnecessary invasive procedures or by improving the survival. In the future, fusion of the CT scan with PET scan into one test may be helpful to further improve the diagnostic accuracy of these non-invasive imaging modalities.

We think that our considerations are not a matter of relearning lessons from the past, but are useful contributions to improvement of clinical staging of NSCLC patients. In that regard, we are making progress.

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CHAPTER 5

Validation of the Charlson comorbidity index in patients with operated primary nonsmall cell lung cancer

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ABSTRACT

Objective: To validate the influence of the Charlson comorbidity index (CCI) in patients with operated primary nonsmall cell lung cancer.

Methods: From January 1996 to December 2001, 205 consecutive resections for nonsmall cell lung cancer were performed at the Erasmus Medical Center Rotterdam. The patients ranged in age from 29 to 82 years, with a mean age of 64 years. In a retrospective study, each patient was scaled according to the CCI and the complications of surgery were determined.

Results: The hospital mortality was 2.4% (5 of 205 patients). Of the 205 patients, 167 (32.7%) experienced minor complications and 32 (15.6%) major complications. In univariate analysis, male gender, grade 3 - 4 of the CCI, any prior tumor treated in the last 5 years and chronic pulmonary disease were significant predictors of adverse outcome. Multivariate analysis showed that only grade 3 - 4 of the CCI was predictive (odds ratio, 9.8; 95% confidence interval, 2.1 to 45.9). Although only comorbidity grades 3 - 4 was a significant predictor, for every increase of the comorbidity grade the relative risk of adverse outcome showed a slight increase.

Conclusions: The CCI is strongly correlated with higher risk of surgery in primary nonsmall cell lung cancer patients and is a better predictor than individual risk factors.

INTRODUCTION

Mortality due to cancer in the Netherlands is the highest for lung cancer in men and the second in place for women [1]. Although pulmonary resection is recognized as the best treatment for lung cancer, there are still questions about the relationship between comorbidity and the 30-day mortality and morbidity. Accurate identification of comorbidity is essential in assessing patient's health status and quantifying risk of mortality and morbidity.

The Charlson comorbidity index (CCI), developed by Charlson and colleagues [2] in 1987, was developed based on a longitudinal study of 559 patients admitted to a medical service during a 1-month period. Nineteen conditions were found to significantly influence survival in the study population and were given a weighted score based on the relative mortality risk (Table 1). The sum of the weighted scores of all of the comorbid conditions present in cancer patients was then scaled to establish the CCI. The score can be divided into four comorbidity grades: 0, 1 - 2, 3 - 4, and 5 or more.

The weighted index was tested for its ability to predict mortality in a cohort of women with histologically proven primary cancer of the breast. With each increased level of the comorbidity index, there was a stepwise increase in the cumulative mortality attributable to comorbid disease [2].

The purpose of this retrospective study was to evaluate the usefulness of the CCI in patients with operated primary nonsmall cell lung cancer (NSCLC).

MATERIAL AND METHODS

We reviewed the medical records of 205 consecutive patients (148 men, 57 women) who underwent resection for primary NSCLC at the Department of Cardio-Thoracic Surgery of the Erasmus Medical Center Rotterdam between January 1, 1996, and December 31, 2001. The patients ranged in age from 29 to 82 years, with a mean age of 64. The patient demographics are listed in Table 4.

Each patient was scaled on the CCI. Patients were considered to have a comorbid condition if a listed disorder was mentioned in the records or if the patient was treated for it. Cardiac disease is associated with a higher risk of operation in patients with lung cancer [3-7]. Therefore, we modified the CCI by scoring all forms of coronary artery disease (myocardial infarction, angina, coronary artery bypass graft, percutaneous transluminal coronary angioplasty) with a value of 1. The comorbid conditions of the patients are summarized in Table 1.

For all cases, preoperative workup included chest radiography, computed tomography scan of the chest and upper abdomen, bronchoscopy, electrocardiography, basic biochemical tests, liver and kidney function tests and pulmonary function studies. Additional staging procedures, i.e. mediastinoscopy, liver, bone and brain scans were selectively performed to aid in treatment planning.

The types of procedures performed consisted of pneumonectomy (55), bilobectomy (19), lobectomy (126) and wedge resection (4). The histological typing occurred according to The World Health Organization Histological Typing of Lung Tumours [8]. All tumors were staged according to the international tumor-node-metastases (TNM) classification [9]. Staging was based on pathological assessment of the primary tumor and surgical sampling of bronchopulmonary, hilar and mediastinal lymph nodes. Histological subtypes and stage of disease are presented in Table 2.

The length of hospital stay (LOS) was calculated as the difference, in days, between date of discharge and date of surgery. Complications were classified as minor (non-life-threatening) or major (potentially life-threatening), occurring within 30 days of the operation or during a longer period in the same postoperative hospital stay [10]. When a given patient had both minor and major postoperative complications, he was coded as having major complications only, although the nature of the minor complication was also recorded. Hospital mortality was defined as death occurring within 30 days of surgery or any death later in the same postoperative hospital stay.

The χ^2 or Fisher exact test was used to analyse the categorical data. Continuous variables were analysed using the Student's t-test. Univariate and multivariate logistic regression analysis was used to discriminate independent risk factors for major complications after surgical resection. One-way analysis was used to determine the

influence of comorbidity on length of hospital stay. All data analysis was performed with SPSS for Windows (release 10.1; SPSS Inc, Chicago, IL). A p value < 0.05 was considered significant.

Table 1. Charlson comorbidity index and prevalence of comorbid conditions among 205 operated primary nonsmall cell lung cancer patients

Score	Condition	Number of patients	%
1	Coronary artery disease[a]	47	22.9
	Congestive heart failure	22	10.7
	Chronic pulmonary disease	76	37.1
	Peptic ulcer disease	15	7.3
	Peripheral vascular disease	53	25.9
	Mild liver disease	1	0.5
	Cerebrovascular disease	11	5.4
	Connective tissue disease	7	3.4
	Diabetes	15	7.3
	Dementia	2	1.0
2	Hemiplegia	1	0.5
	Moderate to severe renal disease	2	1.0
	Diabetes with end organ damage	0	0
	Any prior tumor (within 5 years of diagnosis)[b]	30	14.6
	Leukemia	3	1.5
	Lymphoma	1	0.5
3	Moderate to severe liver disease	2	1.0
6	Metastatic solid tumor	0	0
	AIDS (not only HIV positive)	0	0

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris; [b] Except basal cell skin carcinoma
AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus

Table 2. Histology and pathological TNM stage

Characteristic	Number of patients	%
Histological subtypes		
Squamous cell carcinoma	85	41.5
Adenocarcinoma	78	38.0
Large cell carcinoma	29	14.1
Carcinoid	9	3.6
Bronchoalveolar cell carcinoma	4	2.0
Pathological stage		
IA	76	37.1
IB	68	33.2
IIA	9	4.4
IIB	27	13.2
IIIA	20	9.8
IIIB	2	1.0
IV	4	2.0

RESULTS

When comparing gender, the prevalence of comorbidity was not significantly ($p = 0.179$) higher in males compared with females (79% versus 70%). The prevalence of comorbidity for lung cancer in patients > 70 years was significantly ($p = 0.009$) higher than for younger patients (89% versus 72%).

Of the 205 patients, 67 (32.7%) experienced minor complications and 32 (15.6%) major complications (Table 3). The most common complications were supraventricular arrhythmia and air leak lasting more than 5 days. Five patients (2.4%) died postoperatively. The causes of death were inferior myocardial infarction (n = 1), cardiac failure (n = 1), multiple pulmonary embolism (n = 1) and empyema (n = 2). These patients had a CCI of respectively 2, 3, 3, 1 and 0.

Univariate analysis showed that significant predictors of major complications were male gender, grade 3 - 4 of the CCI, any prior tumor treated in the last 5 years and chronic pulmonary disease (Table 4). Although only comorbidity grades 3 - 4 was a significant predictor, for every increase of the comorbidity grade the relative risk of major complications showed a slight increase.

Age, pneumonectomy, squamous cell carcinoma, smoking, diabetes, congestive heart failure, coronary artery disease and respiratory function were not significant predictors of major complications.

In the multivariate model only grade 3 - 4 of the CCI was associated with an increased risk of major complications (odds ratio, 9.8; 95% confidence interval, 2.1 to 45.9). Given these results, the CCI is a better predictive factor than individual risk factors.

The mean length of hospital stay was 14.4 days, ranging from 2 to 116. An increase of comorbidity grade showed a slight increase of the LOS, although this was not significant ($p = 0.107$) (Table 5).

Table 3. Incidence of complications

Complications	Number of patients	%
Minor complications	67	32.7
Supraventricular arrhythmia	45	22.0
Air leak > 5 days	34	16.6
Atelectasis	8	3.9
Transfusion	6	2.9
Infection[a]	4	2.0
Paresis of recurrent nerve	4	2.0
Major complications	32	15.6
Rethoracotomy[b]	18	8.8
Empyema	8	3.9
Pneumonia	8	3.9
Pleural effusion	6	2.9
Bronchopleural fistula	4	2.0
Ventilatory support > 72h	4	2.0
ARDS[c]	2	1.0
Ventricular arrhythmia	2	1.0
Pulmonary embolism	2	1.0
Cardiac failure	1	0.5
Myocardial infarction	1	0.5

[a] Included wound sepsis and infection of the bronchial tubes

[b] Included rethoracotomy for postoperative bleeding or not curative resection

ARDS = adult respiratory distress syndrome

Table 4. Risk factors related to early death or other major complications in univariate and multivariate logistic regression

Characteristic	Number of patients	Major complications		Univariate	
		n	%	OR	95% CI
Gender					
Male	148	28	18.9		
Female	57	4	7.0	0.3	0.1 - 0.9
Age					
≤ 50	21	2	9.5		
50 - ≤ 60	31	3	9.7	1.1	0.2 - 6.9
60 - ≤ 70	98	15	15.3	1.7	0.4 - 8.1
> 70	55	12	21.8	2.6	0.5 - 12.7
Pneumonectomy					
No	150	20	13.3		
Yes	55	12	21.8	1.8	0.8 - 3.9
Squamous cell carcinoma					
No	120	6	16.7		
Yes	85	26	14.1	0.8	0.4 - 1.8
Current or former smoker					
No	42	6	14.3		
Yes	163	26	16.0	1.1	0.4 - 3.0
Diabetes					
No	190	30	15.8		
Yes	15	2	13.3	0.8	0.2 - 3.8
Congestive heart failure					
No	183	27	14.8		
Yes	22	5	22.7	1.7	0.6 - 5.0
Any prior tumor[a]					
No	175	23	13.1		
Yes	30	9	30.0	2.8	1.2 - 6.9
Coronary artery disease					
No	158	23	14.6		
Yes	47	9	19.1	1.4	0.6 - 3.3
Comorbidity grade[b]					
0	48	2	4.2		
1 - 2	107	15	14.0	3.8	0.8 - 17.1
3 - 4	47	14	29.8	9.8	2.1 - 45.9
≥ 5	3	1	33.3	11.5	0.7 - 186.6
Chronic pulmonary disease					
No	129	14	10.9		
Yes	76	18	23.7	2.5	1.2 - 5.5
FEV_1%[c]					
< 70%	44	9	20.5		
≥ 70%	150	20	13.3	0.6	0.3 - 1.4
Pathological TNM stage					
IA	76	11	14.5		
IB	68	11	16.2	1.1	0.5 - 2.8
IIA	9	2	25.0	2.0	0.4 - 11.0
IIB	27	4	14.8	1.0	0.3 - 3.5
IIIA	20	3	15.0	1.0	0.3 - 4.2
IIIB	2	0	0	-[d]	-
IV	4	1	25.0	2.0	0.2 - 20.7

[a] Within 5 years of diagnosis, except basal cell skin carcinoma; [b] Also significant in the multivariate analysis; [c] FEV_1% was unknown in 11 patients; [d] not defined; OR = odds ratio; CI = confidence interval; FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

Table 5. Influence of comorbidity grade on the length of hospital stay (LOS)[a]

Comorbidity grade	Number of patients	Mean LOS (days)	Range
0	48	11.2	6 - 23
1 - 2	107	14.7	3 - 116
3 - 4	47	16.9	2 - 77
≥ 5	3	16.3	10 - 28
Total	205	14.4	2 - 116

[a] p-value = 0.107

COMMENT

Comorbidity in general has been considered to be an important prognostic factor in patients operated for cancer [11]. The presence of clinical data (symptoms) and comorbidity have been repeatedly evaluated as prognostic factors [12-14]. Battafarano et al. [15] concluded in a prospective study of 451 patients who underwent surgical resection for pathological stage I NSCLC that comorbidity has a significant impact on survival. Even in the presence of another tumor with a theoretical good prognosis (for example squamous cell cancer of the skin), survival decreases in patients with lung cancer [16].

In this series of patients with NSCLC the 76% prevalence of comorbidity is comparable with the comorbidity rate reported in other series of lung cancer (range, 68.5% to 73%) [15, 17].

In general, the reported morbidity after operative treatment of lung cancer is high, because the majority of patients are elderly and most have chronic obstructive pulmonary disease. Diffusing capacity of the lung for carbon monoxide, predictive postoperative FEV1% and VO2max are respiratory function tests which can be used to assess these patients and which have been proven to be a predictive value for postoperative outcome [18]. A few reports [19-23] have shown, however, that advanced age is not necessarily associated with a higher morbidity. They reported an overall mortality rate from 1.2% to 7.4% in patients older than 70 years and concluded that no patients should be denied thoracotomy because of age alone. In the present study age was also not a significant risk factor for major complications.

Pneumonectomy is considered to be a predictor of postoperative complications, in particular mortality [10]. However in this series only two patients died after pneumonectomy. In the logistic regression analysis the odds ratio of pneumonectomy for major complications was 1.8, which points to a predictive effect of type of resection on major complications. However, probably due to the small number of patients, the odds ratio was not significant. This finding underscores our conclusion that in many instances it is better to use a morbidity index score than a single variable to predict postoperative outcome.

The CCI has been found to be useful in some reports. Beddhu et al. [24] used the CCI in a retrospective study of peritoneal dialysis and haemodialysis patients and found that the CCI was a strong predictor. Fried et al. [25] also found that the CCI was a strong predictor of mortality in peritoneal dialysis patients. Singh and colleagues [26] reported in a multi-institutional study of patients with head and neck cancer that the CCI was a valid prognostic indicator. In this study we also found that the CCI is the best predictor of major complications of surgery. Most of

the factors necessary for the CCI are standard clinical variables. These factors are easy to find in clinical records. In our retrospective study only data on FEV_1% were incomplete in 5% of the cases.

In summary, we conclude that the CCI is a strong predictor of major complications of surgery in NSCLC patients and is a better predictor than individual risk factors. The index is easy to use and could have widespread applicability.

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CHAPTER 6

Charlson comorbidity index as a predictor of long-term outcome after surgery for nonsmall cell lung cancer

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ABSTRACT

Objective: To evaluate the impact of the Charlson comorbidity index on long-term survival in nonsmall cell lung cancer surgery and determine whether this index is a better predictor of long-term survival than individual comorbid conditions.

Methods: From January 1989 to December 2001, 433 (340 men, 93 women) consecutive curative resections for nonsmall cell lung cancer were performed. Each patient was preoperatively assessed according to the Charlson comorbidity index. Survival curves were estimated by the Kaplan-Meier method. Risk factors for overall and disease free survival were determined by univariate and multivariate Cox regression analysis.

Results: The patients ranged in age from 37 to 82 years, with a mean age of 65 years. Hospital mortality was 3.7%. Five-year overall and disease free survival was 45% and 43%, respectively. Among patients with Charlson comorbidity grade 0, five-year overall survival was 52%, among patients with Charlson comorbidity grade 1 - 2 it was 48%, and among patients with Charlson comorbidity grade ≥ 3 it was 28%. Univariate analysis showed that male gender, age, congestive heart failure, chronic pulmonary disease, Charlson comorbidity index, clinical stage, pathological stage, and type of resection were significantly associated with an impaired survival. Multivariate analysis showed that age (relative risk, 1.02; 95% confidence interval, 1.01 to 1.03), Charlson comorbidity grade 1 - 2 (relative risk, 1.4; 95% confidence interval, 1.0 to 1.8), Charlson comorbidity grade ≥ 3 (relative risk, 2.2; 95% confidence interval, 1.5 to 3.1), bilobectomy (relative risk, 1.7; 95% confidence interval, 1.2 to 2.5), pneumonectomy (relative risk, 1.5; 95% confidence interval, 1.1 to 2.0), pathological stage IB (relative risk, 1.5; 95% confidence interval, 1.1 to 2.2), IIB (relative risk, 1.9; 95% confidence interval, 1.2 to 3.0), IIIA (relative risk, 1.9; 95% confidence interval, 1.1 to 3.1), IIIB (relative risk, 2.8; 95% confidence interval, 1.2 to 6.8), and IV (relative risk, 12.4; 95% confidence interval, 3.2 to 48.2), were associated with an impaired survival.

Conclusions: The Charlson comorbidity index is a better predictor of survival than individual comorbid conditions in nonsmall cell lung cancer surgery. We recommend the use of a validated comorbidity index in the selection of patients for NSCLC surgery.

INTRODUCTION

Although pulmonary resection is recognized as the treatment of choice for early-stage nonsmall cell lung cancer (NSCLC), actuarial five-year survival following curative resection is disappointing, ranging from 67% to 38% in pathological stages IA to IIB [1]. Survival is not only dependent on pathological stage but also on other factors, such as comorbidity. The presence of comorbidity has been evaluated repeatedly as an important prognostic factor for survival in patients with NSCLC [2-4]. As the mean age in patients with NSCLC increases due to the increased life expectancy, the proportion of patients with serious comorbidity who are considered for surgical resection also increases [5, 6]. For major postoperative complications the Charlson comorbidity index (CCI) proved to be a prognostic marker as was previously validated by us in patients operated on for primary NSCLC [7]. However, this comorbidity index has not been validated yet for prognostic impact on long-term survival in NSCLC surgery.

Therefore, the objective of this retrospective study was to evaluate the impact of the CCI on long-term survival in NSCLC surgery and determine whether this index is a better predictor of long-term survival than individual comorbid conditions.

MATERIAL AND METHODS

The medical records of 433 consecutive patients who underwent curative resection for primary NSCLC at the Department of Cardio-Thoracic Surgery of the Erasmus MC Rotterdam between January 1, 1989, and December 31, 2001 were reviewed. Patients were followed with regular visits to the outpatient clinic. Civil administrations were consulted to assess late mortality. Follow-up was completed in all patients through August 2004. Median follow-up time was 4.3 ± 0.4 years (range, 0.0 to 14.9 years). Overall survival time was defined as the difference between the date of surgery and the date of last follow-up. Disease free survival time was defined as the difference between the date of surgery and the date of local or distant recurrence of disease or the date of last follow-up in case of no recurrence. Hospital mortality was defined as death occurring within 30 days of surgery or any death later during the same postoperative hospital stay.

In all patients preoperative diagnostic workup included a complete medical history, physical examination, plain chest radiography, electrocardiography, routine laboratory tests, lung function tests and computed tomography of the chest and upper abdomen. Additional staging procedures, i.e., mediastinoscopy, liver, bone and brain scans were selectively performed to aid in treatment planning according to best clinical practice at the time of presentation. Each patient was assessed preoperatively according to the CCI, and was categorized in one of the four comorbidity grades: 0, 1 to 2, 3 to 4 and 5 or more [7, 8].

Histological typing occurred according to The World Health Organization Histological Typing of Lung Tumours [9]. Clinical and pathologic staging of the patients occurred according to the international TNM classification for lung cancer [1].

The following risk factors for overall and disease free survival were evaluated: sex, age, smoking, type of resection, histological cell type, forced expiratory volume in 1 second (FEV_1; unknown in 21 patients), clinical stage, pathological stage, and the CCI as well as the most common comorbidities of the CCI.

Statistical Analysis

Discrete variables are displayed as proportions, continuous variables as means ± standard deviations unless specified otherwise. The χ^2 or Fisher exact test was used to analyze the categorical data. Continuous variables were analyzed using the Student t-test. Survival curves were estimated by the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard analysis within different time intervals determined risk factors for survival. The Cox proportional multivariate analyses were performed with a stepwise forward regression model in which each

variable with a p-value of less than 0.20 in the univariate analysis was entered in the model. Relative risks are reported with 95% confidence intervals. All data analysis was performed with SPSS for Windows (release 12.0; SPSS Inc, Chicago, Ill).

RESULTS

Of the 433 patients included in this analysis, 340 (79%) were men and 93 (21%) women. The mean age at time of diagnosis was 65 ± 9 years (range, 37 to 82 years). The patient's preoperative characteristics are outlined in Table 1. The CCI and the comorbid conditions are presented in Table 2. The types of procedures performed consisted of a wedge resection in 14 (3%) patients, a lobectomy in 244 (56%) patients, a bilobectomy in 45 (10%) patients, and a pneumonectomy in 130 (30%) patients. Tumors were classified histologically as squamous cell carcinoma (215; 50%), adenocarcinoma (143; 33%), large cell carcinoma (55; 13%), and bronchoalveolar cell carcinoma (20; 5%). The patient's operative demographics are listed in Table 3. Surgical-pathologic upstaging was observed in 31% (133/433) of the patients.

Hospital mortality was 3.7% (16 of 433 patients). Operations in these patients were wedge resection (1), lobectomy (4), bilobectomy (3), and pneumonectomy (8). Hospital mortality rate was significantly ($p = 0.03$) higher after pneumonectomy compared with lesser resections.

One, two and five-year overall survival was 81% (95% confidence interval, 77 to 85), 66% (95% confidence interval, 62 to 71), and 45% (95% confidence interval, 40 to 50), respectively. One, two, and five-year disease free survival was 74% (95% confidence interval, 70 to 78), 61% (95% confidence interval, 56 to 65), and 43% (95% confidence interval, 38 to 48), respectively. Among patients with Charlson comorbidity grade 0, five-year overall survival was 52% (95% confidence interval, 43 to 61), among patients with Charlson comorbidity grade 1 - 2 it was 48% (95% confidence interval, 39 to 57), and among patients with Charlson comorbidity grade ≥ 3 it was 28% (95% confidence interval, 18 to 38) (Fig. 1).

When evaluating risk factors for overall survival with the Cox proportional hazards analysis, in univariate analysis male gender, age, congestive heart failure, chronic pulmonary disease, CCI, clinical stage, pathological stage, and type of resection were significantly associated with an impaired survival (Table 4). In multivariate analysis, age (relative risk, 1.02; 95% confidence interval, 1.01 to 1.03), Charlson comorbidity grade 1 - 2 (relative risk, 1.4; 95% confidence interval, 1.0 to 1.8), Charlson comorbidity grade ≥ 3 (relative risk, 2.2; 95% confidence interval, 1.5 to 3.1), bilobectomy (relative risk, 1.7; 95% confidence interval, 1.2 to 2.5), pneumonectomy (relative risk, 1.5; 95% confidence interval, 1.1 to 2.0), pathological stage IB (relative risk, 1.5; 95% confidence interval, 1.1 to 2.2), IIB (relative risk, 1.9; 95% confidence interval, 1.2 to 3.0), IIIA (relative risk, 1.9; 95% confidence interval, 1.1 to 3.1), IIIB (relative risk, 2.8; 95% confidence interval, 1.2 to 6.8), and

IV (relative risk, 12.4; 95% confidence interval, 3.2 to 48.2), were associated with an impaired overall survival (Table 4). For disease free survival the same risk factors were identified in the multivariate analysis.

Table 1. Patient characteristics

Characteristic	Number of patients	%
Sex		
Male	340	79
Female	93	21
Age (mean ± SD in years)	65 ± 9	
Follow-up (median ± SD in years)	4.3 ± 0.4	
Smoking habits		
Nonsmoker	57	13
Current or former smoker	376	87
FEV_1%[a]		
< 70	115	28
≥ 70	297	72
Charlson comorbidity index		
0	131	30
1 - 2	220	51
3 - 4	75	17
≥ 5	7	2
Clinical stage		
IA	202	47
IB	185	43
IIA	5	1
IIB	22	5
IIIA	13	3
IIIB	3	1
IV	3	1

[a] FEV_1% was unknown in 21 patients

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

SD = standard deviation

Table 2. Charlson comorbidity index and prevalence of comorbid conditions

Score	Condition	Number of patients	%
1	Coronary artery disease[a]	90	21
	Congestive heart failure	30	7
	Chronic pulmonary disease	126	29
	Peptic ulcer disease	46	11
	Peripheral vascular disease	86	20
	Mild liver disease	1	0
	Cerebrovascular disease	34	8
	Connective tissue disease	7	2
	Diabetes	24	6
	Dementia	2	1
2	Hemiplegia	2	1
	Moderate to severe renal disease	2	1
	Diabetes with end organ damage	2	1
	Any prior tumor (within 5 years of diagnosis)[b]	60	14
	Leukemia	5	1
	Lymphoma	4	1
3	Moderate to severe liver disease	3	1
6	Metastatic solid tumor	0	0
	AIDS (not only HIV positive)	0	0

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris

[b] Except basal cell skin carcinoma

AIDS = acquired immunodeficiency syndrome

HIV = human immunodeficiency virus

Table 3. Operative characteristics

Characteristic	Number of patients	%
Type of resection		
Wedge resection	14	3
Lobectomy	244	56
Bilobectomy	45	10
Pneumonectomy	130	30
Histology		
Squamous cell carcinoma	215	50
Adenocarcinoma	143	33
Large cell carcinoma	55	13
Bronchoalveolar cell carcinoma	20	5
Pathological stage		
0	1	0
IA	153	35
IB	154	36
IIA	21	5
IIB	52	12
IIIA	36	8
IIIB	7	2
IV	9	2

Figure 1. Overall survival curves after curative resection for nonsmall cell lung cancer according to the Charlson comorbidity index (CCI)

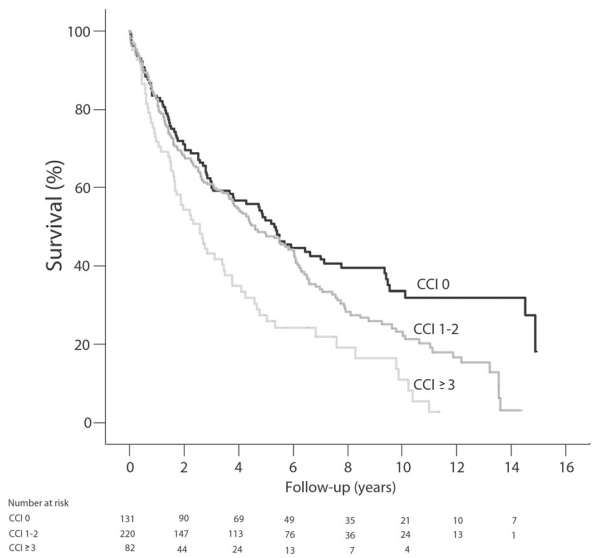

Table 4. Univariate and multivariate Cox proportional hazard analysis of survival

Variable	Number of patients	Univariate		Multivariate	
		RR	95% CI	RR	95% CI
Male sex	340	1.6	1.2 - 2.2		
Age	433	1.02	1.01 - 1.03	1.02	1.01 - 1.03
Current or former smoker	376	0.9	0.6 - 1.2		
FEV_1% ≤ 70[a]	115	1.2	0.9 - 1.6		
Wedge resection	14	2.2	1.3 - 3.9		
Bilobectomy	45	1.7	1.2 - 2.4	1.7	1.2 - 2.5
Pneumonectomy	130	1.5	1.2 - 1.9	1.5	1.1 - 2.0
Squamous cell carcinoma	215	1.1	0.9 - 1.4		
Coronary artery disease[b]	90	1.2	0.9 - 1.6		
Congestive heart failure	30	1.8	1.2 - 2.7		
Chronic pulmonary disease	126	1.5	1.1 - 1.9		
Peptic ulcer disease	46	1.1	0.8 - 1.6		
Peripheral vascular disease	86	1.2	0.9 - 1.5		
Cerebrovascular disease	34	1.2	0.8 - 1.7		
Diabetes	24	0.9	0.6 - 1.5		
Any prior tumor (within 5 years of diagnosis)[c]	60	1.3	0.9 - 1.8		
Charlson comorbidity index					
1 - 2	220	1.3	1.0 - 1.8	1.4	1.0 - 1.8
≥ 3	82	2.1	1.5 - 2.9	2.2	1.5 - 3.1
Clinical stage					
IB	185	1.3	1.0 - 1.7		
IIA	5	3.0	1.2 - 7.5		
IIB	22	2.3	1.4 - 3.8		
IIIA	13	2.1	1.1 - 3.8		
IIIB	3	1.5	0.4 - 6.1		
IV	3	15.7	4.8 - 50.9		
Pathological stage					
IB	154	1.5	1.1 - 1.9	1.5	1.1 - 2.2
IIA	21	1.0	0.5 - 1.7	0.7	0.4 - 1.4
IIB	52	1.7	1.2 - 2.4	1.9	1.2 - 3.0
IIIA	36	2.1	1.3 - 3.2	1.9	1.1 - 3.1
IIIB	7	2.6	1.1 - 5.8	2.8	1.2 - 6.8
IV	9	10.2	5.0 - 20.7	12.4	3.2 - 48.2

[a] FEV_1% was unknown in 21 patients

[b] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris

[c] Except basal cell skin carcinoma

RR = relative risk

CI = confidence interval

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

COMMENT

Not unexpectedly, pathological stage proved to be the most important determinant of long-term survival in this study. Surgical-pathological upstaging was seen in 31% of the patients. Obviously clinical staging with current imaging techniques has its shortcomings indicating the need for further improvement of preoperative staging techniques. Besides tumor stage, in patients with NSCLC comorbid conditions also play a significant role in clinical practice treatment decisions and patients whose outcomes are judged unfavourable because of serious comorbidity are usually selected for non-surgical management. Many reports in the literature have shown the prognostic impact of comorbidity on survival in NSCLC surgery [2, 4, 10, 11].

Summarizing a multidimensional phenomenon such as comorbidity is not an easy matter, and currently no standard method exists for assessing comorbidities collectively in NSCLC surgery patients. In this study the CCI was used to assess comorbidity. This comorbidity index has been used in several clinical studies [12-14] and has previously been validated by us for prediction of major postoperative complications after NSCLC surgery [7]. In this analysis comorbidity severity had a significant negative impact on long-term survival when comorbidity was assessed according to the CCI. After controlling for age, gender, type of resection, clinical stage, pathological stage, and individual comorbid conditions in a multivariate analysis, the relative risk of impaired survival as a function of the CCI was 1.4 times higher among patients with Charlson comorbidity grade 1 - 2, and 2.2 times higher among patients with Charlson comorbidity grade ≥ 3 compared with patients with no comorbidity. This indicates that the CCI is a better predictor of survival than individual comorbid conditions and validates the ability of the CCI to stratify comorbidity severity in NSCLC surgery patients.

The management of patients with NSCLC remains a significant challenge. Comorbidity is common in NSCLC patients and has a major impact on their survival, independent of other factors. Our study shows the importance of the CCI as an independent prognostic factor for impaired survival. This comorbidity index is a better predictor of long-term survival than individual comorbid conditions. We recommend the use of a validated comorbidity index in the selection of patients for NSCLC surgery.

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CHAPTER 7

Lung resection for nonsmall cell lung cancer in patients older than 70: mortality, morbidity, and late survival compared with the general population

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ABSTRACT

Background: Operative mortality and morbidity in elderly patients operated on for nonsmall cell lung cancer are acceptable. However, risk factors for hospital mortality and the benefits for the patients in the long-term are insufficiently defined, and survival compared with the general population is not known.

Methods: From January 1989 to October 2001, 126 consecutive patients older than 70 years of age underwent resection for nonsmall cell lung cancer. Each patient was scaled according to the Charlson comorbidity index. Postoperative events were divided into minor and major complications. Risk factors for complications and long-term survival were assessed by univariate and multivariate logistic regression analysis. Survival was compared with the yearly-expected survival rates of the general population.

Results: The hospital mortality was 3.2%. Minor complications occurred in 71 (57%) patients, major complications, in 16 (13%) patients. No risk factor was predictive for major complications. However, a Charlson comorbidity grade of 3 - 4 was predictive for major complications (odds ratio, 12.6; 95% confidence interval, 1.5 to 108.6). Our study showed a 5- and 10-year survival rate of 37% (95% confidence interval, 23 to 51) and 15% (95% confidence interval, 8 to 22). Smoking (odds ratio, 2.3), chronic obstructive pulmonary disease (odds ratio, 2.1) and pathologic stage IIIA (odds ratio, 2.2) or IIIB (odds ratio, 11.9) were risk factors for long-term survival. The observed survival was lower than the expected survival, but the difference decreased with increasing time after pulmonary resection.

Conclusions: Pulmonary resection for nonsmall cell lung cancer in patients older than 70 years shows acceptable morbidity and mortality. The Charlson index is a better predictor of complications than individual risk factors. In time survival is no longer correlated with the disease but follows the same pattern as the general population.

INTRODUCTION

The incidence of lung cancer in men in the Netherlands has decreased from 109 per 100,000 per year in 1989 to 1991 to 93 in 1995 to 1997, whereas in women the incidence has increased from 18 to 23 per 100,000 per year. Lung cancer mortality in men has decreased from 106 to 91 per 100,000 per year and has increased in women from 15 to 20 per 100,000 per year [1]. There is a general trend worldwide of an increasing lung cancer incidence of the elderly population as well as the proportion of patients with serious comorbidity.

Resection still represents the main curative treatment modality for patients with nonsmall cell lung cancer (NSCLC). The risk of operation is higher in patients with concomitant respiratory or cardiac disease [2-4]. Recent data suggest that the operative mortality rate in the elderly is acceptable [2, 5-9]. However, the benefits for the patients in the long-term are less well defined, and survival compared with the general population is not known.

The aim of this study is to assess the early morbidity and mortality and the late survival of elderly patients operated on for NSCLC, to identify risk factors, and to compare the long-term results with the survival of the general population stratified according to age and sex.

MATERIAL AND METHODS

Data collection

Clinical data were obtained from the medical records. All electrocardiograms were evaluated for signs of myocardial infarction, left ventricular hypertrophy and arrhythmias. Follow-up was completed in all patients through February 2002. Patients were followed up with regular visits to the outpatient clinic. Civil administrations provided the date of death; the cause of death was obtained from the general practitioner in case of out-of-hospital death. The following risk factors were evaluated: sex, type of surgery, histologic cell type, pathologic stage, smoking habits, diabetes, coronary artery disease, forced expiratory volume in 1 second expressed as a percent of predicted (FEV_1%, unknown in 17 patients), and chronic obstructive pulmonary disease. All patients who used oral bronchodilatators were considered as having chronic obstructive pulmonary disease. Each patient was scaled on the Charlson comorbidity index (CCI) [10], a weighted index of 19 conditions found to significantly influence survival in cancer patients and given a score based on the relative mortality risk. The score can be divided into four comorbidity grades: 0, 1 - 2, 3 - 4, and 5 or more. Patients were considered to have a comorbid condition if a listed disorder was mentioned in the records or if the patient was treated for it. Cardiac disease is associated with a higher risk of operation in patients with lung cancer [2-4, 11, 12]. Therefore, we modified the CCI by scoring all forms of coronary artery disease (myocardial infarction, angina, coronary artery bypass grafting, and percutaneous transluminal coronary angioplasty) with a value of 1.

Histologic typing occurred according to The World Health Organization Histological Typing of Lung Tumours [13]. The postsurgical (pathologic) stages of the patients were determined according to the international TNM classification for lung cancer [14].

Hospital mortality included all deaths during the first 30 days, or during the postoperative hospital stay. Complications were classified as minor (non-life-threatening) or major (potentially life-threatening), occurring within 30 days of surgery, or within 3 months in case of empyema or bronchopleural fistula [15]. Patients having both minor and major postoperative complications were coded as having major complications only, although the nature of the minor complication was also recorded.

Patients

Between January 1, 1989, and October 31, 2001, 126 patients (101 men, 25

women), who were 70 years or older, underwent pulmonary resection for NSCLC at the Department of Cardio-Thoracic Surgery of the Erasmus Medical Center, Rotterdam. Three men and 2 women underwent surgery at different time intervals for a second tumor or a tumor recurrence. One woman left the country and was lost to follow-up; 125 patients who were operated on were included in this study. The mean age at time of surgery was 74 years (range, 70 to 82 years); 7 patients were octogenarians.

Data analysis

Univariate logistic regression analysis was used to discriminate independent risk factors for major complications after surgical resection. Long-term survival curve was estimated by the Kaplan-Meier method; 5 and 10-year survival are expressed as percentage ± 95% confidence intervals (CI). Cox proportional hazard analysis was used to determine risk factors for long-term survival. Both the logistic and Cox proportional multivariate analyses were performed with a stepwise forward regression model in which each variable with a p value of less than 0.1 in the univariate analysis was entered in the model.

Yearly expected survival rates for the 125 patients were calculated from age-specific and sex-specific mortality data of the Dutch general population. The age was updated annually, correcting for withdrawals during follow-up. Poisson regression was used to test whether there was a difference between the observed (including hospital deaths) and expected survival rates, and a rate ratio (or relative risk) was estimated. To test whether this difference changed with time since pulmonary resection, time was entered into the Poisson model as a linear continuous variable. The resulting estimate has the interpretation of decrease of the rate ratio per additional year of follow-up.

RESULTS

A history of myocardial infarction was present in 22% of this study group. None of these patients underwent lung resection within 6 months after infarction. Six patients had undergone a prior coronary artery bypass surgery; 2 patients underwent coronary artery bypass surgery and lobectomy in one session. Left ventricular hypertrophy was diagnosed in 16% and atrial fibrillation in 5% (Table 1).

Preoperative radiation therapy was not given to any patient. Preoperative chemotherapy was given in 2 cases. Postoperative radiation therapy was given in 14 patients, one of whom received chemotherapy preoperatively. None of the patients received postoperative chemotherapy.

The prevalence of comorbid conditions of the CCI is listed in Table 2. The CCI was 0 in 25 patients, 1 in 42, 2 in 29, 3 in 24, 4 in 5, and 5 or more in none (Table 1). Operative characteristics are listed in Table 3.

Table 1. Preoperative clinical characteristics

Characteristic	Number of patients	%
Sex		
Male	101	81
Female	24	19
Coronary artery disease	41	33
Left ventriclular hypertrophy	20	16
Atrial fibrillation	6	5
COPD	10	8
Smoking (current or former)	109	87
Weight loss	24	19
Diabetes	10	8
Hypertension	36	29
Vascular disease	34	27
Chronic renal failure	1	1
History of CVA / TIA	14	11
Obesity	2	2
Occupational exposure	21	17
Previous lobectomy	6	5
Comorbidity grade		
0	25	20
1 - 2	71	57
3 - 4	29	23
≥ 5	0	0

COPD = chronic obstructive pulmonary disease
CVA = cerebrovascular disease
TIA = transient ischemic attack

Table 2. Charlson comorbidity index and prevalence of comorbid conditions among 125 patients operated on for nonsmall cell lung cancer

Score	Condition	Number of patients	%
1	Coronary artery disease[a]	41	33
	Congestive heart failure	9	7
	Chronic pulmonary disease	35	28
	Peptic ulcer disease	8	6
	Peripheral vascular disease	32	26
	Mild liver disease	0	0
	Cerebrovascular disease	14	11
	Connective tissue disease	2	2
	Diabetes	10	8
	Dementia	0	0
2	Hemiplegia	0	0
	Moderate to severe renal disease	1	1
	Diabetes with end-organ damage	0	0
	Any prior tumor (within 5 years of diagnosis)[b]	19	15
	Leukemia	1	1
	Lymphoma	0	0
3	Moderate to severe liver disease	0	0
6	Metastatic solid tumor	0	0
	AIDS (not only HIV positive)	0	0

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and angina pectoris

[b] Except basal cell skin carcinoma

AIDS = acquired immunodeficiency syndrome

HIV = human immunodeficiency virus

Table 3. Operative characteristics

Characteristic	Number of patients	%
Type of resection		
Lobectomy	77	62
Bilobectomy	17	14
Pneumonectomy	23	18
Wedge resection	8	6
Pathological stage		
0	1	1
IA	39	31
IB	56	45
IIA	2	2
IIB	7	6
IIIA	14	11
IIIB	3	2
IV	1	1
Unknown	2	2
Histologic cell type		
Squamous cell carcinoma	59	47
Adenocarcinoma	38	30
Bronchoalveolar cell carcinoma	5	4
Large cell carcinoma	18	14
Carcinoid	4	3
Non-mucous carcinoma	1	1

Hospital mortality

Four patients (3.2%) died within 30 days (day 2, 17, and 26) of operation or in the same postoperative hospital stay (day 77). The causes of death were empyema, postpneumonectomy pulmonary edema, inferior myocardial infarction, and cardiac arrest. The mortality rate for lobectomy was 2.6% (2 of 77 patients), bilobectomy 11.8% (2 of 17 patients), and pneumonectomy 0% (0 of 23 patients). The number of deaths was too low to identify any significant risk factors.

Complications

Complications occurred in 58%. Minor complications occurred in 71 patients (57%). The most common complications were arrhythmia (31%) and air leak lasting more than 5 days (21%). Major complications occurred in 16 patients (13%; Table 4). None of the female patients experienced a major complication. This study

showed a postoperative myocardial infarction rate of 1.6% (2 cases). In one of the 27 cases with a history of myocardial infarction, a reinfarction was noted (reinfarction rate of 3.7%). The second case of infarction postoperatively led to death two days after surgery.

The type of resection was not predictive for major complications. There was no significant difference between pneumonectomy and other resections. Smoking, diabetes, coronary artery disease, squamous cell carcinoma, FEV_1%, and chronic obstructive pulmonary disease were also not significantly predictive for major complications. However, a Charlson comorbidity grade of 3 - 4 was a significant risk factor for major complications (odds ratio, 12.6; 95% confidence interval, 1.5 to 108.6; Table 5).

Table 4. Incidence of complications

Complication	Number of patients	%
Minor complications	71	57
Supraventricular arrhythmia	38	30
Air leak > 5 days	26	21
Transfusion	19	15
Atelectasis	9	7
Infection[a]	6	5
Paresis of recurrent nerve	3	2
Major complications	16	13
Empyema	6	5
Pneumonia	5	4
Myocardial infarction	2	2
Bronchopleural fistula	2	2
ARDS	2	2
Ventricular arrhythmia	1	1
Ventilatory support > 72h	1	1
Pulmonary edema	1	1
Cardiac failure	1	1
Renal failure	1	1
CVA / TIA	0	0

[a] Included wound sepsis and infection of the bronchial tree

ARDS = adult respiratory distress syndrome

CVA = cerebrovascular disease

TIA = transient ischemic attack

Table 5. Risk factors related to major complications in univariate logistic regression

Risk factor	Number of patients	Major complications		Univariate	
		n	%	OR	95% CI
Sex					
Female	24	0	0		
Male	101	16	16	…[a]	
Pneumonectomy					
No	102	13	13	1.0	
Yes	23	3	13	1.0	0.3 - 3.9
Squamous cell carcinoma					
No	66	8	12	1.0	
Yes	59	8	14	1.1	0.4 - 3.2
Smoking habits					
Nonsmoker	16	1	6	1.0	
Current or former smoker	109	15	14	2.4	0.3 - 19.5
Diabetes					
No	115	15	13	1.0	
Yes	10	1	10	0.7	0.1 - 6.3
Coronary artery disease					
No	84	10	12	1.0	
Yes	41	6	15	1.3	0.4 - 7.8
COPD					
No	115	15	13	1.0	
Yes	10	1	10	0.7	0.9 - 6.3
FEV_1%[b]					
≤ 70	29	7	35	1.0	
> 70	79	8	10	0.4	0.1 - 1.1
Comorbidity grade					
0	25	1	4	1.0	
1 - 2	71	5	7	1.8	0.2 - 16.4
3 - 4	29	10	35	12.6	1.5 - 108.6
≥ 5	0	0	0		

[a] Could not be analyzed because none of the female patients had major complications

[b] FEV_1% was unknown in 17 patients

OR = odds ratio

CI = confidence interval

COPD = chronic obstructive pulmonary disease

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

Long-term survival

Our study showed a 5-year survival rate of 37% (95% confidence interval, 23 to 51); the 10-year survival was 15% (95% confidence interval, 8 to 22). The median survival time was 3.8 years. In the multivariate analysis smoking (odds ratio, 2.6; 95% confidence interval, 1.1 to 6.2), chronic obstructive pulmonary disease (odds ratio, 2.7; 95% confidence interval, 1.7 to 5.9), and pathologic stage (stage IIIA, odds ratio, 2.9; 95% confidence interval, 1.4 to 6.2; stage IIIB odds ratio, 15.3; 95% confidence interval, 4.2 to 55.3) were significant risk factors for overall survival. With respect to type of resection, histologic cell type, diabetes, sex, coronary artery disease, FEV_1%, and CCI, no significant difference was noted (Table 6).

The most common cause of death was lung cancer (47 patients; 57%). Cardiac disease was the cause in 19 patients (23%), ARDS in 2 (2%), and other causes in 8 patients (10%). The cause of death was unknown in 6 patients (5%).

To determine the difference in survival between patients operated on for NSCLC and the general population we compared the survival of the present series (observed) to the expected survival of the elderly general population (70 years or older) in the Netherlands (Fig. 1). The observed survival was significantly ($p < 0.001$) lower than the expected survival, but the difference significantly ($p = 0.01$) decreased with increasing time after pulmonary resection.

Table 6. Univariate and multivariate Cox proportional hazard analysis of long-term survival (postoperative deaths excluded)

Factor	OR	95% CI
Female sex	0.6	0.3 - 1.1
Pneumonectomy	1.6	0.9 - 2.9
Squamous cell carcinoma	1.1	0.7 - 1.8
Current or former smoker[a]	2.3	1.0 - 5.4
Diabetes	0.5	0.2 - 1.3
Coronary artery disease	0.9	0.6 - 1.6
COPD[a]	2.1	1.0 - 4.4
Pathologic stage		
II	2.0	0.9 - 4.8
IIIA[a]	2.2	1.1 - 4.5
IIIB[a]	11.9	3.3 - 42.4
IV	6.4	0.9 - 49.0
FEV_1% ≤ 70[b]	1.2	0.7 - 2.0
Comorbidity grade		
1 - 2	0.9	0.5 - 1.6
3 - 4	1.4	0.7 - 2.6

[a] Also significant in the multivariate analysis

[b] FEV_1% was unknown in 17 patients

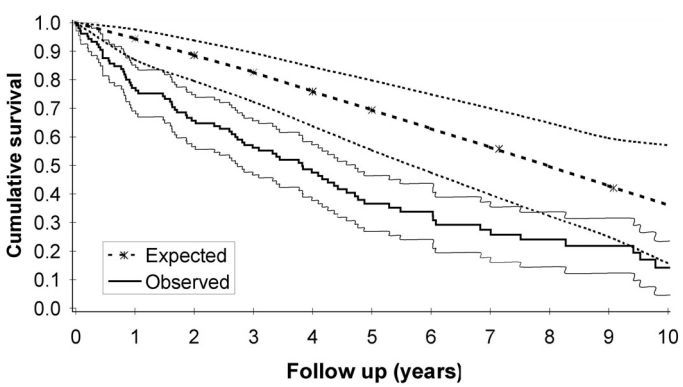
OR = odds ratio

CI = confidence interval

COPD = chronic obstructive pulmonary disease

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

Figure 1. Expected versus observed survival, with 95% confidence limits (postoperative deaths included)



COMMENT

The morbidity and mortality after pulmonary resection for NSCLC are significant. The most frequently reported complications are arrhythmia (range, 4% to 14%) and air leak (range, 7% to 11%) [2, 5, 8, 16]. In our series the incidence of arrhythmia was 31% and air leak lasting more than 5 days 21%. The explanation for the higher rate of these two complications in our series is that all arrhythmias were included and not only arrhythmias for which cardioversion was necessary [8, 16]. Our criteria for persistent air leak was 5 days, whereas others reported air leak lasting more than 7 days [8, 16].

Studies indicate that patients undergoing major noncardiac surgery within 3 months of a myocardial infarction have a high reinfarction rate of up to 37%, whereas patients undergoing major noncardiac surgery more than 6 months after a myocardial infarction have a lower reinfarction rate of approximately 5% [17]. Our results (reinfarction rate of 3.7%) confirm that patients can safely undergo a pulmonary resection 6 months after a myocardial infarction. It is not certain that with current interventional cardiology techniques surgery has to be delayed until 6 months after a myocardial infarction.

It is well known that pneumonectomy, especially right-sided pneumonectomy, is associated with higher incidence of complications when compared with limited resections [15, 18], and higher mortality rates in some series can partly be explained by the higher percentage of pneumonectomies [5, 7, 8, 18]. The British Thoracic Society [3] noted that pneumonectomy is associated with a higher mortality risk in the elderly and that age should be a factor in deciding suitability for pneumonectomy. However, Ginsberg and colleagues [6] reported a lower mortality rate in pneumonectomies in elderly patients (5.9%) compared with lobectomies (7.3%). Also in our series no mortality was observed in the pneumonectomy group, and this procedure was also not associated with a higher incidence of major complications. Patient selection is the most suitable reason for this observation. No individual risk factor was significantly predictive for major postoperative complications. However, as we also showed in an earlier series [19], the CCI, a morbidity index score, was correlated with a higher risk for major postoperative complications.

The operative mortality rate of 3.2% is well within the range published by other investigators, who reported a hospital mortality ranging from 1.2% to 12.8% [2, 5-9, 16] (Table 7). It is also comparable to the mortality rates of lung cancer resection in the population younger than 70 years [2, 5, 7, 9, 16]. The low mortality rate of 1.2% in the series of Morandi and colleagues [9] can partly be explained by excluding patients who underwent surgery after neoadjuvant chemotherapy.

Because of the exclusion of these patients, who most probably represent a group with advanced stage NSCLC, a selection bias is introduced.

Pathologic stage has proven to be the most important prognostic factor for long-term survival [2, 8, 9]. In our series pathologic stages IIIA and IIIB were significant risk factors for long-term survival. Pathologic stages II and IV showed a higher risk (positive odds ratio) than stage I, but were not significantly different. This can be attributed to the small number of patients in these two subgroups.

Older age at operation is described as a risk factor with regard to late survival. Our study shows a 5-year survival rate of 37%. Other investigators noted a 5-year survival rate ranging from 28% to 48% [2, 5, 8, 9] (Table 6). Roxburgh and colleagues [7] reported a 4-year survival of 67%. This high survival rate can be attributed to a strict selection protocol and the fact that postoperative deaths were excluded. The difference in survival between the patients and the general Dutch population significantly decreases with time, which indicates that with time survival is no longer correlated with the disease but follows the same pattern as for the general population.

The limitation of this study is that it is retrospective in design, and in 17 patients data on FEV_1%, and in 2, data on pathologic stage, were missing.

We conclude that pulmonary resection for NSCLC is justified in patients older than 70 years; its morbidity, mortality and survival are acceptable. The CCI is a better predictor of major postoperative complications than individual risk factors. Despite a certain frequency of minor and major complications, patients older than 70 years can be operated on with a good survival irrespective of the type and extent of resection. In time, survival is no longer correlated with the disease but follows the same pattern as the general population.

Table 7. Lung cancer resection in the elderly; data from the literature

Author	Year of publication	Number of resections	Mortality (%)				Overall survival
			Overall	Lobectomy		Pneumonectomy	
Ginsberg [6]	1983	453	7.1	7.3	(27/368)	5.9 (5/85)	…
Ishida [2]	1990	185	3.2	3.5	(6/137)	0 (0/11)	48% at 5 years
Roxburg [7]	1991	43	6.9	4.7	(1/21)	9.1 (2/22)	67% at 4 years[a]
Thomas [5]	1993	47	12.8	…		…	30% at 5 years
Morandi [9]	1997	85	1.2	0	(0/58)	9.1 (1/11)	28% at 5 years
Thomas [8]	1998	500	7.4	11.8	(3/34)	8.1 (11/136)	34% at 5 years
Pagni [16]	1998	385	4.2	2.4	(7/293)	12.5 (3/24)	…
Present paper	…	125	3.2	2.6	(2/77)	0 (0/23)	37% at 5 years

[a] Postoperative deaths excluded

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CHAPTER 8

Survival after pathological stage IA nonsmall cell lung cancer: Tumor size matters

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ABSTRACT

Background: This study evaluates prognostic factors for survival in completely resected pathological stage IA nonsmall cell lung cancer with special emphasis on tumor size and assesses tumor recurrence rate by actual and actuarial analysis.

Methods: From January 1989 to December 2001, 130 consecutive resections for pathological stage IA nonsmall cell lung cancer were performed. Pathological tumor size was categorized into 0 to 20 mm and 21 to 30 mm. Each patient was scaled according to the Charlson comorbidity index. The Kaplan-Meier method was used for estimation of actuarial recurrence rate and the cumulative incidence method was used to estimate the actual recurrence rate. Risk factors for overall and disease free survival were determined by univariate and multivariate Cox regression analysis.

Results: Overall 5-year survival for patients with tumors 0 to 20 mm and 21 to 30 mm was 69% and 51%, respectively ($p = 0.038$). Disease-free survival at 5 years was 68% and 48%, respectively ($p = 0.015$). Only 27 patients had a recurrence and 69 patients died during follow-up. The actual 10-year recurrence rate was lower than the actuarial recurrence rate (23% versus 29%). Larger tumor size (relative risk, 1.6; 95% confidence interval, 1.0 to 2.7), Charlson comorbidity index score ≥ 3 (relative risk, 3.7; 95% confidence interval, 1.7 to 8.0), and pneumonectomy (relative risk, 2.1; 95% confidence interval, 1.1 to 4.2) independently predicted adverse outcome.

Conclusions: Tumor size affects survival in resected stage IA nonsmall cell lung cancer. Current definition of stage IA disease should be substaged into two separate stages. In patients with early-stage lung cancer and relatively good prognosis actual recurrence rate is more realistic than the actuarial recurrence rate.

INTRODUCTION

The incidence of nonsmall cell lung cancer (NSCLC) is increasing in the western world and still remains the leading cause of cancer-related mortality for both men and women [1]. Early-stage disease is usually treated surgically when possible and has the best prognosis. Several studies have demonstrated that tumor size is highly prognostic for survival [2, 3]. As a result stage I was subdivided into IA (tumor size ≤ 3 cm, T1N0M0), and IB (tumor size > 3 cm, T2N0M0), in the current staging system in 1997 [4].

In recent years, there has been regained interest for the early screening and detection of lung cancer [5, 6]. However, more frequent chest radiographic screening has not shown to result in reduced lung cancer mortality [7]. With the widespread availability and increasing use of advanced staging techniques, such as spiral computed tomography (CT) scan, lesions smaller than 1 cm can be identified [8]. Nevertheless, if detection and treatment of smaller lesions is not associated with improved survival, early screening of lung cancer using CT scan may not result in reduced lung cancer mortality. Until now there is only limited and conflicting evidence available on the affect of tumor size on prognosis of patients with pathological stage IA NSCLC [2, 9-12].

Recurrence rate is thought to be the lowest in stage IA NSCLC patients. Patients within this stage do not always die as a result of their tumor. Currently, the Kaplan-Meier (actuarial) method [13] is generally used to estimate the recurrence rate in lung cancer patients. However, recently the cumulative incidence (actual) method proved to be a more valid method for estimating the probability of occurrence of a nonfatal time-related event because it estimates the percentage of patients who will actually have an event [14-16].

Therefore, the aims of this study were to evaluate tumor size as a prognostic factor for survival in completely resected pathologic stage IA NSCLC patients, and to estimate the actual versus actuarial risk of tumor recurrence.

MATERIAL AND METHODS

Retrospectively, the medical records of 139 consecutive patients who underwent complete resection for pathologic stage IA primary NSCLC at the Department of Cardio-Thoracic Surgery of the Erasmus MC Rotterdam (between January 1, 1989, and December 31, 2001) have been reviewed. Patients who had a second primary lung tumor were included in this study. Patients were followed with regular visits to the outpatient clinic. Civil administrations were consulted to assess late mortality. Follow-up was completed in all patients through July 2003. Median follow-up was 6.8 years. Overall survival time was defined as the difference between the date of surgery and the date of last follow-up. Disease-free survival was defined as the difference between the date of surgery and the date of local or distant recurrence of disease or the date of last follow-up in case of no recurrence. Hospital mortality was defined as death occurring within 30 days of surgery or any death later during the same postoperative hospital stay.

In all patients diagnostic workup included a complete medical history, physical examination, plain chest radiography, electrocardiography, routine laboratory tests, lung function tests and CT of the chest and upper abdomen. Patients were found to have positive mediastinal lymph nodes if mediastinal lymph nodes on CT scan were more than 10 mm in diameter. Additional staging procedures, i.e., mediastinoscopy, liver, bone and brain scans were selectively performed to aid in treatment planning according to best clinical practice at the time of presentation. Each patient was scaled preoperatively according to the Charlson comorbidity index [17-19]. The index can be divided into four comorbidity grades: 0, 1 to 2, 3 to 4, and 5 or more.

Histologic typing occurred according to The World Health Organization Histologic Typing of Lung Tumours [20]. Pathologic staging of the patients occurred according to the international TNM classification for lung cancer [4]. Staging was based on pathological assessment of the primary tumor and lymph node assessment was carried out with preoperative mediastinoscopy or surgical sampling of bronchopulmonary, hilar and mediastinal lymph nodes. The surgical-pathologic size of the primary tumor was obtained by measuring the greatest diameter of the fresh surgical specimen by the pathologist. Patients were categorized as patients with pathologic tumors of 0 to 20 mm in diameter (n = 75) and 21 to 30 mm in diameter (n = 55).

The following risk factors for overall and disease free survival were evaluated: sex, age, type of surgery, histologic cell type, tumor size, congestive heart failure, coronary artery disease, chronic obstructive pulmonary disease, forced expiratory volume in 1 second (unknown in 9 patients), and Charlson comorbidity index.

Discrete variables are displayed as proportions, continuous variables as means ± standard deviations unless specified otherwise. The χ^2 or Fisher exact test was used to analyze the categorical data. Continuous variables were analyzed using the Student t-test. Long-term survival curves were estimated by the Kaplan-Meier method, and the resulting survival curves were compared with the Breslow test. The Kaplan-Meier method was used for estimation of actuarial recurrence rate and the cumulative incidence method was used to estimate the actual recurrence rate. Univariate and multivariate Cox proportional hazard analysis within different time intervals determined risk factors for long-term survival. The Cox proportional multivariate analyses were performed with a stepwise forward regression model in which each variable with a p-value of less than 0.20 in the univariate analysis was entered in the model. Relative risks are reported with 95% confidence intervals.

RESULTS

Of the 139 patients, 6 patients received neoadjuvant therapy (chemotherapy or radiotherapy) and were excluded from this study. The remaining 133 patients had no positive mediastinal lymph nodes on CT scanning or mediastinal lymph node sampling by mediastinoscopy. Hospital mortality occurred in 3 patients (2.3%) and they were excluded from further analysis. Of the 130 patients enrolled in this analysis 94 (72%) were men and 36 (28%) were women. The mean age was 63 ± 9 years (range, 37 to 81 years old). The types of procedures performed consisted of pneumonectomy (11; 8%), bilobectomy (12; 9%), lobectomy (103; 79%), and wedge resection (4; 3%). Tumors were classified histologically as squamous cell carcinoma (56; 43%), adenocarcinoma (53; 41%), large cell carcinoma (16; 12%), and bronchoalveolar cell carcinoma (5; 4%). The mean pathologic tumor size was 20 ± 6 mm (range, 5 to 30 mm). Tumor size distribution is illustrated in Figure 1. The patient demographics are listed in Table 1.

Mean overall survival of the total study group was 7.7 years and the mean disease-free survival was 7.5 years. Five-year overall survival was 62% (95% confidence interval, 53 to 71) and disease-free survival was 59% (95% confidence interval, 50 to 68). Patients with tumors 0 to 20 mm in diameter had a five-year overall and disease-free survival of 69% (95% confidence interval, 58 to 80) and 68% (95% confidence interval, 57 to 79), respectively. The 5-year overall and disease-free survival for patients with tumors 21 to 30 mm was 51% (95% confidence interval, 37 to 65) and 48% (95% confidence interval, 34 to 62), respectively. The difference in overall and disease-free survival between the two groups was highly significant ($p = 0.038$ and $p = 0.015$, respectively). The Kaplan-Meier overall survival curves are shown in Figure 2.

Of the total study population, 27 patients had a recurrence and 69 patients died during follow-up. The actual recurrence rate within 10 years was lower than the actuarial recurrence rate (23% versus 29%). The 2-year, 5-year, and 10-year actuarial freedom from recurrence was 88%, 81%, and 71%, respectively. Actual analysis yielded slightly higher percentages of freedom from recurrence: 89%, 83%, and 77%, respectively. When comparing patients with tumors 0 to 20 mm and 21 to 30 mm, 5-year actual freedom from recurrence was 88% versus 76%, respectively.

When evaluating risk factors for overall survival with the Cox proportional hazards analysis, in univariate analysis Charlson comorbidity index score ≥ 3, larger tumor size, and pneumonectomy were predictive for impaired survival. In multivariate analysis, larger tumor size (relative risk, 1.6; 95% confidence interval, 1.0 to 2.7), Charlson comorbidity index score ≥ 3 (relative risk, 3.7; 95%

confidence interval, 1.7 to 8.0), and pneumonectomy (relative risk, 2.1; 95% confidence interval, 1.1 to 4.2) were associated with an impaired overall survival (Table 2). When assessing risk factors for disease-free survival, the same three risk factors were identified in the multivariate analysis.

Figure 1. Distribution of pathological tumor size

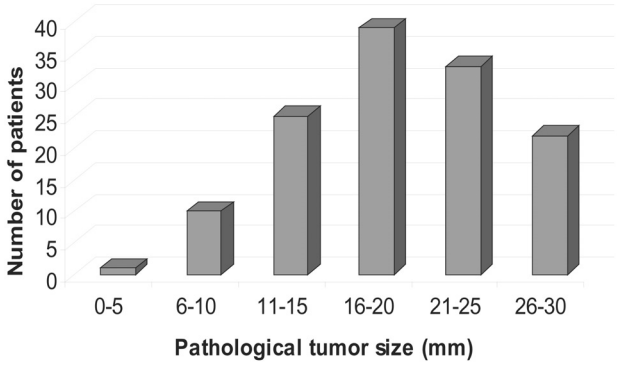

Table 1. Patient characteristics

Characteristic	Number of patients	%
Sex		
Male	94	72
Female	36	28
Age (years)		
≤ 70	97	75
> 70	33	25
Mean ± SD	64 ± 9	
Median follow-up (years)	6.8	
Histology		
Squamous cell carcinoma	56	43
Adenocarcinoma	53	41
Large cell carcinoma	16	12
Bronchoalveolar cell carcinoma	5	4
Tumor size		
0 - 20 mm	75	58
21 - 30 mm	55	42
Smoking habits		
Nonsmoker	28	22
Current or former smoker	108	78
FEV_1%[a]		
< 70	32	26
≥ 70	89	74
Charlson comorbidity index		
0	28	22
1 - 2	71	55
3 - 4	29	22
≥ 5	2	2

[a] FEV_1% was unknown in 9 patients
FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted
SD = standard deviation

Figure 2. Overall survival curves for patients with tumors 0 to 20 mm and 21 to 30 mm in diameter

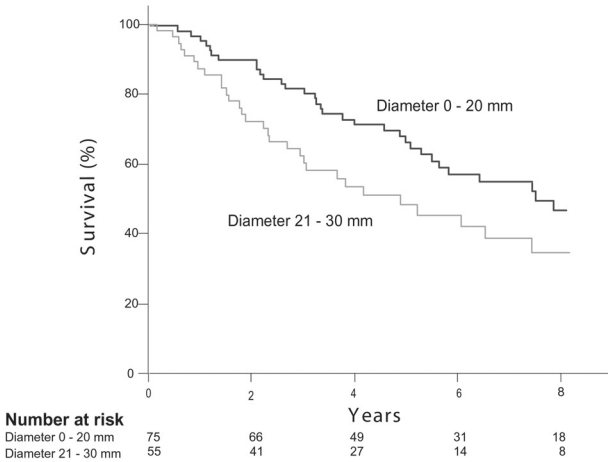

Table 2. Univariate and multivariate Cox proportional hazard analysis of survival

Variable	Number of patients	Univariate		Multivariate	
		RR	95% CI	RR	95% CI
Female sex	36	0.6	0.3 - 1.1		
Age	130	1.0	1.0 - 1.0		
Congestive heart failure	8	1.5	0.5 - 4.1		
Coronary artery disease	27	1.6	0.9 - 3.0		
Chronic pulmonary disease	45	1.6	1.0 - 2.7		
$FEV_1\% < 70$[a]	32	1.0	0.9 - 1.1		
Pneumonectomy	11	1.9	0.9 - 3.8	2.1	1.1 - 4.2
Squamous cell carcinoma	41	1.2	0.7 - 2.0		
Charlson comorbidity index					
1 - 2	71	1.4	0.7 - 2.8		
≥ 3	31	3.3	1.5 - 7.2	3.7	1.7 - 8.0
Tumor size					
21 - 30 mm	55	1.6	1.0 - 2.7	1.6	1.0 - 2.7

[a] $FEV_1\%$ was unknown in 9 patients

RR = relative risk

CI = confidence interval

$FEV_1\%$ = forced expiratory volume in 1 second expressed as a percent of predicted

COMMENT

According to the current lung cancer staging system stage I patients are subdivided in patients with tumors less than 3 cm and those greater than 3 cm. This difference is a result from several retrospective studies that have shown a survival advantage for patients with tumors less than 3 cm [2, 3]. These patients are categorized as stage IA. The survival of stage IA patients in our population was 62%, which is comparable to the 67% published by Mountain [4]. However our study clearly demonstrates that there is a survival benefit for patients with tumors 0 to 20 mm compared with tumors 20 to 30 mm in diameter. Early detection of small tumors may have its impact on survival although lead-time bias, length-time bias, and overdiagnosis bias may play an important role. There is conflicting evidence to support the impact of tumor size as prognostic risk factor for survival in stage IA NSCLC patients [2, 9-12]. Table 3 summarizes studies of the prognosis of tumor size in patients with pathological stage IA NSCLC. Patz and coworkers [11] evaluated the relation between tumor size and survival in 510 consecutive patients with stage IA NSCLC and found no correlation between tumor size and survival. However they reported observed survival based on deaths from all causes rather than disease free survival, which is inappropriate in patients with stage IA disease because it is not unlikely that these patients die of another cause than lung cancer. In a review of 598 patients with stage I NSCLC, Martini and associates [2] demonstrated that size did impact survival within stage IA; the survival of patients with tumors less than 1 cm was higher than those whose tumors were between 1 cm and 3 cm. In another study by Port and colleagues [10], a difference in the 5-year lung cancer specific survival for stage IA tumors was noted for tumors less than 2 cm and those between 2 to 3 cm in diameter. Read et al. [12] also found a survival benefit for patients with tumors less than 2 cm.

An explanation for the impaired survival in patients with larger tumors is an increase in the incidence of micrometastatic lymph nodes at the time of surgery. There is some evidence that smaller tumors metastasize to lymph nodes infrequently and thereby offer a greater chance of true cure following resection. In a study by Saito and coworkers [21], no nodal metastases were found in 55 patients with tumors less than 1 cm, whereas 4 of 46 patients with tumors 1 to 1.9 cm were found to have nodal spread. Therefore, earlier detection and treatment of NSCLC might increase the probability of curing lung cancer. However occult lymph node metastases may be present in small tumors at the time of diagnosis, and thus represent advanced stage disease despite their small size [22]. Preliminary spiral CT screening trials determined that up to 30% of small primary tumors metastasized to

regional lymph nodes or distant sites on initial examination [6, 23]. In some cases tumors metastasize even when they are less than 1 mm [24], while others may remain curable until they reach several centimeters. In this regard, recurrence rate is thought to be the lowest in pathological stage IA NSCLC patients. Not all of these patients die as a result of their tumor. Currently, the Kaplan-Meier (actuarial) method is widely used and accepted as method to estimate the recurrence rate in NSCLC patients. However, death is competing with recurrence in this method because patients who died without recurrence are censored as patients who can still have a recurrence. It is important to estimate the recurrence rate as accurate as possible to give the best and correct advise to patients on the probability of ever developing a recurrence after surgical resection. The cumulative incidence analysis corrects major errors that can occur when failures due to other causes are treated as censored observations in a Kaplan-Meier analysis [14, 15]. When compared to standard actuarial analysis, recurrence rate according to the actual method yielded more favorable results for the long-term in our series. The most suitable reason for the small difference between actual and actuarial recurrence rate in our analysis is the small number of patients included. It is to be expected that this difference will be larger in larger series.

A limitation of our study is to be seen in its retrospective design. It is impossible to know what the cause of death was in some patients in whom recurrence was not mentioned in the records and no autopsy was performed, which may have influenced the results of our analysis.

In conclusion, the results obtained in this study highlight that size of the tumor affects survival in surgically resected stage IA NSCLC. Given that our results are consistent with most of the prior literature it is time to reconsider the current definition of stage IA disease and substage stage IA lesions in two separate stages. Because of the different cutoff points used for tumor size in the prior literature, it will be necessary to conduct further prospective research to obtain the best cutoff point. As size seems to be a prognostic factor for survival, improved small nodule detection may significantly improve lung cancer mortality. At this time one can only speculate about the potential role of spiral CT screening in the early diagnosis of lung cancer until more data are available from randomized clinical lung cancer screening trials. Actuarial analysis underestimates the recurrence free survival compared to actual analysis by censoring all deaths without a recurrence. In patients with early-stage lung cancer and relatively good prognosis actual recurrence rate is more realistic than the actuarial recurrence rate.

Table 3. Summary of the literature assessing prognostic significance of tumor size in pathological stage IA nonsmall cell lung cancer

Reference, year	Patients (% male)	Mean age (years)	Tumor size (mm)	5-year overall survival (%)	p-value	5-year disease-free survival (%)	5-year lung cancer specific survival (%)	p-value
Gajra (2003) [9]	246 (58)	66	0 - 30	81		75		
			≤ 15	86	0.05	82		0.03
			16 - 30	79		71		
Port (2003) [10]	244 (46)	67	0 - 30	71			75	
			≤ 20	77	0.03		81	0.02
			20 - 30	60			63	
Patz (2000) [11]	510 (56)	63	2.7 - 9.6	80				
			9.6 - 16.5	85	0.597			
			16.5 - 23.4	87				
			23.4 - 30	81				
Martini (1995) [2]	291	_	0 - 30	82				
			≤ 10	97	0.01			
			10 - 30	80				
Read (1990) [12]	244 (99)	62	0 - 30	78				
			≤ 20	82	< 0.003			
			20 - 30	65				
Present paper	130 (72)	64	0 - 30	62		59		
			0 - 20	69	0.038	68		0.015
			21 - 30	51		48		

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CHAPTER 9

Proper treatment selection may improve survival in patients with clinical early-stage nonsmall cell lung cancer

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ABSTRACT

Background: In patients with early-stage nonsmall cell lung cancer treatment selection is rarely assessed. Many surgical papers report only the outcome of patients who underwent surgery although selection may influence the outcome. In this report, treatment selection and the outcome of both surgically and nonsurgically treated patients is evaluated.

Methods: Three hundred sixty patients (269 surgically treated and 91 nonsurgically treated) with clinical stage I and II were included. Risk factors were scaled according to the Charlson comorbidity index (CCI). Hospital morbidity and long-term survival were evaluated.

Results: Mean age was 64 years for the surgical and 74 for the nonsurgical patients. Mean CCI score was 1.3 and 2.4, and 5-year survival was 47% and 3%, respectively. Male sex, pneumonectomy, and CCI score of 3 or more were predictive for major postoperative complications. For the nonsurgical patients receiving radiotherapy, the 2-year survival was 40%; for the patients receiving no radiotherapy, 2-year survival was 5%. Male sex, age, treatment, and clinical stage were prognostic for survival. Patients with a CCI score of 3 or more showed a better survival after surgery than after radiotherapy. Patients with a CCI score of 3 or more who were surgically treated had a higher prevalence of forced expiratory volume in 1 second of 70% or more compared with the patients receiving radiotherapy.

Conclusions: Patients with a CCI score of 3 or more have an increased risk of major postoperative complications. Nevertheless, patients with a CCI score of 3 or more show a better survival after surgery than after radiotherapy. For patients with significant comorbidity but with sufficient pulmonary reserve, surgery offers the best outcome. For patients with a high CCI score and insufficient pulmonary reserve or for those who refuse surgery, curative radiotherapy is a good alternative.

INTRODUCTION

For patients with stage I and II nonsmall cell lung cancer (NSCLC), surgical resection is usually regarded as the treatment of choice. The most frequent reasons for denying surgery in these patients are associated comorbidity, patient refusal to undergo surgery, or advanced age. The presence of severe comorbidity in NSCLC patients is increasing owing to the increase of lung cancer incidence among the elderly as a consequence of increased life expectancy. Careful selection of candidates suitable for curative surgery is the key issue for optimal treatment. For patients with severe comorbidity who are inoperable, radiotherapy is frequently regarded as the treatment of choice [1]. However, owing to improvements in surgical techniques and postoperative care, patients with severe comorbid disease might nowadays do better after surgery than after radiotherapy. It is very unlikely that this question will ever be answered in a prospective randomized clinical trial.

In the surgical literature, usually only cohorts of patients who underwent surgery are presented although selection of patients may influence the outcomes. In this regard, treatment selection of patients with stage I and II disease is of utmost importance. Therefore, the purposes of the present study were as follows: (1) to retrospectively assess treatment selection in clinical stage I and II (T1-2, N0-1, M0) NSCLC patients, and (2) to evaluate whether the survival of patients with clinical stage I or II NSCLC who underwent surgery was superior to that of patients who did not undergo surgery.

MATERIAL AND METHODS

From the database of the Rotterdam Cancer Registry, a consecutive series of patients with clinical stage I and II (T1-2, N0-1, M0) NSCLC diagnosed or suspected between January 1, 1989, and December 31, 2001, was provided. All these patients were treated at the Erasmus MC Rotterdam. The medical records of surgically and nonsurgically treated patients were reviewed. Patients were followed up with regular visits to the outpatient clinic. Civil administrations provided the date of death. Follow-up was completed in all patients through July 2003. Survival time was defined as the difference between date of diagnosis and date of last follow-up or date of death.

For all cases, diagnostic workup included a complete medical history, physical examination, plain chest radiography, electrocardiography, routine laboratory tests, lung function tests (pretreatment forced expiratory volume in 1 second [FEV_1%] was unknown in 29 patients), and computed tomography of the chest and upper abdomen. Additional staging procedures, namely, bronchoscopy, mediastinoscopy, and liver, bone and brain scans, were selectively performed to aid in treatment planning according to best clinical practice at the time of presentation. Pathologic lymph node staging of the surgically treated patients was based on lymph node assessment by preoperative mediastinoscopy or surgical sampling of bronchopulmonary, hilar and mediastinal lymph nodes, or both.

Histologic typing was done according to The World Health Organization Histologic Typing of Lung Tumours [2]. The histologic or cytologic diagnosis of the nonsurgically treated patients was achieved by fiberoptic bronchoscopy or percutaneous transthoracic needle biopsies. The histologic or cytologic diagnosis was unknown in 17 nonsurgically treated patients, but in all cases the probability of NSCLC was high according to medical history and the presentation on computed tomography.

The clinical stage was determined according to the international TNM classification for lung cancer [3]. Most of the nonsurgically treated patients did not undergo mediastinoscopy and their staging was based on computed tomography findings only (negative lymph nodes if mediastinal lymph nodes were ≤ 10 mm in short-axis diameter).

For the surgically treated patients, the length of hospital stay was calculated as the difference between date of surgery and date of discharge. Complications were classified as minor (nonlife-threatening: air leak lasting more than 5 days, supraventricular arrhythmia, atelectasis, transfusion, infection, paresis of the recurrent nerve), and major (life-threatening: empyema, pneumonia, pleural

effusion needing pleural drainage, bronchopleural fistula, ventilatory support for more than 72 hours, cerebrovascular accident, transient ischemic attack, renal failure, ventricular arrhythmia, pulmonary embolism, rethoracotomy, acute respiratory distress syndrome, myocardial infarction or failure). Patients with both minor and major complications were coded as having major complications only, although the nature of the minor complication was also recorded. Hospital mortality was defined as death occurring within 30 days after surgery or any death later in the same postoperative hospital stay.

Comorbidity evaluation

Comorbidity was scored according to the Charlson comorbidity index (CCI) [4]. The CCI consists of the sum of the weighted scores based on the relative mortality risk of 19 conditions that significantly influence survival. The index can be divided into four comorbidity grades: 0, 1 to 2, 3 to 4, and 5 or more. Because cardiac disease is associated with a higher risk of operation in patients with lung cancer [5-7], we modified the CCI by scoring all forms of coronary artery disease (myocardial infarction, angina, coronary artery bypass graft, and percutaneous transluminal coronary angioplasty) with a value of 1 [8, 9]. Patients were considered to have a comorbid condition if one of the diseases mentioned in the CCI was present in the records or if the patient was treated for it.

Statistical analysis

The χ^2 or Fisher exact test was used to analyze the categorical data. Continuous variables were analyzed using the Student t-test. Univariate and multivariate logistic regression analysis was used to discriminate independent risk factors for major complications. Survival curves were estimated by the Kaplan-Meier method. The log-rank test was used to compare survival curves. Univariate and multivariate Cox proportional hazard analysis determined risk factors for survival. Both the logistic and Cox proportional multivariate analyses were performed with a stepwise backward regression model in which each variable with a p-value of less than 0.20 in the univariate analysis was entered in the model. Odds ratios are reported with 95% confidence intervals. A p value of less than 0.05 was considered significant.

RESULTS

Patients

Three hundred and seventy-three patients with clinical stage I or II (T1-2, N0-1, M0) NSCLC were retrieved from the database of the Rotterdam Cancer Registry. No additional data were available in 13 patients who were excluded from further analysis. A total of 360 patients were analyzed, of whom 269 (75%) were treated surgically and 91 (25%) nonsurgically. The study group consisted of 286 male patients (79%) and 74 female patients (21%). The mean age at diagnosis was 66 years (range, 37 to 90 years) and the median follow-up time was 2.7 years.

Surgically treated patients

Of the 269 surgically treated patients, 208 (77%) were men and 61 (23%) were women. The mean age at time of diagnosis was 64 years (range, 37 to 82 years). The patient characteristics are described in Table 1. The CCI and the comorbid conditions are presented in Table 2, and the distribution of the CCI score in Table 3. The mean CCI score was 1.3 (range, 0 to 6). The operations performed were wedge resection (10), lobectomy (157), bilobectomy (26), pneumonectomy (67), and explorative thoracotomy (9). Ten patients received neoadjuvant chemotherapy. Surgical-pathologic upstaging was observed in 81 (30%) of the patients. Because of positive mediastinal lymph nodes or invasion of extraparenchymal tissue, adjuvant chemotherapy was administered to 3 and radiotherapy to 30 patients.

Hospital mortality was 3.3% (9 of 269 patients). Operations in these patients were lobectomy (3), bilobectomy (1), and pneumonectomy (5). Causes of death were cardiac failure (4), cardiac arrest (1), empyema (2), respiratory insufficiency (1), and multiple organ failure (1). Minor postoperative complications occurred in 111 patients (41%), the majority of which concerned supraventricular arrhythmia (n = 61; 23%) and air leak lasting more than 5 days (n = 59; 22%). Major complications occurred in 35 patients (13%), and concerned mainly rethoracotomy (n = 19; 7%) and empyema (n = 14; 5%). None of the patients who underwent an explorative thoracotomy or a wedge resection experienced major complications. In multivariate logistic regression analysis, male sex (odds ratio, 4.5; 95% confidence interval, 1.0 to 19.7), pneumonectomy (odds ratio, 2.5; 95% confidence interval, 1.1 to 6.4), and CCI grade 3 - 4 (odds ratio, 3.6; 95% confidence interval, 1.2 to 11.0) were associated with an increased risk of major complications. Mean hospital stay was 15.5 days (range, 6 to 138 days). No difference in length of hospital stay was seen between the operative procedures performed.

One-, 2-, and 5-year overall survival was 85%, 69%, and 47%, respectively

(Fig. 1). Survival for the 41 patients with a CCI score of 3 or more was 83%, 66%, and 36% after 1, 2, and 5 years, respectively (Fig. 2).

Table 1. Base-line characteristics of surgically and nonsurgically treated patients with clinical early-stage nonsmall cell lung cancer

Characteristic	Surgically treated (n=269) (%)	Nonsurgically treated (n=91) (%)	p-value
Sex			0.09
Male	208 (77)	78 (86)	
Female	61 (23)	13 (14)	
Age (years)			
≤ 70	212 (79)	29 (32)	
> 70	57 (21)	62 (68)	
Mean (± SD)	64 ± 9	74 ± 8	< 0.0001
Median follow-up (years)	0.9	4.5	< 0.0001
Clinical Stage			0.7
IA	124 (46)	36 (40)	
IB	135 (50)	51 (56)	
IIA	6 (2)	2 (2)	
IIB (only T2N1M0)	14 (5)	4 (4)	
Histology[a]			< 0.0001
Squamous cell carcinoma	129 (48)	46 (50)	
Adenocarcinoma	81 (30)	9 (10)	
Large cell carcinoma	41 (15)	17 (19)	
Bronchoalveolar cell carcinoma	18 (7)	2 (2)	
Smoking habits			0.105
Nonsmoker	37 (14)	19 (21)	
Current or former smoker	232 (86)	72 (79)	
FEV_1%[b]			< 0.0001
< 70	64 (25)	51 (65)	
≥ 70	187 (75)	28 (35)	
Mean (± SD)	82 ± 18	63 ± 25	
Charlson comorbidity grade			< 0.0001
0	82 (30)	8 (9)	
1 - 2	146 (54)	43 (47)	
3 - 4	36 (13)	31 (34)	
≥ 5	5 (2)	9 (10)	

[a] Histology was unknown in 17 nonsurgically treated patients

[b] FEV_1% was unknown in 17 surgically treated patients and 12 nonsurgically treated patients

SD = standard deviation

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

Table 2. Charlson comorbidity index and prevalence of comorbid conditions among 269 surgically and 91 nonsurgically treated patients with clinical early-stage nonsmall cell lung cancer

Score	Condition	Number of patients (%)	
		Surgically treated	Nonsurgically treated
1	Coronary artery disease[a]	54 (20)	26 (29)
	Congestive heart failure	12 (4)	9 (10)
	Chronic pulmonary disease	85 (32)	53 (58)
	Peptic ulcer disease	29 (11)	10 (11)
	Peripheral vascular disease	46 (17)	17 (19)
	Mild liver disease	0 (0)	1 (1)
	Cerebrovascular disease	19 (7)	13 (14)
	Connective tissue disease	3 (1)	0 (0)
	Diabetes	15 (6)	12 (13)
	Dementia	2 (1)	3 (3)
2	Hemiplegia	2 (1)	0 (0)
	Moderate to severe renal disease	2 (1)	4 (4)
	Diabetes with end-organ damage	0 (0)	2 (2)
	Any prior tumor (within 5 years of diagnosis)[b]	38 (14)	26 (29)
	Leukemia	3 (1)	0 (0)
	Lymphoma	2 (1)	1 (1)
3	Moderate to severe liver disease	0 (0)	0 (0)
6	Metastatic solid tumor	0 (0)	1 (1)
	AIDS (not only HIV positive)	0 (0)	0 (0)

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty and angina pectoris

[b] Except basal cell skin carcinoma

AIDS = acquired immuno deficiency syndrome

HIV = human immunodeficiency virus

Table 3. Charlson comorbidity index score among the surgically and nonsurgically treated patients with clinical early-stage nonsmall cell lung cancer

CCI score	Surgically treated (n=269)	%	Nonsurgically treated (n=91)	%
0	82	30	8	9
1	76	28	20	22
2	70	26	23	25
3	28	10	23	25
4	8	3	8	9
5	4	1	6	7
6	1	0	2	2
7	0	0	1	1

CCI = Charlson comorbidity index

Figure 1. Survival rates for surgically and nonsurgically treated patients with clinical early-stage nonsmall cell lung cancer

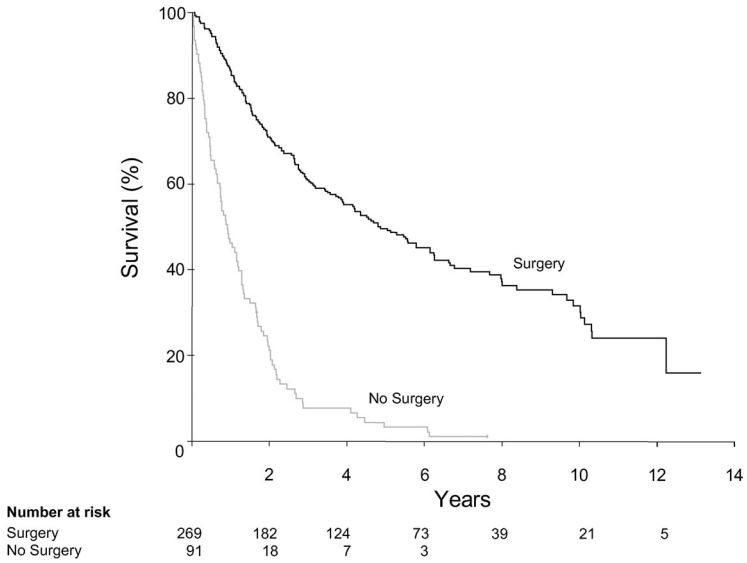
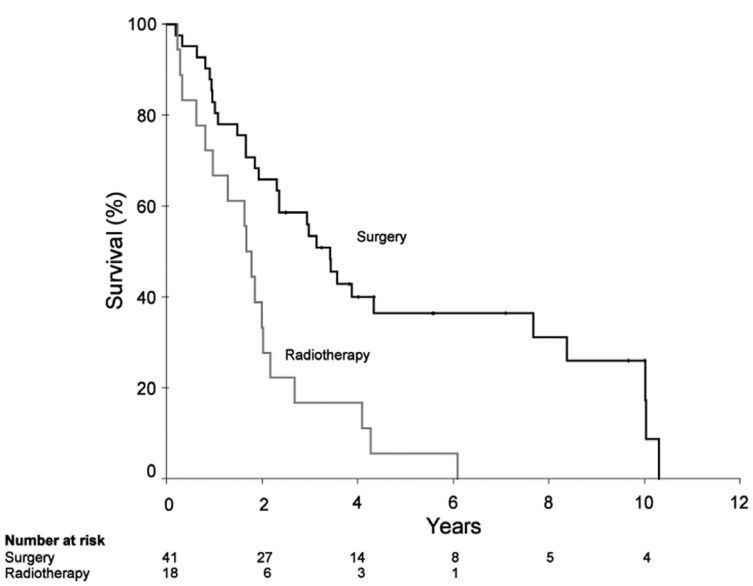


Figure 2. Survival rates for patients with a Charlson comorbidity index score of 3 or more treated surgically or with radiotherapy

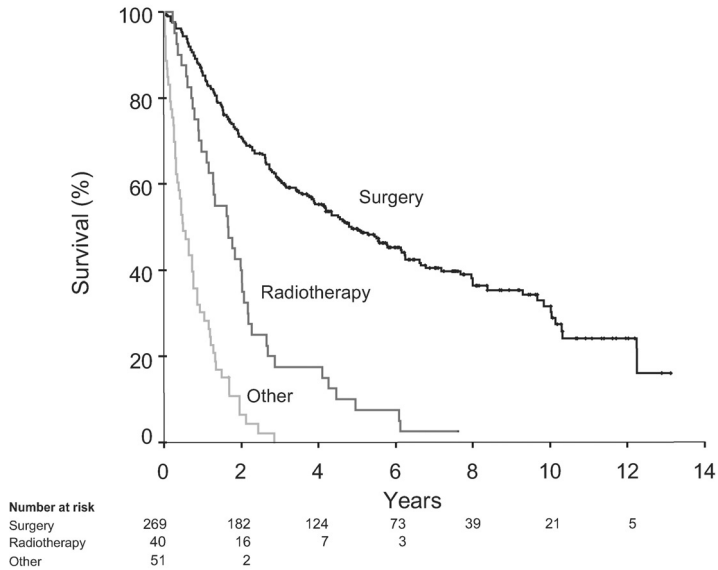


Nonsurgically treated patients

Of the 91 nonsurgically treated patients, 78 (86%) were men and 13 (14%) were women. The mean age at time of diagnosis was 74 years (range, 50 to 90 years). The patient characteristics are described in Table 1. Two patients had two primary lung tumors with a different histology diagnosed at the same time. The second primary tumor was located in the contralateral lung in both patients. Clinical stage and histologic diagnosis were obtained from the largest tumor. The reasons for a nonsurgical approach were patient refusal to undergo surgery in 23 (25%), insufficient predicted postoperative pulmonary reserve in 37 (41%), poor performance status in 12 (13%), cardiac comorbidity in 4 (4%), advanced age in 6 (7%), and other reasons in 9 (10%). Forty patients (44%) were treated with radiotherapy with a curative intent, 5 (5%) received palliative chemotherapy, 2 (2%) patients were treated with induction chemotherapy followed by radiotherapy, and 44 patients (48%) did not receive any treatment at all. The mean CCI score was 2.4 (range, 0 to 7). Of the 8 patients with a CCI score of 0, 5 refused surgery, 2 were rejected because of age, and 1 had insufficient predicted postoperative pulmonary reserve.

One-, 2-, and 5-year overall survival of the nonsurgical group was 46%, 21%, and 3%, respectively (Fig. 1). The 1-, 2-, and 5-year survival of patients receiving radiotherapy was 68%, 40%, and 8%; and of the patients receiving no radiotherapy was 29%, 5%, and 0% (Fig. 3). Survival of patients who received radiotherapy was significantly ($p < 0.0001$) higher compared with patients receiving no radiotherapy. Survival for the 18 patients with a CCI score of 3 or more who received radiotherapy was 67%, 33%, and 6% after 1, 2, and 5 years, respectively (Fig. 2).

Figure 3. Survival rates for surgically treated patients, patients receiving radiotherapy, and the remaining patients with clinical early-stage nonsmall cell lung cancer



Comparison of surgically and nonsurgically treated patients

Mean age was 74 years for the nonsurgical and 64 years for the surgical patients ($p < 0.0001$, Table 1). No significant difference was found in the clinical stage and sex. The mean CCI score was higher in nonsurgically treated patients (2.4 versus 1.3, $p < 0.0001$). Five-year survival was higher for the surgically treated patients (47% versus 3%, $p < 0.0001$). Three-year survival of the patients who received radiotherapy was 18% whereas none of the patients who did not receive radiotherapy survived for more than 3 years ($p < 0.0001$).

Assessment of the prognostic factors for survival in the total population, using the univariate Cox proportional hazard analysis, revealed that male sex, age over 70 years, a pretreatment FEV_1% less than 70, nonsurgical treatment, any prior tumor within 5 years of diagnosis, chronic pulmonary disease, CCI grades 3 - 4 and 5 or more, and clinical stages IB, IIA, and IIB, were significant negative risk factors for survival (Table 4). Multivariate analysis showed that male sex (odds ratio, 1.8; 95% confidence interval, 1.2 to 1.9), age over 70 years (odds ratio, 1.3; 95% confidence interval, 1.0 to 1.8), nonsurgical treatment (odds ratio, 3.4; 95% confidence interval, 2.3 to 5.0), and clinical stages IB (odds ratio, 1.4; 95% confidence interval, 1.0 to 1.9), IIA (odds ratio, 3.2; 95% confidence interval, 1.5 to 7.2), and IIB (odds ratio, 2.6; 95% confidence interval, 1.4 to 4.6) were independent

negative risk factors for survival (Table 4). The prognostic effects of CCI, FEV_1%, any prior tumor within 5 years of diagnosis, and chronic pulmonary disease disappeared in the multivariate analysis.

Survival for the 41 surgically treated patients with a CCI score of 3 or more was higher than for the 18 patients with a CCI score of 3 or more who received radiotherapy (36% versus 6%, $p < 0.0001$; Fig. 2). In this group of patients, in both univariate and multivariate analysis, only surgery was prognostic for survival (odds ratio, 0.4; confidence interval, 0.2 to 0.7). A higher prevalence of a FEV_1% of 70 or more in the surgically treated group (82% versus 23%, $p < 0.0001$) was the only difference in risk factors between these two groups.

Table 4. Univariate and multivariate Cox proportional hazard analysis of survival of the total study population

Variable	Number of patients	Univariate		Multivariate	
		OR	95% CI	OR	95% CI
Male sex	286	1.9	1.3 - 2.7	1.8	1.2 - 1.9
Age > 70 years	121	2.2	1.7 - 2.8	1.3	1.0 - 1.8
No surgical treatment	91	4.5	3.4 - 5.9	3.4	2.3 - 5.0
Current or former smoker	304	0.9	0.6 - 1.2		
Diabetes	27	1.0	0.7 - 1.6		
Congestive heart failure	175	1.1	0.9 - 1.4		
Any prior tumor[a]	21	1.5	0.9 - 2.5		
Coronary artery disease	64	1.4	1.0 - 1.9	1.2	0.8 - 1.7
Chronic pulmonary disease	80	1.1	0.9 - 1.5		
FEV_1% < 70[b]	138	1.6	1.3 - 2.1	1.4	0.9 - 2.0
Comorbidity grade	115	1.8	1.4 - 2.3	1.0	0.7 - 1.4
1 - 2					
3 - 4	188	1.2	0.8 - 1.6	0.8	0.5 - 1.1
≥ 5	68	1.8	1.3 - 2.6	0.9	0.5 - 1.5
Clinical TNM stage	14	2.6	1.4 - 4.9	1.0	0.5 - 2.2
IB					
IIA	176	1.5	1.1 - 1.9	1.4	1.0 - 1.9
IIB (only T2N1M0)	8	2.3	1.0 - 4.9	3.2	1.5 - 7.2

[a] Within 5 years of diagnosis, except basal cell skin carcinoma

[b] FEV_1% was unknown in 31 patients

OR = odds ratio

CI = confidence interval

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

COMMENT

Currently, surgery and complete removal of the primary tumor and its involved lymph nodes is the gold standard of treatment in early stages of NSCLC. The careful selection of patients for surgery is a very important factor in all circumstances, and is particularly important among elderly patients. A subset of early-stage NSCLC patients will require a viable alternative to surgery because they are either unwilling to undergo surgery or are considered inoperable.

In this study, there was an important survival difference of 44% at 5 years between the surgically and nonsurgically treated patients in favor of the surgically treated patients. Treatment selection was obviously based on the presence of severe comorbidity and pulmonary function. In the univariate analysis surgery, CCI score of 3 or more, and FEV_1% of less than 70 were associated with poor survival. However, in the multivariate analysis, surgery proved to be significant and the prognostic effects of the CCI score of 3 or more and FEV_1% less than 70 disappeared. This underlines that we predominantly selected patients for surgery on comorbidity score and pulmonary function and not on other factors, such as clinical stage, sex, or age.

In the high-risk patient, radiotherapy is frequently regarded as the treatment of choice. For patients with early-stage NSCLC who refuse surgery or who are considered inoperable, curative radiotherapy results in a 5-year survival rate ranging from 5% to 30% [10, 11]. This is supported by our data, which showed an 8% 5-year survival for patients who received radiotherapy.

With current surgical techniques, experience, and improved postoperative care, patients with a high comorbidity rate can be operated upon. Despite a higher rate of major postoperative complications in patients with a high comorbidity rate (CCI score of 3 or more) as shown in this study and others [8, 9], these patients have a higher 5-year survival than patients receiving radiotherapy (36% versus 6%). Patients with a high comorbidity rate who were operated on had a higher mean FEV_1% compared with patients receiving curative radiotherapy. This indicates that for patients with significant comorbidity but with a sufficient pulmonary reserve, surgical resection offers the best outcome.

The morbidity and mortality after pulmonary resection for NSCLC are significant [8, 9, 12, 13], with arrhythmia (23%) and air leak lasting more than 5 days (22%) occurring as the most frequent complications. It is well known that pneumonectomy, especially right-sided pneumonectomy, is associated with higher incidence of complications when compared with limited resections [14, 15]. In our multivariate analysis, male sex, pneumonectomy and the CCI were the determinants

associated with an increased risk of major postoperative complications.

The limitations of this study were that it is retrospective in design, the nonsurgically treated patients were less rigorously staged, and complete data on these patients was not always available. The FEV_1% was not available for 17 surgically treated patients and 12 nonsurgically treated patients. Histology was not determined for 17 nonsurgically treated patients. This reflects clinical practice, in which sometimes clinical suspicion of NSCLC is high and patients are treated accordingly. Additionally, information on posttreatment morbidity and treatment-related toxicity in the nonsurgically treated group is lacking.

The presence of significant comorbidity is an important prognostic factor in early-stage NSCLC. This study illustrates that patients with severe comorbidity are generally treated nonsurgically especially when the comorbidity include impaired pulmonary function. If patients with high comorbidity are treated surgically, they have an increased risk of major postoperative complications. Nevertheless, these patients have a better survival compared with radiotherapy. In patients with high comorbidity but with sufficient pulmonary reserve, surgical resection offers the best outcome. For patients with high comorbidity and insufficient pulmonary reserve or for those who refuse surgery, curative radiotherapy is a good alternative.

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CHAPTER 10

Long-term survival after nonsmall cell lung cancer surgery: development and validation of a prognostic model with a preoperative and postoperative mode

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ABSTRACT

Background: At present, there is no prognostic model that is specific for prediction of survival after nonsmall cell lung cancer (NSCLC) surgery. We aimed to develop a prognostic model that can be used to estimate the postoperative survival of individual patients.

Methods: 766 patients underwent resection for primary NSCLC. Comorbid conditions were scaled according to the Charlson comorbidity index (CCI). Cox proportional hazard analyses were used to determine risk factors for survival. A prognostic model for survival with a preoperative and postoperative mode was established. Performance of the prognostic model, the CCI, and pathological tumor stage were quantified by a concordance statistic to indicate discriminative ability.

Results: The factors associated with an impaired survival were male sex, age, COPD, congestive heart failure, any prior tumor, moderate to severe renal disease (pre-and postoperative mode), clinical tumor stage (preoperative mode), type of resection, and pathological tumor stage (postoperative mode). The discriminative performance was poor for the CCI ($c = 0.55$), better for pathological tumor stage ($c = 0.60$) and for the preoperative mode ($c = 0.61$), and best for the postoperative mode ($c = 0.65$). The discriminative performance of the postoperative mode was better than the discriminative performance of the CCI ($p < 0.0001$), the preoperative mode ($p < 0.0002$), and pathological tumor stage ($p < 0.0001$). The discriminative performance of the preoperative mode was better than the discriminative performance of the CCI ($p < 0.0001$), and similar ($p = 0.90$) to a model that only included pathological tumor stage.

Conclusions: The prognostic model, particularly the postoperative mode, successfully estimates long-term survival of individual patients, and could help clinicians in clinical decision-making and treatment tailoring.

INTRODUCTION

Surgical resection is generally the mainstay of curative treatment in early-stage nonsmall cell lung cancer (NSCLC). Survival is mainly dependent on pathological tumor stage, with 5-year survival that ranges between 67% and 38% for pathological tumor stage IA to IIB [1, 2]. However, many other factors also have an impact on survival, such as comorbidity, age, and type of resection [3-6]. Owing to the increasing age of the population diagnosed with NSCLC, the incidence of comorbidity and consequently high-risk patients also increases. The most frequent comorbidities in NSCLC patients are cardiovascular disease (23%), chronic obstructive pulmonary disease (COPD) (22%), and other malignancies (15%) [7].

Several scoring systems based on various comorbid conditions have previously been used in order to stratify patients according to risk of complications and long-term survival following NSCLC surgery [8-11]. In previously published studies we found the Charlson comorbidity index (CCI) to predict postoperative outcome more accurately than the individual comorbid conditions [8, 9]. However, these scoring systems are developed in other patient populations and thus may be suboptimal for application in NSCLC surgery patients. In addition, these models do not include several other prognostic factors in NSCLC surgery patients, such as gender, age, extent of resection, and tumor stage. Furthermore, these models do not estimate the long-term survival of individual patients after surgical resection. At present, there is no accepted prognostic model that is specific for NSCLC patients and one that can be used to estimate the long-term survival of individual patients after surgical resection of NSCLC.

In addition to provide surgeons and patients with better quality information on risk assessment and postoperative survival we performed this retrospective study. We aimed to identify prognostic factors for survival in NSCLC surgery, to develop a prognostic model with a preoperative and a postoperative mode to estimate survival of individual patients, and to compare the predictive accuracy of the prognostic model with the predictive accuracy of the CCI and pathological tumor stage.

MATERIAL AND METHODS

Patients

We retrospectively reviewed the medical records of 766 consecutive patients who underwent resection for primary NSCLC at the Departments of Cardio-Thoracic Surgery of the Erasmus MC Rotterdam (433 patients) and the Leiden University Medical Center (333 patients), from January 1, 1989, through December 31, 2001. Patients were followed with regular visits to the outpatient clinic. Civil administrations were consulted to assess late mortality. Follow-up was completed through August 2004. Survival time was defined as the difference between the date of surgery and the date of last follow-up. Hospital mortality was defined as death occurring within 30 days of surgery or any death later during the same postoperative hospital stay.

In all patients, preoperative diagnostic workup included a complete medical history, physical examination, plain chest radiography, electrocardiography, routine laboratory tests, lung function tests and computed tomography of the chest and upper abdomen. Additional staging procedures, namely, mediastinoscopy, liver, bone and brain scans were selectively performed to aid in treatment planning according to best clinical practice at the time of presentation. In retrospect, each patient was assessed for preoperative CCI [8, 9]. The index can be divided into four comorbidity grades: 0, 1 to 2, 3 to 4, and 5 or more.

Chronic obstructive pulmonary disease as a comorbid condition is defined according to the GOLD criteria as a postbronchodilator forced expiratory volume in 1 second (FEV_1) / forced vital capacity (FVC) ratio < 70% [12].

Histological typing occurred according to The World Health Organization Histologic Typing of Lung Tumours [13]. Clinical and pathological staging of the patients occurred according to the international TNM classification for lung cancer [1]. Staging was based on pathological assessment of the primary tumor and lymph node assessment was carried out with preoperative mediastinoscopy (clinical-pathological staging) or surgical sampling of bronchopulmonary, hilar and mediastinal lymph nodes (pathological staging).

The following risk factors for survival were evaluated: sex, age, type of resection, histological cell type, smoking, COPD (unknown in 57 patients), FEV_1% (unknown in 46 patients), clinical tumor stage, pathological tumor stage, and each common condition of the CCI.

Statistical analysis and development of the prognostic model

Discrete variables are displayed as proportions, continuous variables as means ±

standard deviations unless specified otherwise. We used Cox proportional hazard analysis to determine risk factors for survival, where effects were expressed as relative risks with 95% confidence intervals. Multivariate analysis was performed with stepwise backward elimination of variables, starting with a model in which each variable with a p-value of less than 0.20 in the univariate analysis was entered. Because COPD, FEV_1%, and chronic pulmonary disease were correlated to each other, we only entered the most significant factor (COPD) in the multivariate analysis. In the multivariate analysis the estimated mean value of COPD was imputed for the 57 missing values.

A preoperative and a postoperative mode of the prognostic model for survival were established. This model considered sex and age and included those factors that were available preoperative or postoperative which were associated with an impaired survival in the multivariate analysis. Factors that were less important but almost significant, such as COPD, congestive heart failure, and left-sided pneumonectomy, were retained in the model because of their documented relevance in the literature [5, 14-16]. The performance of the prognostic model, the CCI, and pathological tumor stage were quantified by a concordance statistic (c statistic), which is similar to the area under the receiver operating characteristic (ROC) curve for binary data [17]. A c statistic of 0.5 indicates that the model has no discriminative ability, and a c statistic of 1 indicates that the model perfectly distinguishes between those who die early and those who die later.

Bootstrapping techniques were used for internal validation of the c statistic of the models [14, 18]. Bootstrap samples were drawn with replacement and with the same size as the original sample. Regression models were created in each bootstrap sample, and tested on the original sample. This procedure was repeated 200 times to obtain stable estimates of the optimism of the model, i.e. how much the model performance was expected to decrease when applied in future patients [19].

Bootstrap resampling was also used to test differences in performance between alternative models. The mean difference and standard error was estimated from 2000 bootstraps.

For practical application we developed an Excel spreadsheet where preoperative and postoperative characteristics can be entered and the predicted survival with 95% confidence interval is automatically calculated. This Excel spreadsheet for easy access and use by clinicians is available on the Internet (http://www.cardiothoracicresearch.nl). Statistical calculations were performed with SPSS (version 12.0; SPSS Inc, Chicago, Ill) and S-plus (version 6.0; Insightful Corp, Seattle, WA).

RESULTS

Of the 766 patients enrolled in this analysis, 600 (78%) were men and 166 (22%) were women. Median follow-up time was 3.5 ± 0.3 years. The mean age at operation was 64.5 ± 9.2 years (range, 37 to 84 years old). The patient's preoperative characteristics are outlined in Table 1 and Table 2. The types of procedures performed consisted of a wedge resection (17; 2%), a lobectomy (470; 61%), a bilobectomy (73; 10%), a left-sided pneumonectomy (105; 14%), and a right-sided pneumonectomy (101; 13%). Tumors were classified histologically as squamous cell carcinoma (386; 50%), adenocarcinoma (246; 32%), large cell carcinoma (82; 11%), and bronchoalveolar cell carcinoma (52; 7%). The patient's operative demographics are listed in Table 3.

Hospital mortality occurred in 34 patients (4.4%). Of all 766 patients, 528 (69%) had died and 238 (31%) were alive at the end of follow-up. Mean overall survival was 5.4 ± 0.2 years, with 77% (95% confidence interval, 74 to 81) surviving at 1 year, 62% (95% confidence interval, 58 to 66) at 2 years, and 40% (95% confidence interval, 36 to 44) at 5 years.

Predictors for impaired survival in the univariate analysis included male sex, age, COPD, $FEV_1\% < 70$, type of resection, CCI score ≥ 3, congestive heart failure, chronic pulmonary disease, any prior tumor within 5 years of diagnosis, moderate to severe renal disease, leukemia, lymphoma, clinical tumor stage, and pathological tumor stage (Table 4). The factors associated with an impaired survival in the multivariate analysis were male sex, age, COPD, type of resection, congestive heart failure, any prior tumor within 5 years of diagnosis, moderate to severe renal disease, clinical tumor stage, and pathological tumor stage (Table 4). The developed Excel spreadsheet of the preoperative mode and postoperative mode of the model is illustrated in Figure 1 and Figure 2, respectively. In Figure 1, the clinical factors of a 64-year old male with clinical tumor stage IB NSCLC are filled in and the 5-year survival rate is estimated to be 33%. When this patient undergoes lobectomy for pathological tumor stage IB, the 5-year survival rate is estimated to be 45% (Fig. 2).

The discriminative performance (c statistic) was poor for the CCI (c = 0.55), better for pathological tumor stage (c = 0.60) and for the preoperative mode (c = 0.61), and best for the postoperative mode (c = 0.65). Bootstrapping revealed limited optimism of the model, with a decrease of the c statistic from 0.61 to 0.59 for the preoperative mode, and from 0.65 to 0.63 for the postoperative mode. The discriminative performance of the postoperative mode was better than the discriminative performance of the CCI ($p < 0.0001$), the preoperative mode ($p < 0.0002$), and pathological tumor stage ($p < 0.0001$). The discriminative performance of the preoperative mode was better than the discriminative

performance of the CCI ($p < 0.0001$), and similar ($p = 0.90$) to a model that only included pathological tumor stage.

Table 1. Patient characteristics

Characteristic	Number of patients	%
Sex		
Male	600	78
Female	166	22
Age (years)		
< 70	534	70
≥ 70	232	30
Mean ± SD	64.5 ± 9.2	
Median follow-up (years) ± SD	3.5 ± 0.3	
Smoking habits		
Nonsmoker	88	11
Current or former smoker	678	89
COPD[a]		
No	245	35
Yes	464	65
FEV_1%[b]		
< 70	186	26
≥ 70	534	74
Charlson comorbidity index		
0	228	30
1 - 2	382	50
3 - 4	136	18
≥ 5	20	3
Clinical stage		
IA	341	45
IB	291	38
IIA	17	2
IIB	57	7
IIIA	37	5
IIIB	17	2
IV	5	1

[a] COPD was unknown in 57 patients

[b] FEV_1% was unknown in 46 patients

SD = standard deviation

COPD = chronic obstructive pulmonary disease

FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

Table 2. Charlson comorbidity index and prevalence of comorbid conditions among 766 patients operated on for nonsmall cell lung cancer

Score	Condition	Number of patients	%
1	Coronary artery disease[a]	141	18.4
	Congestive heart failure	145	18.9
	Chronic pulmonary disease	226	29.5
	Peptic ulcer disease	46	6.0
	Peripheral vascular disease	86	11.2
	Mild liver disease	1	0.1
	Cerebrovascular disease	50	6.5
	Connective tissue disease	7	0.9
	Diabetes	40	5.2
	Dementia	2	0.3
2	Hemiplegia	2	0.3
	Moderate to severe renal disease	20	2.6
	Diabetes with end-organ damage	2	0.3
	Any prior tumor (within 5 years of diagnosis)[b]	140	18.3
	Leukemia	5	0.7
	Lymphoma	10	1.3
3	Moderate to severe liver disease	3	0.4
6	Metastatic solid tumor	2	0.3
	AIDS (not only HIV positive)	0	0

[a] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and angina pectoris
[b] Except basal cell skin carcinoma
AIDS = acquired immunodeficiency syndrome
HIV = human immunodeficiency virus

Table 3. Operative characteristics

Characteristic	Number of patients	%
Type of resection		
Wedge resection	17	2
Lobectomy	470	61
Bilobectomy	73	10
Pneumonectomy	206	27
Left-sided	105	14
Right-sided	101	13
Histology		
Squamous cell carcinoma	386	50
Adenocarcinoma	246	32
Large cell carcinoma	82	11
Bronchoalveolar cell carcinoma	52	7
Pathological stage		
0	1	0.1
IA	244	32
IB	251	33
IIA	35	5
IIB	110	14
IIIA	72	9
IIIB	39	5
IV	13	2

Table 4. Univariate and multivariate Cox proportional hazard analysis of survival

Variable	Number of patients	Univariate		Multivariate			
				Preoperative		Postoperative	
		RR	95% CI	RR	95% CI	RR	95% CI
Male sex	600	1.3	1.1 - 1.7	1.1	0.9 - 1.4	1.2	0.9 - 1.5
Age	766	1.02	1.01 - 1.03	1.02	1.01 - 1.03	1.02	1.01 - 1.03
COPD[a]	464	1.2	1.0 - 1.5	1.3	1.0 - 1.4	1.1	0.9 - 1.4
FEV_1% < 70	186	1.2	1.0 - 1.5				
Type of resection							
Wedge resection	17	2.1	1.3 - 3.4			1.5	0.9 - 2.6
Bilobectomy	73	1.4	1.1 - 1.9			1.3	1.0 - 1.7
Left-sided pneumonectomy	105	1.5	1.1 - 1.8			1.2	0.9 - 1.5
Right-sided pneumonectomy	101	1.7	1.3 - 2.2			1.6	1.2 - 2.0
Charlson comorbidity index							
Score 1 - 2	382	1.1	0.9 - 1.4				
Score ≥ 3	156	1.6	1.2 - 2.0				
Coronary artery disease[b]	141	1.1	0.9 - 1.4				
Chronic pulmonary disease	226	1.2	1.0 - 1.5				
Congestive heart failure	145	1.2	1.0 - 1.5	1.1	0.9 - 1.4	1.2	0.9 - 1.4
Moderate to severe renal disease	20	1.7	1.0 - 2.9	1.6	1.0 - 2.8	2.1	1.2 - 3.5
Any prior tumor[c]	140	1.2	1.0 - 1.5	1.3	1.0 - 1.6	1.2	1.0 - 1.5
Peptic ulcer disease	46	1.0	0.7 - 1.4				
Peripheral vascular disease	86	1.0	0.8 - 1.3				
Cerbrovascular disease	50	1.1	0.8 - 1.6				
Diabetes	40	1.0	0.7 - 1.4				
Leukemia	5	2.1	0.8 - 5.7				
Lymphoma	10	3.3	1.6 - 6.6				
Clinical stage							
IB	291	1.4	1.2 - 1.7	1.5	1.2 - 1.8		
IIA	17	1.9	1.1 - 3.3	2.0	1.1 - 3.5		
IIB	57	1.9	1.4 - 2.7	2.0	1.4 - 2.8		
IIIA	37	1.7	1.1 - 2.6	1.8	1.2 - 2.7		
IIIB	17	1.9	1.0 - 3.5	2.1	1.2 - 3.9		
IV	5	10.2	4.2 - 25.1	15.9	6.3 - 39.7		
Pathological stage							
IB	251	1.4	1.1 - 1.7			1.3	1.0 - 1.6
IIA	35	1.3	0.9 - 2.0			1.3	0.9 - 2.0
IIB	110	2.2	1.7 - 2.9			2.2	1.7 - 2.9
IIIA	72	2.6	1.9 - 3.5			2.7	1.9 - 3.7
IIIB	39	2.6	1.8 - 3.9			2.4	1.6 - 3.6
IV	13	9.0	5.0 - 16.2			10.7	5.9 - 19.3

[a] COPD was unknown in 57 patients

[b] Including myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and angina pectoris

[c] Within 5 years of diagnosis, except basal cell skin carcinoma

RR = relative risk

CI = confidence interval

COPD = chronic obstructive pulmonary disease

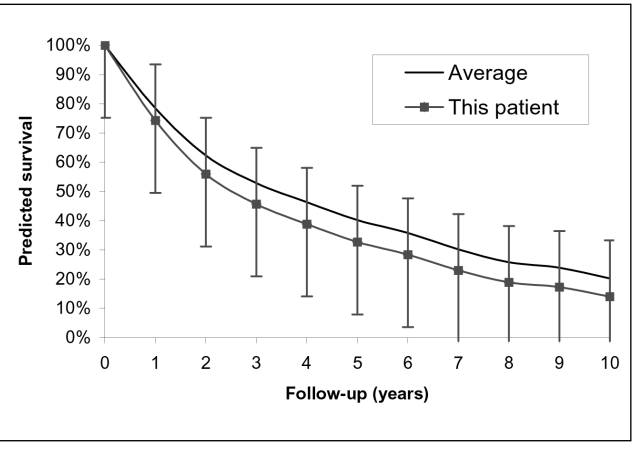
FEV_1% = forced expiratory volume in 1 second expressed as a percent of predicted

Figure 1. Preoperative mode of the prognostic model: predicted survival of a 64-year old male with COPD, congestive heart failure, and clinical tumor stage IB

Prediction of survival after nonsmall cell lung cancer surgery

Nr: 1

		Value
Preoperative predictors		
Sex	Male=1 / Female=0	1
Age	Years	64
COPD	Yes=1 / No=0	1
Congestive heart failure	Yes=1 / No=0	1
Renal disease	Moderate to severe=1 / No=0	0
Any prior tumor	Yes=1 / No=0	0
Clinical stage	IA=1 / IB=2 / IIA-IIIB=3 / IV=4	2
Postoperative predictors		
Type of resection	Lobectomy=1 / Wedge=2 / Bilobectomy=3 / Left-sided pneumonectomy=4 / Right-sided pneumonectomy=5	
Pathological stage	IA=1 / IB-IIA=2 / IIB-IIIB=3 / IV=4	



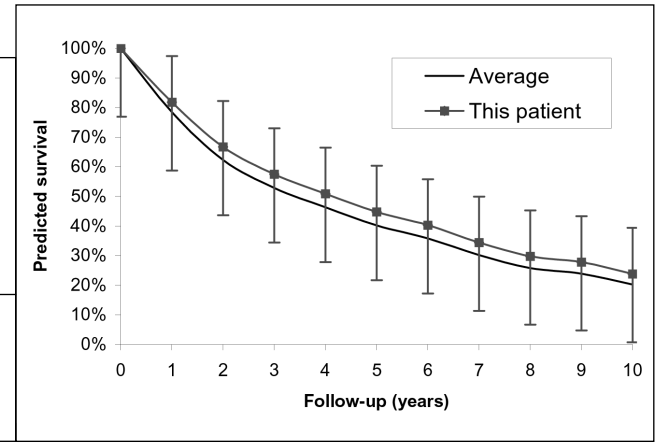
	Formula	See Figure for graphical illustration
1-year survival [95% confidence interval]	**74%**	**55% - 86%**
2-year survival [95% confidence interval]	**56%**	**31% - 75%**
5-year survival [95% confidence interval]	**33%**	**11% - 57%**
10-year survival [95% confidence interval]	**14%**	**2% - 38%**

Figure 2. Postoperative mode of the prognostic model: predicted survival of a 64-year old male with COPD and congestive heart failure who underwent lobectomy for pathological tumor stage IB

Prediction of survival after nonsmall cell lung cancer surgery

Nr: 2

		Value
Preoperative predictors		
Sex	Male=1 / Female=0	1
Age	Years	64
COPD	Yes=1 / No=0	1
Congestive heart failure	Yes=1 / No=0	1
Renal disease	Moderate to severe=1 / No=0	0
Any prior tumor	Yes=1 / No=0	0
Clinical stage	IA=1 / IB=2 / IIA-IIIB=3 / IV=4	
Postoperative predictors		
Type of resection	Lobectomy=1 / Wedge=2 / Bilobectomy=3 / Left-sided pneumonectomy=4 / Right-sided pneumonectomy=5	1
Pathological stage	IA=1 / IB-IIA=2 / IIB-IIIB=3 / IV=4	2



	Formula	See Figure for graphical illustration
1-year survival [95% confidence interval]	**82%**	**66% - 90%**
2-year survival [95% confidence interval]	**67%**	**44% - 82%**
5-year survival [95% confidence interval]	**45%**	**19% - 67%**
10-year survival [95% confidence interval]	**24%**	**5% - 48%**

COMMENT

In terms of survival, NSCLC is a heterogeneous disease with a remarkable variation in outcome among individual patients. During the past decades, researchers have attempted to identify factors that can be used to predict outcome of NSCLC patients. Besides tumor stage, other factors, such as comorbidity and extent of resection, also have been proven to predict survival after NSCLC surgery [3-6]. In previously published studies we found the CCI to predict postoperative outcome more accurately than the individual comorbid conditions [8, 9]. However, this comorbidity index was not developed specifically for NSCLC surgery patients. Therefore, only individual comorbid conditions of the CCI which were associated with an impaired survival in the multivariate analysis were included in our prognostic model. In addition, the CCI does not include several other prognostic factors in NSCLC surgery patients, such as gender, age, extent of resection, and tumor stage, and it does not estimate the long-term survival of individual patients after surgical resection.

We developed a prognostic model with a preoperative and a postoperative mode, including tumor-related factors, treatment-related factors, and clinical variables, for prediction of survival of individual patients after NSCLC surgery. We included prognostic factors that are all readily available and interpretable to the clinician. Most factors have been recognized as predictive in previous studies on patients operated on for NSCLC [1, 2, 4, 5]. We note that if some apparently obvious risk factor does not appear significantly predictive ($p < 0.05$) in a multivariate model, such as congestive heart failure and COPD in our study, one cannot conclude that this is irrelevant to outcome and exclude this particular risk factor out of the prognostic model.

The postoperative mode of the prognostic model, including pathological tumor stage and type of resection, provided substantially better discrimination than a comorbidity index such as the CCI (c statistic 0.65 versus 0.55, $p < 0.0001$), the preoperative mode (c statistic 0.65 versus 0.61, $p = 0.0002$), or only pathological tumor stage (c statistic 0.65 versus 0.60, $p < 0.0001$). Nevertheless, it is well recognized that pathological tumor stage is the most powerful predictor of long-term survival and the present postoperative mode of the prognostic model provides only slightly better discrimination than only pathological tumor stage. Moreover, due to similar relative risks of some tumor stages in our multivariate analysis, we combined these tumor stages in one subgroup. More patient data will be needed to improve the accuracy of this postoperative mode of the model.

Despite the postoperative mode being the most accurate in prediction of

survival, it is important to select poor prognosis patients prior to surgery without knowledge of type of resection and pathological tumor stage. For this purpose, the preoperative mode is more appropriate, which proved to be as accurate as only pathological tumor stage in prediction of survival (c statistic 0.61 versus 0.60, $p = 0.90$), and more accurate than the CCI (c statistic 0.61 versus 0.55, $p < 0.0001$). Therefore, the preoperative mode can be used as a first evaluation to estimate survival of an individual patient and identify poor prognosis patients. Also in this mode of the prognostic model, some tumor stages are combined in one subgroup and more patient data will be necessary to improve the accuracy of this preoperative mode of the model. The postoperative mode can either be used preoperatively to estimate survival assuming the type of resection planned and assuming that clinical tumor stage will not alter after resection, or it can be used postoperatively when type of resection and pathological tumor stage are definite. A practical version of the present prognostic model for easy access and use by clinicians is available on the Internet (http://www.cardiothoracicresearch.nl).

Although bootstrapping techniques were used for internal validation of the model, a limitation of our study is that the prognostic model is not validated by an external test group. This may be essential before further clinical application is initiated [20]. In addition, this study is limited by the relatively small amount of clinical data that was pooled from only two centers, both in terms of number of data as well as availability of data. For example, histopathological cell type failed to predict survival in our analysis, while others have shown an improved survival for squamous cell histology over adenocarcinoma, large cell carcinoma, and bronchoalveolar cell carcinoma [10, 21-23]. Moreover, as we stated before, we combined some tumor stages in one subgroup. We plan to further improve and validate the prognostic model using data from other clinics.

In conclusion, we developed a simple prognostic model with a preoperative and postoperative mode, which may be used for risk assessment in individual patients. The prognostic model successfully estimates long-term survival of individual patients and performed well with assessments of internal validity, with the postoperative mode being the most accurate. We therefore are confident that the model will also perform well for future patients who face the choice between operative treatment and other treatment modalities for NSCLC. Inclusion of more factors with additional prognostic value could potentially further improve the accuracy of the model. If further validated, this prognostic model could help clinicians and patients in clinical decision-making and treatment tailoring based on the estimated survival after surgery.

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CHAPTER 11

General Discussion

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INTRODUCTION

Despite the increased awareness over the past 3 decades of the influence of smoking, exposure to environmental carcinogens, and lifestyle on the risk of cancer, lung cancer remains the leading cause of cancer-related death worldwide [1]. Early-stage NSCLC is regarded as curatively resectable. However, morbidity and mortality after pulmonary resection is significant [2, 3]. Furthermore, disappointing prognosis with actuarial 5-year survival rates ranging from 67% in pathological stage IA to 38% in pathological stage IIB is reported [4]. Because of these figures the need for further investigation of prognostic factors and development of non-invasive diagnostic procedures is evident.

NON-INVASIVE DIAGNOSTIC PROCEDURES

Preoperative staging is an important aid to determine the clinical stage of the patient and consequently the success of treatment [4]. Clearly, a cure to patients with a diagnosis of NSCLC cannot be promised at any stage. However, survival following treatment of this disease is mainly stage related, and patients with the lower-stage disease have the best chance for curative treatment. Currently, the TNM classification system is predominantly used to describe the extent of disease, and has become a tool to determine prognosis and treatment.

Traditional preoperative non-invasive staging modalities include chest radiography, computed tomography (CT), and magnetic resonance imaging (MRI). In many instances, non-invasive radiological tests serve to prevent unnecessary surgical interventions from being performed. If these tests do not suggest the presence of metastatic disease or unresectable local disease, then further invasive staging procedures including mediastinoscopy may be necessary. New non-invasive staging modalities, such as the positron emission tomography (PET) scan, may help to further stratify patients into appropriate therapeutic and prognostic categories, since underestimation and overestimation of tumor stage is still common in NSCLC [5, 6], as we also have shown in two studies (Chapter 5 and Chapter 8).

In the context of staging NSCLC, the limited anatomical resolution of PET prevents accurate assessment of the tumor itself (T stage), and the distinction of intrapulmonary nodes close to the mediastinum from mediastinal nodes. PET scan has been found to be consistently superior to CT scan at detecting or excluding metastatic nodal disease (N stage), in both normal sized and enlarged nodes [7-10]. In line with the results of these studies, our meta-analysis showed FDG PET scan to

be superior to CT scan in detecting mediastinal lymph node metastases (Chapter 3). Due to the low positive predictive value, as with CT scan, invasive mediastinal staging is still required in those with increased nodal uptake so as to prevent denial of potentially curative surgery to a patient on the basis of a false-positive scan. With the high negative predictive value of PET scan, a negative mediastinum on PET can lead directly to thoracotomy, without further invasive preoperative staging. This implementation should be done with caution in case of patients with centrally located tumors, in case of positive central hilar N1-disease, and in case of bronchoalveolar cell carcinoma, due to the higher false-negative rate in these circumstances [11].

In addition, PET scan improves non-invasive clinical staging by detecting extrathoracic metastases without any evidence of metastases after conventional imaging [12, 13], and PET scan can indicate suspected lymph nodes in stations not amenable to mediastinoscopy (e.g. paraesophageal or supraclavicular lymph nodes).

Further support for the use of the PET scan has been derived from models of cost effectiveness [14, 15]. Strategies using a combination of PET scan and CT scan to identify those patients with possible nodal involvement requiring preoperative biopsy appear to be a cost effective means of reducing the probability that a patient with inoperable mediastinal nodal metastases would undergo unnecessary surgery [14, 15]. Translated into clinical terms, if PET was added to the preoperative work-up of patients with a negative mediastinal CT scan as recommended by Dietlein and colleagues [15], PET could prevent approximately one "futile" thoracotomy for every 10 scans performed [16].

Despite its apparent advantages, the PET scan has yet to find widespread application in the clinical work-up of lung cancer. This is in part related to the high cost of PET, limited availability, and the need for stronger evidence of its efficacy. Further investigation is required before conclusions can be made with respect to whether a diagnostic strategy that includes PET can improve survival of NSCLC patients. Nowadays, no single imaging method is conclusive in evaluating operability of NSCLC patients.

Future prospects

The indication of PET scan as a complimentary tool to CT scan in the diagnosis and staging of NSCLC gradually gains widespread acceptance. Its role needs further validation in multi-center large-scale randomized studies, focusing mainly on treatment outcome parameters, on the question whether PET scan actually improves survival prospects, and cost-efficacy issues. Routine use of PET scan in NSCLC staging is still hampered by the high cost and the limited availability of the

technique.

A fascinating development is the introduction of combined PET-CT machines. This technology will probably improve diagnostic accuracy, provide surgical planning and guide biopsies by merging the anatomy and biology into a single procedure.

Currently, mediastinoscopy remains the gold standard for patients with NSCLC with suspected N2 or N3 disease. Although PET reduces the need for mediastinoscopy, it is not fullproof and cannot yet replace mediastinoscopy for assessment of mediastinal lymph nodes. Further investigation is necessary to evaluate the most effective use of mediastinoscopy in patients who have already had a PET scan.

PROGNOSTIC FACTORS

In the surgical treatment of NSCLC, identification of reliable predictors of adverse outcome is of great value, as it would facilitate the identification of patients most likely to benefit from surgical treatment.

It is clear that a major influence on cure, and as a result on long-term prognosis, is tumor stage. For patients with NSCLC who are fit for surgery, pulmonary resection is the best treatment for stage I and stage II disease, but accurate preoperative staging is essential for good results.

The TNM staging system characterizes lung cancer with respect to several factors including tumor size and location, extent of lymphatic invasion, and the presence of extrathoracic metastases. In 1997, a new international staging system was proposed by Mountain [4]. The main modifications in this new staging system were the subdivision of stage I and stage II tumors into “A” and “B”, the placement of T3N0M0 tumors into the stage IIB category, and reclassification of ipsilateral pulmonary metastases. Recently published series have even reported a superior survival for small tumors within stage IA NSCLC [17, 18]. In addition, in our study in pathological stage IA patients we also found a superior survival for patients with tumors of 0 to 20 mm in diameter compared with patients with tumors of 21 to 30 mm in diameter (Chapter 8). However, in a recently published study Takeda and colleagues [19] found that a tumor size of greater than 5 cm was an independent prognostic predictor in patients with pathological N0-disease, whereas no survival difference was seen between patients with tumors of 0 to 20 mm in diameter compared with patients with tumors of 21 to 30 mm in diameter. As a result, controversy regarding the relation between tumor size and patient prognosis persists and the appropriate cut-off point for tumor size to classify T1 and T2 disease

continues to be debated. Further research work is necessary for definition of T stage in the next revision of the TNM staging classification.

The role of surgery in the elderly dramatically changed with time with reports from the 1980s and 1990s gradually including more elderly patients showing unequivocally promising results [20, 21]. This was facilitated by an improvement in operative techniques, anesthetic techniques, and postoperative care, but also accumulated knowledge about risk factors, either pretreatment, such as the existence of concomitant disease, or treatment-related, such as type of resection. A consistent finding over the years is that long-term survival of lung cancer treated with various surgical procedures is influenced by patient age [22-24], which is not surprising since elderly patients do generally have a decreased life expectancy compared with younger patients, regardless of the presence of NSCLC. With regard to operative mortality, recently published series reported operative mortality rates comparable to that of younger subgroups of patients [3, 25, 26]. We also found an acceptable postoperative mortality rate in patients over 70 years old (Chapter 7). Age itself probably reflects other prognostic factors such as cardiovascular function, and pulmonary function. Therefore, at present advanced age should not be the only reason to withhold surgical therapy and these patients should be carefully selected. Particular emphasis must be placed on preoperative evaluation of pulmonary function and cardiac risk.

Despite tremendous advances in operative techniques and perioperative medical care, it seems in general that pneumonectomy carries a higher risk of morbidity and mortality compared with lesser resections [3, 27, 28]. Moreover, right-sided pneumonectomy is reported to carry a higher risk than left-sided pneumonectomy [27, 29]. The average mortality rate associated with left-sided pneumonectomy is approximately 4% to 6%, with reported values ranging between 11% and 37% for right-sided pneumonectomy [27, 30]. Lung-sparing procedures, such as wedge resections and segmental resections, are sometimes performed in patients with impaired pulmonary function at the risk of increasing locoregional recurrences in comparison with pneumonectomy or lobectomy [31]. However, operative mortality and morbidity in lung-sparing procedures are lower compared with lobectomy or pneumonectomy [32]. Therefore, the risk of morbidity and mortality after an operation has to be carefully balanced with the risk of cancer recurrence and long-term survival after surgery. Despite lobectomy still being the surgical treatment of choice for eligible patients with early-stage NSCLC, lung-sparing procedures provide an adequate alternative in patients with associated comorbidity. Pneumonectomy provides no benefits in terms of locoregional recurrence and survival in comparison with lobectomy [33], but because of

anatomical and technical limitations pneumonectomy may sometimes be unavoidable [34].

Accurate identification of comorbidity is essential in assessing patient's health status and quantifying risk of poor outcome following NSCLC surgery. Currently, no standard method exists for assessment of comorbidities collectively in NSCLC surgery patients. We evaluated the ability of the Charlson comorbidity index (CCI) to stratify comorbidity severity in NSCLC surgery patients and predict postoperative outcome. We found the CCI to be a strong predictor of major postoperative complications (including death) (Chapter 5) as well as long-term survival (Chapter 6). The CCI is a better predictor than individual comorbid conditions. We found only a CCI grade of 3 - 4 predictive for major complications. However, only 3 patients were in the CCI grade ≥ 5 group. With regard to survival, we found an impaired survival for every increase in CCI grade. Consequently, it is important to select the best possible treatment for those patients with a CCI score ≥ 3 due to the higher risk of postoperative complications and impaired survival in these patients. Despite the fact that these patients are in the high-risk group, these patients still have a superior survival after surgical treatment than after radiotherapy (Chapter 9), and thus surgical therapy in these patients is the best treatment if pulmonary reserve is sufficient.

Despite the fact that the CCI is a prognostic index for poor postoperative outcome, it is suboptimal for application in NSCLC surgery patients. The CCI does not include several other prognostic factors in NSCLC surgery patients, such as gender, age, extent of resection, and tumor stage. In addition, the CCI does not estimate the survival of individual patients after NSCLC surgery. Therefore, we developed a prognostic model with a preoperative and postoperative mode for estimation of survival after NSCLC surgery that includes clinical factors, tumor-related factors, as well as treatment-related factors (Chapter 10). This prognostic model can be used in daily practice to estimate the survival of individual patients after NSCLC surgery. Although the predictive value of this model is not optimal, it is equal (preoperative mode) or even better (postoperative mode) than the predictive value of pathological tumor stage. Inclusion of more factors with additional prognostic value could potentially further refine the accuracy of this model.

Future prospects

The state of the art of lung cancer surgery is still a complete resection with careful intraoperative assessment of hilar and mediastinal lymph nodes. The challenge for the future will be to continue the search for biomarkers of NSCLC and early

diagnosis, to improve patient selection, and offer patients the best treatment with low morbidity and mortality rates and optimal long-term survival. A better understanding of specific prognostic factors is important to avoid aggressive and unnecessary treatment. As we, with many others, have shown that postoperative outcome is not only dependent on pathological tumor stage but also on many other factors, such as comorbidity, it is of utmost importance to incorporate these predictive factors into prognostic models. We attempted to construct such a prognostic model for survival after surgical resection. Despite the fact that the predictive value of this model is equal or better than the predictive value of only pathological stage, it is still not optimal. More patient data and other risk factors will be needed to improve the prognostic model and its accuracy to estimate survival after NSCLC surgery. In order to improve the treatment decision making of individual patients in relation to prognosis, more research on prognostic factors is necessary.

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CHAPTER 12

Summary & Samenvatting

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SUMMARY

Objective.
Surgical resection remains the treatment modality of choice in early-stage nonsmall cell lung cancer (NSCLC). The prognosis of a patient after surgical resection depends on many factors. The objective of this thesis was to further evaluate prognostic factors for poor outcome and analyze recently developed diagnostic procedures.

Chapter 1. *General introduction*
This chapter is the introduction to this thesis. It provides a short overview about the main features of NSCLC. The histological classification of NSCLC is described. The TNM staging system is illustrated. Advantages and disadvantages of current non-invasive staging modalities, such as CT, MRI and PET, are reviewed. A short overview of the treatment in NSCLC patients, survival, and prognosis is given. Finally, the aims of the studies incorporated in this thesis are outlined.

Chapter 2. *Prognostic factors in nonsmall cell lung cancer surgery*
This chapter describes a review of the current prognostic factors for early postoperative morbidity, mortality, and long-term survival. It is important to know what the risk of poor outcome is in patients referred for surgical resection, first to make an adequate decision of treatment, and second to inform and advice patients about the possible operative risk. The TNM stage and type of resection are the two most predictive factors for poor outcome.

Chapter 3. *Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer*
This chapter describes a meta-analysis in which the diagnostic accuracy of FDG PET and CT on detecting mediastinal lymph node metastases was compared. Preoperative diagnostic work-up of patients with NSCLC is of greatest importance to obtain a clinical TNM stage and offer the patients the best treatment of choice. Since patients with positive N1 lymph nodes are potentially curable with surgical therapy and patients with positive N2 or N3 lymph nodes are not, it is of utmost importance to detect these positive N2 and N3 lymph nodes preoperatively. A systematic review was undertaken to select high quality studies that evaluated the accuracy of both FDG PET as well as CT scan in detecting mediastinal lymph node metastases. Seventeen studies were included. The 17 selected studies included 833

patients. Summary receiver operating characteristic (ROC) curves were constructed and the point on the curve with equal sensitivity and specificity was calculated. The point on the ROC curve with equal sensitivity and specificity for FDG PET was Q* = 0.90 (95% confidence interval, 0.86 to 0.95). For CT it was 0.70 (95% confidence interval, 0.65 to 0.75). The difference was highly significant ($p < 0.0001$). This meta-analysis indicates that FDG PET is more accurate than CT in detecting mediastinal lymph node metastases.

Chapter 4. *Relearning the lesson from the past – are we making progress?*
This chapter containes a replyletter in which we elaborate on the contribution of the PET scan in improvement of clinical staging of NSCLC patients, in particular with regard to the use of mediastinoscopy once a PET scan is performed. Staging of the mediastinum by PET scan is definitely better than staging by CT scan alone. In addition, PET scan has a higher accuracy of detecting extrathoracic metastases compared with CT scan, and PET scan can indicate suspected lymph nodes in stations not amenable to mediastinoscopy. The low positive predictive value of PET makes cytologic or histologic confirmation necessary in case of a positive mediastinum. With the high negative predictive value of PET, a negative mediastinum on PET can lead directly to thoracotomy. This implementation should be done with caution in case of patients with centrally located tumors, in case of positive central hilar N1-disease, and in case of bronchoalveolar cell carcinoma. Although PET scan does not eliminate mediastinoscopy, PET scan does reduce the need for mediastinoscopy.

Chapter 5. *Validation of the Charlson comorbidity index in patients with operated primary nonsmall cell lung cancer*
This chapter describes a retrospective study regarding the validity of the Charlson comorbidity index (CCI) in patients with operated primary NSCLC. Patients included consisted of 205 (148 men, 57 women) consecutive resections for NSCLC. The patients ranged in age from 29 to 82 years, with a mean age of 64 years. Each patient was assessed according to the CCI. Postoperative events were divided into minor and major complications. To discriminate independent risk factors for major complications after surgical resection univariate and multivariate logistic regression analysis were performed. One-way analysis was used to determine the influence of comorbidity on length of hospital stay. Five patients (2.4%) died postoperatively. In the univariate analysis, male gender, Charlson comorbidity grade 3 - 4, any prior tumor treated in the last 5 years, and chronic pulmonary disease were significant predictors of adverse outcome. In the multivariate analysis only Charlson

comorbidity grade 3 - 4 was associated with an increased risk of major complications (odds ratio, 9.8; 95% confidence interval, 2.1 to 45.9). Although only Charlson comorbidity grade 3 - 4 was a significant predictor, for every increase of the comorbidity grade the relative risk of adverse outcome showed a slight increase. An increase of the comorbidity grade showed a slight increase of length of hospital stay, although this was not significant ($p = 0.107$). Given these results, we conclude that the CCI is a strong predictor of major complications and is a better predictor than individual comorbid conditions.

Chapter 6. *Charlson comorbidity index as a predictor of long-term outcome after surgery for nonsmall cell lung cancer*

This chapter describes a retrospective study regarding the impact of the Charlson comorbidity index (CCI) on long-term survival in patients with curatively resected NSCLC. Patients included consisted of 433 (340 men, 93 women) consecutive resections for NSCLC. The patients ranged in age from 37 to 82 years, with a mean age of 65 years. Each patient was assessed according to the CCI. Survival was estimated by the Kaplan-Meier method. Univariate and multivariate Cox proportional hazard analyses determined risk factors for survival. Sixteen patients (3.7%) died postoperatively. Five-year overall and disease-free survival was 45% and 43%, respectively. Among patients with Charlson comorbidity grade 0, 5-year overall survival was 52%, among patients with Charlson comorbidity grade 1 - 2 it was 48%, and among patients with Charlson comorbidity grade ≥ 3 it was 28%. In the univariate analysis, male gender, age, CCI, congestive heart failure, chronic pulmonary disease, clinical stage, pathological stage, and type of resection were significant predictors of impaired survival. In the multivariate analysis age, Charlson comorbidity grade 1 - 2, Charlson comorbidity grade ≥ 3, bilobectomy, pneumonectomy, and pathological stage were associated with an impaired overall and disease-free survival. We conclude that the CCI is a better predictor of long-term survival than individual comorbid conditions. We recommend the use of a validated comorbidity index in the selection of patients for NSCLC surgery.

Chapter 7. *Lung resection for nonsmall cell lung cancer in patients older than 70: mortality, morbidity, and late survival compared with the general population*

This chapter describes a retrospective study in which prognosis of lung resection for NSCLC in patients older than 70 years old is determined, and survival is compared with survival of the general elderly (> 70 years old) population. One hundred and twenty-six (101 men, 25 women) consecutive patients were included. The mean age

at time of surgery was 74 years (range, 70 to 82 years). Each patient was assessed according to the Charlson comorbidity index (CCI). Postoperative events were divided into minor and major complications. Risk factors for complications and long-term survival were assessed by univariate and multivariate logistic regression analyses and Cox proportional hazard analyses. Survival was compared with the yearly-expected survival rates of the general population. The hospital mortality was 3.2%. Minor complications occurred in 57%, major complications in 13%. Only Charlson comorbidity grade 3 - 4 was predictive for major complications (odds ratio, 12.6; 95% confidence interval, 1.5 to 108.6). Five and ten-year survival rates were 37% and 15%, respectively. Smoking, chronic obstructive pulmonary disease, and pathological stages IIIA and IIIB were risk factors for long-term survival. The observed survival was lower than the expected survival ($p < 0.001$), but the difference decreased with increasing time after pulmonary resection ($p = 0.01$). We conclude that pulmonary resection in patients older than 70 years old shows acceptable morbidity, mortality, and survival. The CCI is a better predictor of major postoperative complications than individual comorbid conditions. With time survival is no longer correlated with the disease but follows the same pattern as for the general population.

Chapter 8. *Survival after pathological stage IA nonsmall cell lung cancer: Tumor size matters*

This chapter describes a retrospective study evaluating the prognostic factors for survival in pathological stage IA NSCLC patients with special emphasis on tumor size, and assessing tumor recurrence rate by actual and actuarial analysis. One hundred and thirty (94 men, 36 women) consecutive patients were included. The mean age at time of surgery was 63 years (range, 37 to 81 years). Each patient was assessed according to the Charlson comorbidity index (CCI). Patients were categorized as patients with pathological tumors of 0 to 20 mm in diameter ($n = 75$) and 21 to 30 mm in diameter ($n = 55$). Risk factors for overall and disease-free survival were determined by Cox proportional hazard analysis. The Kaplan-Meier method was used for estimation of the actuarial recurrence rate and the cumulative incidence method was used to estimate the actual recurrence rate. The mean pathological tumor size was 20 ± 6 mm. Patients with tumors of 0 to 20 mm in diameter had a five-year overall and disease-free survival of 69% and 68%, respectively. The five-year overall and disease-free survival for patients with tumors of 21 to 30 mm in diameter was 51% and 48%, respectively. The difference between the two groups was significant ($p = 0.038$ and $p = 0.015$). In multivariate analysis, larger tumor size, CCI score ≥ 3, and pneumonectomy were associated with an

impaired overall and disease-free survival. The actual recurrence rate within 10 years was lower than the actuarial recurrence rate (23% versus 29%). The results obtained in this study highlight that size of the tumor affects survival in pathological stage IA NSCLC patients and that stage IA disease should be subdivided in two separate stages. In patients with early-stage NSCLC and relatively good prognosis actual recurrence rate is more realistic than the actuarial recurrence rate.

Chapter 9. *Proper treatment selection may improve survival in patients with clinical early-stage nonsmall cell lung cancer*

This chapter describes a retrospective study in which treatment selection and outcome in clinical early-stage NSCLC patients is evaluated. Patients included consisted of 360 (286 men, 74 women) consecutive patients diagnosed with clinical stage IA to IIB (T1-2, N0-1, M0) NSCLC. Patients were divided into surgically treated (n = 269) and nonsurgically treated (n = 91). Each patient was assessed according to the Charlson comorbidity index (CCI). Logistic regression analysis was used to discriminate independent risk factors for major postoperative complications. Cox proportional hazard analysis determined risk factors for survival. Mean age was 64 years for the surgical and 74 years for the nonsurgical patients ($p < 0.0001$). Mean CCI score was 1.3 and 2.4 ($p < 0.0001$), and 5-year survival was 47% and 3% ($p < 0.0001$), respectively. Male sex, pneumonectomy, and CCI score of 3 or more were predictive for major postoperative complications. For the nonsurgical patients receiving radiotherapy the 2-year survival was 40%, for the patients receiving no radiotherapy 5%. Male sex, age, treatment, and clinical stage were prognostic for survival of the total study population. Patients with a CCI score of 3 or more showed a better survival after surgery than after radiotherapy (36% versus 6%, $p < 0.0001$). Patients with a CCI score of 3 or more who were surgically treated had a higher prevalence of FEV_1% of 70 or more compared with the nonsurgically treated patients (82% versus 23%, $p < 0.0001$). We conclude that despite the increased risk of major postoperative complications, patients with a CCI score of 3 or more show a better survival after surgery than after radiotherapy. For patients with high comorbidity but with sufficient pulmonary reserve, surgery offers the best outcome. For patients with high comorbidity and insufficient pulmonary reserve or in those who refuse surgery, curative radiotherapy is an alternative.

Chapter 10. *Long-term survival after nonsmall cell lung cancer surgery: development and validation of a prognostic model with a preoperative and postoperative mode*

This chapter describes a retrospective study in which a prognostic model with a preoperative and a postoperative mode is developed for estimation of survival of each individual patient after NSCLC surgery. Patients included consisted of 766 (600 men, 166 women) consecutive resections. The mean age at time of surgery was 65 years (range, 37 to 84 years). In retrospect, each patient was assessed for preoperative Charlson comorbidity index (CCI). Univariate and multivariate Cox proportional hazard analysis was used to determine risk factors for survival. The performances of the prognostic model, the CCI, and pathological stage were quantified by a concordance statistic (c statistic), and were compared with each other. Hospital mortality occurred in 34 patients (4.4%). Five-year survival was 40% (95% confidence interval, 36 to 44). The discriminative performance was poor for the CCI (c = 0.55), better for pathological stage (c = 0.60) and for the preoperative mode (c = 0.61), and best for the postoperative mode (c = 0.65). We conclude that the prognostic model successfully estimates long-term survival of an individual patient, with the postoperative mode being the most accurate. Inclusion of more factors with additional prognostic value could potentially further improve the accuracy of the models and thereby refine the identification of patients with a relatively poor prognosis. These prognostic models could help clinicians and patients in clinical decision-making and treatment tailoring based on the estimated survival after surgery.

Chapter 11. *General discussion*

This chapter is a comprehensive discussion in which the most important results and conclusions of the studies in previous chapters of this thesis are reviewed. Possible clinical implications of the conclusions provided by this thesis were discussed together with recommendations for further research.

SAMENVATTING

Doel.
Chirurgische resectie is de beste behandelingsoptie in vroege stadia van niet-kleincellig longcarcinoom. De prognose van een patiënt na chirurgische resectie is afhankelijk van vele factoren. Het doel van dit proefschrift is het verder evalueren van prognostische factoren voor postoperatieve complicaties en overleving en het analyseren van recent ontwikkelde diagnostische procedures.

Hoofdstuk 1. *Algemene introductie*
Dit hoofdstuk is de introductie van dit proefschrift. Het geeft een korte samenvatting van de diagnostiek en behandeling van niet-kleincellig longcarcinoom weer. De histologische classificatie van niet-kleincellig longcarcinoom wordt beschreven. Het TNM stadiëringssysteem wordt besproken. Voordelen en nadelen van de huidige niet-invasieve stadiëringsmodaliteiten, zoals CT, MRI, en PET, worden beschreven. Een beknopte beschrijving van de therapie, overleving en prognose volgt. Tenslotte worden de doelen van de studies in dit proefschrift uiteengezet.

Hoofdstuk 2. *Prognostische factoren bij chirurgie voor niet-kleincellig longcarcinoom*
Dit hoofdstuk beschrijft een samenvatting van de huidige prognostische factoren voor postoperatieve morbiditeit, mortaliteit en overleving. Het is belangrijk om te weten wat het risico is op een slechte prognose bij patiënten die worden verwezen voor chirurgie, ten eerste om een adequate therapeutische beslissing te nemen, en ten tweede om patiënten beter in te kunnen lichten en adviseren omtrent de mogelijke operatieve risico's. Zoals we in dit hoofdstuk beschrijven zijn het TNM stadiëringssysteem en type resectie de twee meest voorspellende factoren voor een slechte prognose.

Hoofdstuk 3. *Meta-analyse van positron emission tomography en computed tomography in het detecteren van mediastinale lymfkliermetastasen in niet-kleincellig longcarcinoom*
Dit hoofdstuk beschrijft een meta-analyse waarin de dignostische nauwkeurigheid van FDG PET en CT in het detecteren van mediastinale lymfkliermetastasen wordt vergeleken. Preoperatieve diagnostische work-up van patiënten met een niet-kleincellig longcarcinoom is uiterst belangrijk om een klinisch TNM stadium te verkrijgen en patiënten de best mogelijke behandeling te bieden. Omdat

patiënten met positieve N1 klieren chirurgisch curabel zijn en patiënten met N2 of N3 metastasen niet, is het van groot belang om deze positieve N2 en N3 klieren preoperatief te detecteren. Een systematische review was gedaan om studies van goede kwaliteit te selecteren die zowel de nauwkeurigheid van FDG PET als van CT scan in het detecteren van mediastinale lymfkliermetastasen hebben geëvalueerd. Zeventien studies zijn geïncludeerd. Het totaal aantal patiënten was 833. Summary receiver operating characteristic (ROC) curven werden geconstrueerd en het punt op de curve waarbij sensitiviteit en specificiteit gelijk waren werd berekend. Dit punt op de ROC curve met dezefde sensitiviteit en specificiteit was Q* = 0,90 (95% confidence interval, 0,86 tot 0,95) voor FDG PET. Voor CT was het 0,70 (95% confidence interval, 0,65 tot 0,75). Dit verschil was significant ($p < 0,0001$). Deze meta-analyse laat zien dat FDG PET nauwkeuriger is dan CT in het detecteren van mediastinale lymfkliermetastasen.

Hoofdstuk 4. *Opnieuw leren van lessen uit het verleden – maken we progressie?*
Dit hoofdstuk bevat een antwoordbrief waarin we de bijdrage van de PET scan in het verbeteren van de klinische stradiëring van patiënten met een niet-kleincellig longcarcinoom beschrijven, met name in welke omstandigheden na het maken van een PET scan een mediastinoscopie verricht moet worden. Stadiëring van het mediastinum met de PET scan is veel nauwkeuriger dan met de CT scan. Daarnaast is de PET scan veel nauwkeuriger dan CT scan in het detecteren van metastasen op afstand en kan de PET scan lymfklieren detecteren op plaatsen die niet toegankelijk zijn voor mediastinoscopie. Door de lage positief voorspellende waarde van de PET scan is histologische confirmatie noodzakelijk bij een PET positieve mediastinale lymfklier. Met de hoge negatief voorspellende waarde van de PET scan kan er direct tot operatie worden overgegaan indien de PET scan negatief is. Voorzichtigheid is echter geboden bij patiënten met een centraal gelocaliseerde tumor, bij patiënten met positieve centraal gelegen N1-klieren, en bij patiënten met een bronchoalveolair cel carcinoom. Hoewel mediastinoscopie niet vervangen kan worden door de PET scan, kan het gebruik van de PET scan wel het aantal mediastinoscopieën reduceren.

Hoofdstuk 5. *Validiteit van de Charlson comorbiditeit index in patiënten die geopereerd zijn aan een primair niet-kleincellig longcarcinoom*
Dit hoofdstuk beschrijft een retrospectieve studie betreffende de validiteit van de Charlson comorbiditeit index (CCI) bij patiënten die geopereed zijn aan niet-kleincellig longcarcinoom. Er werden 205 patiënten (148 mannen, 57 vrouwen) geïncludeerd die aan niet-kleincellig longcarcinoom zijn geopereerd. De leeftijd

van de patiënten variëerde van 29 tot 82 jaar, met een gemiddelde leeftijd van 64 jaar. Elke patiënt werd gescoord volgens de CCI. Postoperatieve complicaties werden onderverdeeld in kleine en grote complicaties. Om onafhankelijke risicofactoren voor grote postoperatieve complicaties te analyseren werden univariate en multivariate logistische regressie analyses gedaan. Vijf patiënten (2,4%) stierven postoperatief. Mannelijk geslacht, CCI score 3 - 4, een tumor behandeld in de laatste 5 jaar en chronisch obstructief longlijden waren voorspellend voor grote postoperatieve complicaties in de univariate analyse. In de multivariate analyse was alleen CCI score 3 - 4 geassocieerd met een verhoogde kans op grote postoperatieve complicaties (odss ratio, 9,8; 95% confidence interval, 2,1 tot 45,9). Hoewel alleen CCI score 3 - 4 significant voorspellend is, zie je voor elke verhoging van de comorbiditeitscore een verhoging van het relatieve risico op grote postoperatieve complicaties. Een hogere comorbiditeitscore liet een lichte verlenging van het ziekenhuisverblijf zien maar dit verschil was niet significant (p = 0,107). Gezien de resultaten van deze studie concluderen we dat de CCI een sterke prognostische factor is voor grote postoperatieve complicaties en dat de CCI beter voorspellend is dan de individuele comorbiditeiten.

Hoofdstuk 6. *De Charlson comorbiditeit index als voorspellende factor van langetermijnsoverleving na chirurgie voor niet-kleincellig longcarcinoom*

Dit hoofdstuk beschrijft een retrospectieve studie betreffende de prognostische waarde van de Charlson comorbiditiet index (CCI) voor langetermijnsoverleving van patiënten die geopereerd zijn aan een niet-kleincellig longcarcinoom. Er werden 433 patiënten (340 mannen, 93 vrouwen) geïncludeerd. De leeftijd van de patiënten variëerde van 37 tot 82 jaar, met een gemiddelde leeftijd van 65 jaar. Elke patiënt werd gescoorde volgens de CCI. Onafhankelijke risicofactoren voor langetermijnsoverleving werden geanalyseerd door univariate and multivariate Cox proportionele hazard analyse. Zestien patiënten (3,7%) overleden postoperatief. De totale en recidiefvrije vijfjaarsoverleving was respectievelijk 45% en 43%. Patiënten met een CCI score 0 hadden een totale vijfjaarsoverleving van 52%, patiënten met een CCI score 1 - 2 hadden een vijfjaarsoverleving van 48% en patiënten met een CCI score ≥ 3 hadden een vijfjaarsoverleving van 28%. Mannelijk geslacht, leeftijd, CCI, chronisch hartfalen, chronisch obstructief longlijden, klinisch stadium, pathologisch stadium en type resectie waren voorspellend voor overleving in de univariate analyse. In the multivariate analyse waren leeftijd, CCI score 1 - 2, CCI score ≥ 3, bilobectomie, pneumonectomie en pathologisch stadium voorspellend voor zowel een totale als recidiefvrije overleving. Wij concluderen dat de CCI een

sterk prognostische factor is voor langetermijnsoverleving en dat de CCI beter voorspellend is dan de individuele comorbiditeiten. Wij adviseren het gebruik van een gevalideerde comorbiditeit index bij het selecteren van patiënten met een niet-kleincellig longcarcinoom voor chirurgie.

Hoofdstuk 7. *Long resectie voor niet-kleincellig longcarcinoom bij patiënten ouder dan 70 jaar: mortaliteit, morbiditeit en vergelijking van de langetermijnsoverleving met de normale populatie*

Dit hoofdstuk beschrijft een retrospectieve studie waarin prognose van longresectie bij patiënten ouder dan 70 jaar met niet-kleincellig longcarcinoom wordt geëvalueerd en de overleving wordt vergeleken met de overleving van de normale populatie ouder dan 70 jaar. Er werden 126 patiënten (101 mannen, 25 vrouwen) geïncludeerd. De gemiddelde leeftijd ten tijde van operatie was 74 jaar (variërend van 70 tot 82 jaar). Elke patiënt werd gescoord volgens de Charlson comorbiditeit index (CCI). Postoperatieve complicaties werden onderverdeeld in kleine en grote complicaties. Risicofactoren voor grote complicaties en langetermijnsoverleving werden geanalyseerd door univariate en multivariate logistische regressie analyse en Cox proportionele hazard analyse. Overleving werd vergeleken met de overleving van de normale populatie ouder dan 70 jaar. De ziekenhuismortaliteit was 3,2%. Kleine complicaties kwamen voor in 57%, grote complicaties in 13%. Alleen CCI score 3 - 4 was voorspellend voor grote complicaties (odds ratio, 12,6; 95% confidence interval, 1,5 tot 108,6). De vijf- en tien-jaars overleving waren respectievelijk 37% and 15%. Roken, chronisch obstructief longlijden en pathologische stadia IIIA and IIIB waren risicofactoren voor langetermijnsoverleving. De geobserveerde overleving was lager dan de te verwachten overleving, maar het verschil werd in de tijd na operatie wel kleiner. Wij concluderen dat longresectie in patiënten ouder dan 70 jaar een acceptabele morbiditeit, mortaliteit en overleving geeft. De CCI is een betere voorspellende factor voor grote postoperatieve complicaties dan de individuele risicofactoren. Naar mate de tijd na operatie vordert is overleving niet meer gecorreleerd aan het longcarcinoom maar heeft het hetzelfde beloop als in de normale bevolking.

Hoofdstuk 8. *Overleving van patiënten met een pathologisch stadium IA niet-kleincellig longcarcinoom: Tumorgrootte is van belang*

Dit hoofdstuk beschrijft een retrospectieve studie waarin de prognostische factoren, met speciale aandacht voor tumorgrootte, voor overleving van patiënten met pathologisch stadium IA niet-kleincellig longcarcinoom worden geëvalueerd, en waarin het percentage tumorrecidief wordt berekend aan de hand van actuele en

actuariele analyse. Er werden 130 patiënten (94 mannen, 36 vrouwen) geïncludeerd. De gemiddelde leeftijd ten tijde van operatie was 63 jaar (variërend van 37 tot 81 jaar). Elke patiënt werd gescoord volgens de Charlson comorbiditiet index (CCI). Patiënten waren gecategorizeerd als patiënten met een pathologische tumorgrootte van 0 tot 20 mm in diameter (n = 75) en 21 tot 30 mm in diameter (n = 55). Risicofactoren voor totale en recidiefvrije overleving waren bepaald door Cox proportionele hazard analyse. De Kaplan-Meier methode was gebruikt om het actuariële recidief getal te schatten en de cumulatieve incidentie methode was gebruikt om het actuele recidiefgetal te schatten. De gemiddelde pathologische tumorgrootte was 20 ± 6 mm. Patiënten met tumoren van 0 tot 20 mm in diameter hadden een totale en recidiefvrije vijfjaarsoverleving van respectievelijk 69% en 68%. De totale en recidiefvrije vijfjaarsoverleving voor patiënten met tumoren van 21 tot 30 mm in diameter was respectievelijk 51% en 48%. Het verschil tussen de twee groepen was significant (p = 0,038 and p = 0,015). Het actuele recidiefgetal binnen 10 jaar was lager dan het actuariële recidiefgetal (23% versus 29%). In de multivariate analyse waren tumorgrootte, CCI score ≥ 3 en pneumonectomie geassocieerd met een kortere totale en recidiefvrije overleving. De resultaten verkregen in deze studie laten zien dat tumorgrootte de overleving van patiënten met pathologisch stadium IA niet-kleincellig longcarcinoom beïnvloedt en dat het huidige stadium IA onderverdeeld kan worden in twee nieuwe stadia. Bij patiënten met een vroeg stadium niet-kleincellig longcarcinoom en daardoor een relatief goede prognose is het actuele recidiefgetal realistischer dan het actuariële recidiefgetal.

Hoofdstuk 9. *Juiste behandelingsselectie kan de overleving van patiënten met een klinisch vroeg stadium niet-kleincellig longcarcinoom verbeteren*

Dit hoofdstuk beschrijft een retrospectieve studie waarin behandelingsselectie en prognose van patiënten met een klinisch vroeg stadium niet-kleincellig longcarcinoom wordt geëvalueerd. Er werden 360 patiënten (286 mannen, 74 vrouwen) met een klinisch stadium IA tot IIB (T1-2, N0-1, M0) geïncludeerd. Patiënten werden gescheiden in geopereerde patiënten (n = 269) en niet geopereerde patiënten (n = 91). Elke patiënt werd gescoord volgens de Charlson comorbiditeit index (CCI). Om onafhankelijke risicofactoren voor grote postoperatieve complicaties te analyseren werden logistische regressie analyses gedaan. Risicofactoren voor totale en recidiefvrije overleving waren bepaald door Cox proportionele hazard analyse. De gemiddelde leeftijd van de geopereerde patiënten was 64 jaar en van de niet geopereerde patiënten 74 jaar (p < 0,0001). De gemiddelde CCI score was respectievelijk 1,3 en 2,4 (p < 0,0001) en de

vijfjaarsoverleving was respectievelijk 47% en 3% ($p < 0,0001$). Mannelijk geslacht, pneumonectomie en CCI score ≥ 3 waren predictief voor grote postoperatieve complicaties. Patiënten die niet geopereerd werden maar behandeld werden met radiotherapie hadden een tweejaarsoverleving van 40% en patiënten die geen radiotherapie kregen 5%. Mannelijk geslacht, leeftijd, behandeling en klinisch stadium waren prognostisch voor overleving in de totale studiepopulatie. Patiënten met een CCI score ≥ 3 hadden een betere overleving na chirurgie dan na radiotherapie (36% versus 6%, $p < 0,0001$). Patiënten met een CCI score ≥ 3 die geopereerd waren hadden een hogere prevalentie van $FEV_1\%$ ≥ 70 in vergelijking met patiënten die behandeld zijn met radiotherapie (82% versus 23%, $p < 0,0001$). Wij concluderen dat patiënten met een CCI score ≥ 3, ondanks een verhoogd risico op postoperatieve complicaties, een betere overleving hebben na chirurgie dan na radiotherapie. Bij patiënten met hoge comorbiditeit maar met voldoende longreserve is chirurgie de beste behandelingsoptie. Bij patiënten met hoge comorbiditeit maar met een onvoldoende longreserve of patiënten die chirurgie weigeren is curatieve radiotherapie een alternatief.

Hoofdstuk 10. *Langetermijnsoverleving na chirurgie voor niet-kleincellig longcarcinoom: Ontwikkeling en validatie van een prognostisch model met een preoperatieve en postoperatieve modus*

Dit hoofdstuk beschrijft een retrospectieve studie waarin een prognostisch model met een preoperatieve en een postoperatieve modus is ontwikkeld om overleving te voorspellen van een individuele patiënt na chirurgie voor niet-kleincellig longcarcinoom. Er werden 766 patiënten (600 mannen, 166 vrouwen) geïncludeerd. De gemiddelde leeftijd ten tijde van operatie was 65 jaar (variërend van 37 tot 84 jaar). Elke patiënt werd gescoord volgens de Charlson comorbiditiet index (CCI). Onafhankelijke risicofactoren voor overleving werden geanalyseerd door univariate en multivariate Cox proportionele hazard analyse. De betrouwbaarheid van het prognostisch model, de CCI en pathologisch stadium waren bepaald door een concordance statistic (c statistic) en deze werden met elkaar vergeleken. De ziekenhuismortaliteit was 4,4%. De vijfjaarsoverleving was 40% (95% confidence interval, 36 tot 44). De betrouwbaarheid van de CCI was slecht ($c = 0,55$), van pathologisch stadium ($c = 0,60$) en van de preoperatieve modus ($c = 0,61$) beter en van de postoperatieve modus het best ($c = 0,65$). Wij concluderen dat het prognostisch model de overleving van individuele patiënten goed voorspelt, waarvan de postoperatieve modus het meest betrouwbaar is. Inclusie van meerdere factoren die prognostisch zijn voor overleving kan de nauwkeurigheid van het model verbeteren en daarmee ook de identificatie van patiënten met een relatief

slechte prognose. Het prognostisch model kan zowel de chirurg als de patiënt ondersteunen bij de besluitvorming tot operatief ingrijpen.

Hoofdstuk 11. *Discussie*
In dit hoofdstuk worden de belangrijkste resultaten en conclusies uit de hiervoor beschreven studies nader besproken. Mogelijke klinische implicaties gebaseerd op diverse conclusies en aandachtspunten voor toekomstig onderzoek worden uiteengezet.

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Dear Prof. dr. T. Treasure, I would like to thank you for your participation in the committee and I am pleased with your presence during the ceremony.

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CURRICULUM VITAE

Özcan Birim was born in Rotterdam, the Netherlands, on the 26th of September 1978. He finished secondary school in 1997 at the Thorbecke Lyceum in Rotterdam. In the same year, he started his medical training at the Erasmus University Rotterdam. During his medical study his interest in cardiology and cardio-thoracic surgery was stimulated when he worked as a student assistant in the 'studentteam' at the department of Cardiology in the Erasmus MC Rotterdam. As part of his fourth year he spent four months at the department of Cardio-Thoracic Surgery and performed a retrospective research on elderly nonsmall cell lung cancer patients who underwent surgical resection. His ambition led him to start his PhD training during his internships. In July 2003, he obtained his medical degree at the Erasmus University Rotterdam. In September 2003 he started working as a resident in Cardio-Thoracic Surgery at the Erasmus MC Rotterdam. In November 2003 he was rewarded for the research he did with the 'Gerrit Jan Mulderaward'. In August of 2005 he started his training as a Cardio-Thoracic surgeon at the Erasmus MC Rotterdam (head: Prof. dr. A.J.J.C. Bogers), which includes a two years residency at the department of Surgery of the Reinier de Graaf Groep in Delft.

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Case Report

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