Surgical treatment of T3 and T4 non-small cell lung cancer

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Aan mijn moeder

Contents

CHAPTER 1

General introduction

Epidemiology of lung cancer and risk factors

At the beginning of the 20th century the diagnosis lung cancer was rarely made. Now it is worldwide the leading malignancy both in incidence and mortality. Every year, 1.2 million new cases of lung cancer are diagnosed (12.3% of all cancers worldwide) and 1.1 million patients die due to lung cancer (17.8% of all cancer deaths worldwide). The highest incidence rates are observed in North America and Europe.[1] In Europe, there are nearly 400.000 new cases each year.[2] Women account for 40 percent of all lung cancer cases and their rate is increasing, while the rate in males is beginning to decline. In the Netherlands, same opposite trends in incidence and mortality for lung cancer are described. During the period 1989-2000, the number of newly diagnosed lung cancers in males decreased from 7252 to 6391, whereas in females an increase from 1299 to 2428 was reported.[3]
The most important explanation for this difference is the change in smoking behaviour.[4] Approximately, 85% to 90% of all patients with lung cancer have a history of direct exposure to tobacco. Several studies demonstrated a clear dose-response relation between the development of lung cancer and the degree of exposure to cigarette smoke.[5,6] Other risk factors of lung cancer include exposure to environmental tobacco smoke, asbestos and other occupational and environmental agents like radon, some metals (e.g., nickel, arsenic, cadmium), and ionising radiation.[7,8] Also genetic factors and gender play a role in analysing risk factors. The risk of developing lung cancer increases in first degree relatives of lung cancer patients, independent to tobacco exposure, and in women.[9] Potential biologic explanations include gender differences in nicotine metabolism, male-female variations in cytochrome P-450 enzymes, and the effect of hormones on the development of lung cancer.[10] Some disease entities are associated with an increased risk of lung cancer. Patients with previously treated lung cancer or head and neck cancer have a higher risk of developing lung cancer.[11,12] Also a number of benign lung diseases, like chronic obstructive pulmonary disease, tuberculosis, human immunodeficiency virus (HIV) infection or interstitial pulmonary fibrosis, confer a greater risk.[13-15]

Biomarkers of carcinogenesis

In recent years, progress in understanding the molecular events that occur during carcinogenesis has given more insight into the biology of lung cancer

and potentially significant determinants of prognosis.[16,17] The development of lung cancer is a multistep process that results from a combination of carcinogen exposure and genetic and epigenetic alterations followed by clonal expansion. Chromosomal abnormalities identified in lung cancer include chromosomal aberrations and deletions. Typical features of the carcinogenic process are increased activity of growth stimulating genes, oncogenes, and insensitivity to anti-growth signals, produced by tumour suppressor genes. Oncogenes are dominant genes, whereas tumour suppressor genes are recessive genes. The latter genes are rendered inactive by chromosomal loss of one allele (loss of heterozygosity (LOH)) and damage to the other by genetic mutation or epigenetic hypermethylation.

Important oncogenes are Ras genes, the epidermal growth factor receptor (EGFR), and HER-2/neu. Ras genes regulate signal transduction pathways that control cell growth. In NSCLC, especially adenocarcinoma, almost all mutations affect the K-ras gene. Tumours with K-ras mutations tend to have a worse prognosis.[18]

Epidermal growth factor receptor (EGFR) is a member of the ERBB gene family, which is a group of transmembrane receptor tyrosine kinases. Activation plays an important role in cell division and differentiation. In some studies, expression of EGFR in NSCLC has been correlated with advanced disease stage and poor prognosis.[19,20] Furthermore, expression of EGFR appears to upregulate a matrix metalloproteinase, which regulates tumour invasiveness. ZD 1839 is a specific inhibitor of the EGF activated tyrosine kinase, which is under investigation in several trials.[21]

Another ERBB family member, HER2/neu is expressed in about 30% of NSCLC, especially adenocarcinoma. High levels are associated with the multiple drug resistance phenotype and increased metastatic potential.[22]

An important tumour suppressor gene in lung cancer is the p53 gene. Deletions and point mutations in this gene are commonly acquired genetic lesions. The p53 gene plays a role in the regulation of transcription processes in the cell nucleus. Mutations affect both small cell lung cancers and non-small cell lung cancers. p53 expression is more frequently seen in squamous cell carcinomas and worsens the prognosis.[23,24]

Angiogenesis is an important mechanism in tumour cell proliferation and metastatic capacity. Neovascularisation is stimulated by the production of vascular endothelial growth factor (VEGF). In NSCLC, increased levels of VEGF are generally associated with poor prognosis.[25] Molecules targeting vascular endothelial growth factor (VEGF) or its receptor (VEGFR) seem to control tumour progression and may prolong survival. Several other biomarkers interfere with the process of angiogenesis and various angiogenesis inhibitors, like COX-2

inhibitors and matrix metalloproteinase inhibitors, are under evaluation in clinical trials.[26,27]

Histology

The currently used histological classification for lung cancer was developed by the World Health Organization (WHO) and is revised in 1999 (Table 1.1).[28] The five main tumour categories include squamous cell carcinoma, adeno-carcinoma, large cell carcinoma, adeno-squamous cell carcinoma and small cell carcinoma. Small cell lung cancer (SCLC), which counts for approximately 20 percent of all lung cancers, arises from neuroendocrine cells.[29] It is distinguished from non-small cell lung cancer (NSCLC) by its rapid doubling time, high growth fraction, and the early development of widespread metastases. Squamous cell carcinoma used to be the most common histological type, but recently a shift has been noted and now adenocarcinoma is the most frequent type, particularly in women and non-smokers.[30,31] Histological characteristics of squamous cell carcinoma are intercellular bridging, squamous pearl formation, and keratin formation. Adenocarcinomas are a glandular epithelial malignancy with several histological subtypes, including acinar, papillary, bronchioloalveolar, and solid with mucus formation. Adenosquamous carcinomas have a mix of adeno- and squamous differentiation. Large cell carcinoma is a poorly differentiated NSCLC.

Clinical features

Early detection of lung cancer is difficult because it does not frequently produce symptoms in the beginning of the disease process. Approximately 2 to 15 percent of the patients present without any symptoms.[32] The vast majority of patients is symptomatic at the time of clinical presentation and presents with stage III or IV disease. Symptoms can be related to the primary lung tumour or to intrathoracic spread, distant metastasis, or paraneoplastic syndromes.[33]
The most common symptoms related to the primary tumour or intrathoracic spread are cough, dyspnoea, haemoptysis, chest pain and hoarseness. About one third of patients present with symptoms as a result of distant metastases. Lung tumours frequently metastasize to the liver, bones, brains and adrenal glands. Paraneoplastic syndromes occur in about 10 to 20 percent of patients with a lung tumour and can cause endocrine/metabolic abnormalities, several neuromuscular and dermatologic syndromes, haematological abnormalities and

systemic symptoms, like clubbing, hypertrophic osteoarthropathy, fatigue and cachexia. Severe weight loss and poor performance status have a poor influence on survival.[34]

Table 1.1. 1999 WHO classification of invasive malignant epithelial lung tumours

Histological classification
1 Squamous cell carcinoma
Variants: papillary, clear cell, small cell, basaloid
2 Small cell carcinoma
Variant: combined small cell
3 Adenocarcinoma
Acinar
Papillary
Bronchioloalveolar carcinoma
Non-mucinous
Mucinous
Mixed mucinous and non-mucinous or indeterminate
Solid adenocarcinoma with mucin formation
Adenocarcinoma with mixed subtypes
Variants: well-differentiated foetal adenocarcinoma, mucinous (colloid), mucinous cystadenocarcinoma, signet ring, clear cell
4 Large cell carcinoma
Variants: large cell neuroendocrine carcinoma, combined large cell neuroendocrine carcinoma, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, large cell carcinoma with rhabdoid phenotype
5 Adenosquamous carcinoma
6 Carcinomas with pleomorphic, sarcomatoid or sarcomatous elements
Carcinomas with spindle and/or giant cells
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Others
7 Carcinoid tumours
Typical carcinoid
Atypical carcinoid
8 Carcinomas of salivary gland type
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Others
9 Unclassified carcinoma

Diagnosis

Once history, physical examination, or radiological findings suggest the presence of a malignant pulmonary lesion, further diagnostic evaluation is necessary to establish the diagnosis of lung cancer by tissue morphology (i.e. standard histology), to accurately stage the tumour, and to evaluate cardiopulmonary function if surgical treatment is considered.

The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommend computed tomography (CT) scans of the thorax and upper abdomen to be obtained in all patients with NSCLC to adequately stage the patient by demonstrating invasion of the tumour in surrounding structures, enlarged mediastinal lymph nodes or metastases.[35] However, CT evaluation of mediastinal lymph node metastases has its limitations. A meta-analysis examining the accuracy of CT in detecting positive mediastinal lymph nodes reported a sensitivity of 79 percent and a specificity of 78%, respectively.[36] Radiographic studies of the brain and bones should only be performed when symptoms are present suggesting metastatic disease.[35,37] CT scanning can be useful in detecting cerebral metastases. Magnetic resonance imaging (MRI) is, however, taking over as the investigation of choice in this situation.[38] MRI is also more accurate to prove invasion of the tumour into the mediastinum, great vessels, spine, and chest wall. It is particularly useful in evaluating tumours of the superior sulcus.[39,40] Positron emission tomography (PET) scanning with fluoro-2-deoxyglucose (FDG) is a non-invasive, diagnostic imaging technique for measuring the metabolic activity of cells of the body. The use of PET scanning is based on the fact that most lung tumours have an increased rate of metabolism of glucose when compared to normal tissues. A high sensitivity of approximately 97% and a high specificity of approximately 78% make it a useful diagnostic tool in evaluation of the primary tumour, mediastinum and distant metastases.[41-43] However, a PET scan can be false-positive in granulomas or other types of infection.[44,45] False negative results are less frequent, and generally occur in carcinoid tumours, bronchioloalveolar carcinomas, or small tumours (<1 cm in diameter).[46] PET scanning improves the detection rate of both local and distant metastases and may also avoid unnecessary surgery in patients who appear to have potentially resectable disease by conventional staging methods.[47] The use of recently developed dual-modality PET/CT significantly increases the number of patients with correctly staged NSCLC and thus has a positive effect on treatment.[48]

Sometimes the diagnosis of lung cancer can be established by sputum cytology, but in most patients invasive diagnostic procedures are necessary to achieve a histological or cytological diagnosis of the suspect lesion. Flexible, fiberoptic bronchoscopy is the most important diagnostic tool to obtain a tissue diagnosis.

It also gives information about operability by determining the endobronchial extent of the tumour or by detecting additional endobronchial lesions. Other invasive procedures to prove malignancy include thoracocentesis, thoracoscopy and transthoracic needle aspiration.

Staging

The purpose of a staging system is to define groups of patients based on pathology, with respect to treatment modalities and prognosis. Accurate staging is essential because the stage of the disease at the time of diagnosis represents one of the most important determinants of outcome in NSCLC, with earlier stages having a better chance of long-term survival. The international staging system for non-small cell lung cancer was conceptualised in the late 1940s.[49] In 1974, the American Joint Commission for Cancer (AJCC) introduced a more detailed staging system, which was revised in 1986 and 1997.[50-52]

The staging system for lung cancer is based on the TNM classification. The T-factor is used to describe the extent of the primary tumour, the N factor to describe the extent of regional lymph node involvement, and the M factor to describe the presence of distant metastases. Table 1.2 includes the TNM classification of the international staging system that has been updated in 1997.

Based on the results of a group of 5319 patients treated for non-small cell lung cancer, the TNM subsets have been grouped in stages in order to assess prognosis and treatment. Stages I through III are divided into A and B subcategories (Table 1.3).

Patients are first staged based on clinical information obtained by physical examination, radiographic imaging, bronchoscopy, mediastinoscopy, and/or any other investigation undertaken prior to thoracotomy. This staging is called cTNM (clinical). A post-surgical treatment-pathologic stage (pTNM) is based on the prior studies as well as the pathological evaluation of the resected tumour and lymph nodes. This staging is more precise than the clinical staging.

Because the therapy of NSCLC is influenced by the presence of mediastinal lymph node metastases, it is essential to stage the mediastinum carefully. Cervical mediastinoscopy is the most accurate method to investigate the superior mediastinal lymph nodes.[53] Regional lymph nodes are divided into stations based upon an internationally accepted schema.[54] Intrapulmonary and hilar lymph nodes (N1) are indicated by double digits (station 10-14) and mediastinal lymph nodes (N2/3) are indicated by single digits (station 1-9). The lymph nodes accessible to cervical mediastinoscopy are right and left upper paratracheal (stations 2L and 2R), pretracheal (station 3), right and left lower paratracheal (stations 4R and 4L) and anterior subcarinal nodes (station 7). Posterior

subcarinal lymph nodes (station 7) and lymph nodes located in the aortopulmonary window (station 5) or para-aortic (station 6) can be reached by thoracoscopy, anterior mediastinotomy, or by endoscopic ultrasound echography (EUS). EUS can also establish a cytological diagnosis in para-oesophageal lymph nodes (station 8) and pulmonary ligament lymph nodes (station 9).[55]

Table 1.2. TNM definitions[#]

TNM definitions	
Tumour stage (T)	
TX	Primary tumour cannot be assessed: presence of malignant cells without visible tumour
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour ≤3 cm in size, no invasion more proximal than the lobar bronchus
T2	Tumour >3 cm in size; involvement of main bronchus≥2 cm distal to the carina; invasion of the visceral pleura; partial atelectasis
T3	Tumour of any size invading the chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, pericardium; or tumour in main bronchus <2 cm distal to the main carina; or tumour associated with atelectasis / obstructive pneumonitis of the entire lung
T4	Tumour of any size invading the mediastinum, heart, great vessels, oesophagus, trachea, vertebral body, or main carina; presence of malignant pleural or pericardial effusion; satellite tumour nodulus in the same lobe
Nodal stage (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases of ipsilateral hilar and/or ipsilateral peribronchial lymph nodes, and intrapulmonary nodes involved by direct extension of primary tumour
N2	Metastases of ipsilateral mediastinal and/ or subcarinal lymph nodes
N3	Metastases of contralateral mediastinal or hilar lymph nodes or ipsilateral or contralateral scalene or supraclavicular lymph nodes
Metastatic stage (M)	
Mx	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases present, including metastatic tumour nodule(s) in the non-primary tumour lobe

[#] adapted from Mountain[52]

Table 1.3. Stage grouping[#]

Stage	TNM subset
0	Carcinoma in situ
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0
	T3N0M0
IIIA	T3N1M0
	T1-3N2M0
IIIB	Any T N3M0
	T4 any N M0
IV	any T, any N, M1

[#] adapted from Mountain[52]

Treatment

The primary goal of lung cancer therapy is complete eradication of the disease. The therapeutic approach is based upon the histopathological type of tumour, the stage of the tumour, performance status and comorbidity. Treatment of lung cancer is multidisciplinary and needs close cooperation between the pulmonologist, surgeon and radiation therapist. After the initial therapy careful follow-up is essential for early detection and treatment of recurrent disease.
Small cell carcinoma of the lung is managed primarily with systemic chemotherapy, due to its early development of distant metastases. Surgery remains the most curative modality for NSCLC. The goal of surgical treatment is to perform a complete resection. Resectability is closely related to the stage of the disease.

Stage I and II

The essential similarity between stage I and stage II is the absence of extrapulmonary lymph node involvement. Both stages are usually treated with surgery, assuming the patient has sufficient respiratory reserve. Adequate surgery usually consists of a lobectomy, bilobectomy, sleeve lobectomy, or a pneumonectomy with mediastinal node sampling for staging purposes. Lesser procedures are associated with higher rates of local recurrence and a trend toward decreased survival.[56] Thoracoscopy or thoracotomy with limited resection is done by some in patients who cannot tolerate a lobectomy due to poor pulmonary function, and in elderly or high-risk patients.[57]

Patients who are inoperable for medical reasons are often referred for radiation therapy alone. However, the outcomes following radiation therapy alone for NSCLC are inferior to those achieved with surgical resection.[58] In patients with incomplete resections, postoperative radiotherapy reduces local recurrence rates, but does not favourably affect survival.[59,60] The addition of radiotherapy does also not improve survival in patients with a complete resection. Administration of postoperative chemotherapy or combined chemo-radiotherapy is currently not considered to be a standard therapy. At this moment, also the role of neo-adjuvant chemotherapy in resectable stage I and II NSCLC remains uncertain, as results of several studies are conflicting. Its use should be limited to patients enrolled in trials.[61,62]

Stage III

The treatment of patients with stage III disease is controversial. Stage IIIA was originally intended to imply regionally advanced, yet potentially resectable disease, while stage IIIB represented regionally advanced unresectable disease. However, the introduction of combined modality treatment has allowed patients with good performance status presenting with T4 (IIIB) tumours to undergo induction therapy, followed by reassessment of resectability.

The aims of induction or neoadjuvant chemotherapy prior to resection or radiotherapy are to improve local control by downstaging the primary tumour and nodal metastases and to eradicate systemic micrometastases. Over the past years, many trials in regionally advanced NSCLC have been conducted to search the optimal combination of chemotherapy and to evaluate the role of multimodality therapy, consisting of combinations of chemotherapy and locoregional therapy (radiotherapy and/or surgery).[63] A number of new agents were found to be effective against lung cancer, like docetaxel, gemcitabine, irinotecan, paclitaxel or vinorelbine. They have all been incorporated in a number of combination chemotherapeutic regimens, many of which included platinum based chemotherapy. Until now, no regimen appears superior to another.[64] Most trials also report that combined modality treatment is associated with better local control and survival than locoregional therapy alone.[61,65,66] Results of current programs are such that for patients with stage IIIA disease no specific regimen can be regarded as standard therapy. Trials examining the effect of surgery or radiotherapy after induction chemotherapy in stage IIIA are conducted and will help to define the optimal therapy for this group of patients. Patients with stage IIIB disease are suitable for combined modality treatment with chemotherapy and radiotherapy. Some selected patients with a T4 tumour, may be candidates for surgery after induction chemotherapy.

Stage IV

Options for patients found to have stage IV disease are palliative chemotherapy or radiation therapy for the treatment of bronchial obstruction, painful bone metastases, or central nervous system metastases.[67,68] Patients with good performance status and little weight loss are those most likely to respond to chemotherapy. Stage IV patients with significant comorbid illnesses may be candidates for best supportive care only.
Regardless of histology or stage, unresectable tumours, which compromise the trachea or large airways, may be palliated by local techniques like brachytherapy, laser therapy, airway stents, and/or photodynamic therapy.

Survival and prognosis

Despite improvement in understanding the aetiology and treatment of lung cancer, survival has not clearly improved during the past decades. The expected 5-year survival rate for all patients in whom lung cancer is diagnosed is 15%.[69] This poor prognosis is largely due to the advanced stage of the tumour at presentation, in which treatment rarely will result in cure. Five–year survival for these patients is less than 5%. Early stages of the disease offer the best prognosis, with a 5-year survival of 40-70%.[52] The main prognostic factors for patients with lung cancer are tumour stage and performance status. Other factors include severe weight loss and presence of comorbidity precluding radical therapy. Although a 15% 5-year survival rate is meagre, a number of promising new diagnostic modalities and drugs are developed and have been incorporated into clinical trials.

T3 and T4 non-small cell lung cancer

Patients with advanced locoregional disease constitute a heterogeneous group. At present, they are divided into stage IIB (T3N0M0 tumours) and stage III (T3-4N1-3M0). Prior to 1997, T3N0M0 tumours were also included in the stage III grouping, but because of their favourable outcome with resection they are now classified as stage IIB.[52] The historical difference between T3 and T4 tumours is resectability. T3 tumours are generally resectable without requiring major surgery, whereasT4 tumours invade more vital structures, which complicates surgery.

T3 tumours

T3 tumours comprise a heterogeneous group, including tumours with invasion of the chest wall, mediastinal structures, or diaphragm, Pancoast tumours, tumours with involvement of a main bronchus within 2 cm of the carina, and tumours associated with atelectasis or obstructive pneumonitis of the entire lung. Of patients who undergo thoracotomy for lung cancer, approximately 10% have a T3 tumour. These tumours have varying prognoses depending upon the completeness of resection and the patient's lymph node status.[70,71] Five-year survival rates are 38% and 25%, respectively for pT3N0 and pT3N1 tumours.[52] Some studies reported no significant difference in survival between the several subgroups.[70,72] Other studies, however, demonstrated a survival benefit for tumours with chest wall invasion.[73,74] The two largest groups of T3 tumours include tumours with chest wall invasion and tumours invading mediastinal structures. In approximately 80% of these patients a complete resection is achieved. Most studies about surgical resection of T3 tumours only include tumours with chest wall invasion. N0 disease is a common feature in this subgroup and has the best outcome with 5–year survival up to 49%.[75] Surgery consists of either an extrapleural dissection or an en bloc resection. Controversial results have been reported for depth of invasion of the chest wall as being a prognostic factor.[70,76,77] Completeness of resection is the most important prognostic factor. Postoperative radiotherapy does not improve survival.[75-77]

Pancoast tumours can be staged as T3 or T4. Due to the localisation in the apex of the lung with invasion of adjacent structures, they cause characteristic symptoms, like arm or shoulder pain or Horner's syndrome. The tumour can be resected by the classic posterior Shaw-Paulson approach or the newer anterior transcervical approach, introduced by Dartevelle. Regarding the extent of pulmonary resection, en bloc resection of the involved ribs with a lobectomy is recommended. The 5-year survival of pre-operative radiotherapy and resection is about 27%.[78] Recent multimodality studies, involving chemoradiotherapy and surgical resection, show promising results regarding completeness of resection, local recurrence and survival.[79]

Few studies are published about patients with lung tumours invading the diaphragm, because these tumours are very rare.[80,81] In most cases, diaphragmatic involvement is diffuse or very deep, which makes complete resection impossible. In selected patients combined resection of the lung and diaphragm is possible with reasonable survival results.

Central T3 tumours include tumours with invasion of mediastinal structures and tumours located in the main bronchus within 2 cm of the carina. In this subgroup, squamous cell carcinomas form a frequent histological subtype.[70]

Surgery mostly consists of a pneumonectomy or sleeve lobectomy and results are best for patients with T3N0 tumours due to proximity to the carina. Five-year survival for all patients is 25%.[71] Tumours with extension into mediastinal structures have invasion of the mediastinal pleura, pericardium, or phrenic nerve. Regarding the invasion of these structures, there is no significant difference in survival. For patients with minimal invasion of the mediastinal pleura surgery is the treatment of choice. Most of these patients are peroperatively staged as T3. In patients presenting with invasion of the mediastinum on CT scanning or MRI, it may be difficult to distinguish T3 from T4 tumours.

T4 tumours

Characterisation of the primary tumour as T4 involves the presence of any of the following: invasion of the mediastinum, heart or great vessels, trachea, oesophagus, vertebral body, or the carina, the presence of a malignant pleural or pericardial effusion or satellite tumour nodule(s) within the same lobe as the primary tumour. Thus T4 tumours also encompass heterogeneous subgroups. As surgery is not accessible for patients with a T4 tumour due to presence of malignant pleural or pericardial effusion, its role for T4 tumours invading adjacent structures remains doubtful. Some studies about extended resection of T4 tumours have been published and surgery appears to be beneficial and radical resection of the tumour has a potential for cure in the absence of mediastinal lymph node metastases.[82] However, hospital morbidity and mortality are high. Best results have been reported in selected patients with carinal or tracheal invasion.[82,83] The outcome in patients with invasion of the oesophagus or vertebrae is poor and these tumours mostly are considered unresectable.[84,85]

Under the new staging system T4 tumours also include carcinomas with a satellite tumour in the same lobe. It is sometimes difficult to examine if these lesions are metastases of the primary tumour or a second primary. The outcome of this subgroup is significantly better than of patients with invasion of vital structures.[85,86]

Recently, preoperative chemotherapy or chemoradiotherapy in patients with T4 tumours has been reported in several trials with encouraging results.[87,88]

Outline of the thesis

Surgical resection is the treatment of choice in patients with non-small cell lung cancer in the absence of distant metastases. Resectability is closely related to the stage of the disease. Whereas stage I and stage II tumours are considered to be resectable, the role of surgery for stage III tumours remains unclear. The studies in this thesis were performed to clarify the role of surgical treatment of T3 and T4 tumours by analysing the characteristics and prognosis of several subgroups.

The best operative procedure for lung cancer with chest wall invasion (T3) is still controversial. In **chapter 2** results of 125 patients who underwent either en bloc resection or extrapleural dissection for non-small cell lung cancer invading the chest wall are analysed in order to evaluate these operative procedures and to determine survival characteristics.

Chapter 3 describes the results of surgery of 2 other subgroups of patients with a T3 tumour. Results of resection of T3 tumours invading mediastinal structures (mediastinal pleura, pericardium, or phrenic nerve) and of T3 tumours located in the main bronchus less than 2 cm distal to the main carina are studied to investigate survival characteristics.

In **chapter 4** recent literature on Pancoast tumours is reviewed. These tumours can be staged as either T3 or T4. Clinical characteristics, diagnosis, and tumour staging are studied. Also several treatment possibilities, survival, as well as recurrence and prognostic factors are discussed.

Because of localisation and invasion of surrounding structures, the role of surgical treatment for T4 tumours is doubtful. Extended resections carry a high mortality and should be restricted for selected patients. **Chapter 5** gives the results of surgical resection of T4 non-small cell lung cancer in 89 patients and clarifies the selection-process.

Recently, multimodality treatment has become the standard therapy for patients with locally advanced tumours. In **chapter 6** the role of surgery after neoadjuvant chemotherapy in patients with stage IIIB non-small cell lung cancer was evaluated. The diagnostic value of repeat mediastinoscopy after neoadjuvant chemotherapy for mediastinal staging was also analysed.

Chapter 7 presents the summary and conclusion of the thesis.

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CHAPTER 2

Surgical treatment of 125 patients with non-small cell lung cancer and chest wall involvement

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Abstract

Background
The optimum operative procedure for lung cancer with chest wall invasion (T3) remains controversial. In this study, results of en bloc resection and extrapleural dissection are reviewed to determine survival characteristics.

Methods
Between 1977 and 1993, 125 patients underwent surgery for primary non-small cell lung cancer with chest wall invasion. Patients with superior sulcus tumours, metastatic carcinomas, synchronous tumours or recurrences were excluded. Extrapleural dissection was performed in 73 patients and en bloc resection (range 1 to 4 ribs) in 52. Resection was regarded as complete in 86 and incomplete in 39 patients. Actuarial survival time was estimated and risk factors for late death were identified.

Results
Hospital mortality was 3.2% (n=4). Estimated mean 5-year survival was 24% for all hospital survivors (n=121), 11% for patients with incomplete resection, and 29% for patients having a complete resection. In patients who underwent complete resection, mediastinal lymph node involvement and intrapleural tumour spill worsened the prognosis. Patients with adenocarcinoma had a better chance of long term survival. No relationship was found between survival and age, type of operative procedure, depth of chest wall invasion and postoperative radiotherapy.

Conclusion
Both operative procedures show reasonable survival results. Incomplete resection, mediastinal lymph node involvement, and intrapleural tumour spill adversely influence survival.

Introduction

Surgical resection of non-small cell lung tumours and regional lymph nodes is the treatment of choice in the absence of distant metastases.
Of patients who undergo thoracotomy for lung cancer, 5-8% have chest wall invasion.[1-3] The prognostic implication of this finding has been disputed and, formerly, thoracic wall involvement was considered to be irresectable and unfavourable. Good survival rates after en bloc resection were first reported by Coleman in 1947[4] and Grillo et al. in 1966[1], and subsequent reports have supported the surgical treatment of these tumours.[3,5-7]
In this retrospective study we have analysed our experience of 125 patients who underwent either en bloc resection or extrapleural dissection for non-small cell lung cancer involving the chest wall in order to evaluate these operative procedures and to determine survival characteristics.

Patients and methods

Two thousand and nine patients with lung cancer underwent resection at our hospital between January 1977 and December 1993, of whom 125 patients (6.2%) had a primary non-small cell lung cancer with chest wall invasion. Patients with distant metastases at presentation were excluded as were patients with superior sulcus tumours, synchronous tumours, metastatic carcinomas, and recurrent disease. All patients had tumour involvement of the parietal pleura or the skeletal muscles or ribs at pathological examination and were staged as T3 according to the TNM classification.[8] Resection was regarded as complete when the surgeon felt certain that all visible disease was removed, resection margins were free at pathological examination, and the highest mediastinal lymph node was negative at microscopy. In some patients, the tumour was opened by chance during surgery. This peroperative tumour spill was scored separately.
The ages of the patients ranged from 34 to 80 years with a mean of 62.4 years. There were 111 men, and 114 patients were smokers. Presenting symptoms included chest pain in 72 patients (57.6%), cough in 58 patients (46.4%), dyspnoea in 44 patients (35.2%) and haemoptysis in 30 patients (24%). Twenty-four patients (19.2%) were asymptomatic.
A histological or cytological diagnosis was obtained preoperatively in 103 patients (82.4%). Bronchoscopy was diagnostic in 60 (58.3%), percutaneous

needle aspiration biopsy in 33 (32.1%), cervical mediastinoscopy in 6 (5.8%), rib puncture in 2 (1.9%) and sputum cytology in 2 patients (1.9%).
When invasion of the thoracic wall was proven pre-operatively by pathological examination, en bloc resection was performed. Otherwise, the decision as to which operative procedure should be performed was made peroperatively by the surgeon. Extrapleural dissection was performed when the parietal pleura was easily removed from the ribs, but en bloc resection was used when there was fixation of the tumour to the thoracic wall.
Follow-up was completed in all patients in January 1995. Survival was estimated from the date of operation, using the Kaplan-Meier survival analysis method.[9] Hospital deaths were excluded. Differences in observed survival between groups were tested for statistical significance using the log-rank test.[10] Incremental risk factors affecting survival were evaluated using Cox's proportional hazards model.[11]

Results

Cervical mediastinoscopy was negative in 112 patients (89.6%). Eight patients had positive lymph nodes at mediastinoscopy. The decision to proceed to surgery in these cases was based on their young age in four patients, a single positive lymph node at the ipsilateral tracheobronchial angle in three patients, and at the patient's own request in the remaining case. Cervical mediastinoscopy was not performed in 5 patients. Table 2.1 shows the extent of pulmonary resection. In 1 patient who had a bullectomy and pleurectomy because of persistent pneumothorax, the tumour was an incidental finding at pathological examination. One patient underwent a combined lobectomy and coronary artery revascularisation.

Table 2.1. Extent of pulmonary resection in all patients (n=125) and those who underwent complete resection (n=86)

Operative procedure	All patients		Patients with complete resection	
	Extrapleural (n=73)	En bloc (n=52)	Extrapleural (n=45)	En bloc (n=41)
Pneumonectomy	19	5	15	5
Bilobectomy	1	1	1	1
Lobectomy + segmental / wedge resection	2	9	1	8
Lobectomy	44	31	23	22
Segmental resection	5	5	5	5
Wedge resection	1	1	0	0
Bullectomy/pleurectomy	1	0	0	0

In 52 patients a combined en bloc resection of the carcinoma and chest wall was performed. The number of resected ribs ranged from 1 to 4: one in 10 patients, two in 20 patients, three in 14 patients, four in 8 patients. Reconstruction of the chest wall by Marlex mesh was necessary in 11 of 52 patients. No prosthetic materials were used in any other instance to fill the defect. There were no wound complications. Resection was judged to be complete in 41 patients. The remaining 73 patients underwent an extrapleural dissection which was complete in 45 patients.
The tumour was opened by chance peroperatively in 8 of 125 patients.
Table 2.2 shows tumour cell type and pTNM staging of all patients and those with complete resection. One patient who had a bullectomy and pleurectomy was staged as T3NxM0 because he had no cervical mediastinoscopy and no lymph nodes were sampled peroperatively.

Table 2.2. Cell types and pTNM staging in all patients (n=125) and those who underwent complete resection (n=86)

Variable		All patients (n=125)	Patients with complete resection (n=86)
Cell type			
	Squamous cell carcinoma	69	48
	Adenocarcinoma	42	30
	Adenosquamous carcinoma	13	7
	Large cell carcinoma	1	1
pTNM staging			
	pT3N0M0	71	52
	pT3N0M1	2	0
	pT3N1M0	24	19
	pT3N1M1	1	0
	pT3N2M0	25	15
	pT3N3M0	1	0
	pT3NxM0	1	0

The depth of chest wall invasion is shown in Table 2.3. In the group of 72 patients with only parietal pleura involvement, a complete resection was obtained in 44 patients who underwent extrapleural dissection and in 9 patients who had en bloc resection. Extrapleural dissection was incomplete at the parietal pleura in 4 patients. The remaining 12 patients had an incomplete resection because of positive resection margins at the bronchus, tumour involvement of adjacent organs or of mediastinal lymph nodes, or distant metastases. In patients who underwent en bloc resection, 3 resections were judged to be incomplete because of positive mediastinal lymph nodes or a positive resection margin at the subclavian artery.

Table 2.3. Depth of chest wall invasion in all patients (n=125) and in those who underwent complete resection (n=86)

Invasion of chest wall	All patients		Patients with complete resection	
	Extrapleural (n=73)	En bloc (n=52)	Extrapleural (n=45)	En bloc (n=41)
Parietal pleura	60	12	44	9
Intercostal muscles/ribs	13	39	1	32
Transverse processes	0	1	0	0

Tumour involvement extended beyond the parietal pleura in 53 patients. An extrapleural dissection was performed in 13 patients, which was incomplete in 12. In 2 patients postoperative biopsy specimens of the thoracic wall showed tumour involvement, although the surgeon was certain that all tumour had been removed. Complete resection was achieved in 32 patients who underwent en bloc resection and 1 patient who underwent extrapleural dissection. In this patient, who had involvement of the intercostal muscles and the periosteum of the second rib, an extrapleural dissection with resection of the periosteum and part of the intercostal muscles was performed which was judged to be complete. Three patients received preoperative radiotherapy (30 Gy) to reduce the size of the tumour.

Postoperative radiation therapy was given to 60 patients in doses of 27-66 Gy. Thirty-three patients who had complete resection received postoperative radiotherapy. Thirteen of these had mediastinal lymph node metastases and all were treated with postoperative radiotherapy at the mediastinum. The remaining 27 patients were irradiated postoperatively at the mediastinum or the chest wall because of incomplete resection.

Preoperative chemotherapy was given to 1 patient who had a positive ipsilateral paratracheal lymph node at cervical mediastinoscopy. Four patients received postoperative chemotherapy because of incomplete resection (n=3) and lung metastases (n=1).

The overall hospital mortality was 3.2% (n=4). Two deaths were due to respiratory failure, 1 to sepsis and 1 to myocardial infarction. Three deaths followed extrapleural dissection and one followed en bloc resection. All these patients had a lobectomy. The estimated mean 5-year survival for all 125 patients was 23%, and for hospital survivors (n=121) it was 24%.

Complete resection was achieved in 83 hospital survivors (68.6%) and these patients had a mean 5-year survival of 29%. Thirty-eight patients who had an incomplete resection had a mean 5-year survival of only 11% ($p<0.001$) (Figure 2.1).

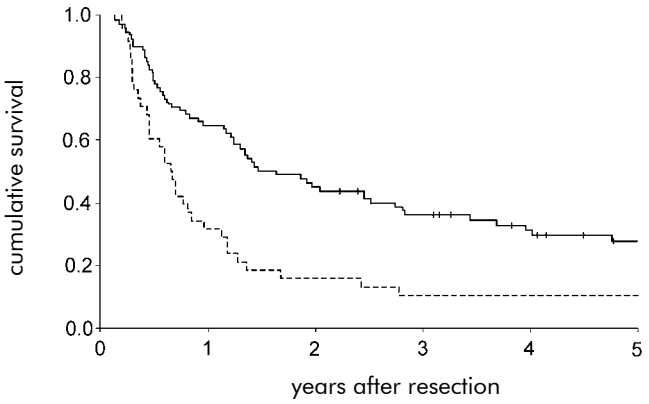

Figure 2.1. Estimated survival in patients with complete resection (——) and incomplete resection (- - -). + = censored cases.

Because of the significant difference in survival between hospital survivors who underwent complete and incomplete resection, it was decided to analyse only the results of those 83 who had complete resection with regard to other survival characteristics. In the univariate analysis survival was strongly related to mediastinal lymph node involvement. The mean 5-year survival for patients with N0 tumours was 36% compared with 23% and 14%, respectively, for those with N1 and N2 tumours. The difference between N0 and N2 tumours was statistically significant ($p<0.05$) (Figure 2.2).

Similarly, survival was related to spill of tumour (Figure 2.3). The tumour was opened peroperatively in 7 of 121 hospital survivors, all of whom died within 16 months because of distant metastases (n=4), respiratory failure (n=2), and local recurrence (n=1). Patients without intrapleural tumour spill had a mean 5-year survival of 32% ($p<0.0001$).

Patients with adenocarcinoma had a better mean 5-year survival (40%) than those with squamous cell carcinoma (26%), although the difference was not statistically significant.

Age, depth of chest wall involvement, and type of operative procedure did not significantly influence survival.

The use of postoperative radiotherapy had no statistically significant effect on survival in our series, neither for patients who underwent en bloc resection nor for those who had extrapleural dissection.

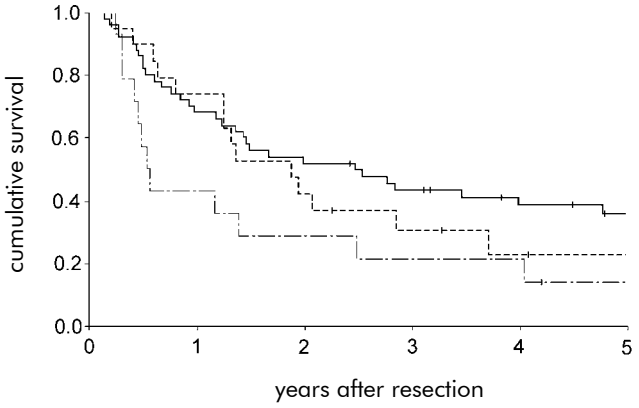

Figure 2.2 Estimated survival following complete resection with (N1 - - -, N2 — - —) and without (N0 ——) lymph node involvement. + = censored cases.

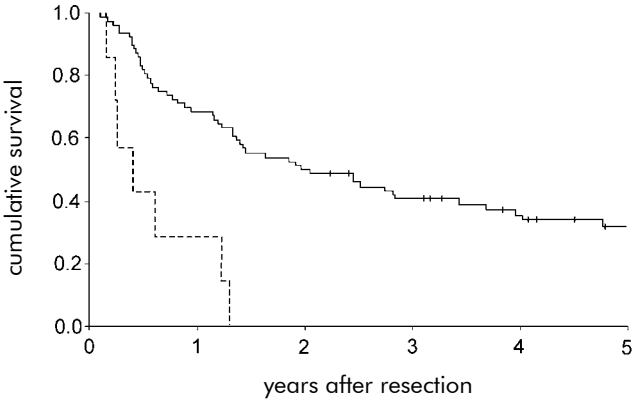

Figure 2.3 Estimated survival following complete resection with (- - -) and without (——) intrapleural tumour spill. + = censored cases.

According to the multivariate analysis, sex, intrapleural tumour spill, and mediastinal lymph node involvement were identified as prognostic factors (Table 2.4).

Local recurrence of malignancy was found in 13 of 83 hospital survivors who underwent complete resection (15.7%), eight after en bloc resection, and five after extrapleural dissection.

Table 2.4. Proportional hazards regression model based on 83 patients with complete resection

Variable	ß	SE	Hazard ratio	95% CI
Sex*	0.78	0.38	2.17	1.04 to 4.53
Tumour spill**	-1.51	0.36	0.22	0.11 to 0.44
pTNM†	0.14	0.30	1.15	0.64 to 2.07
pTNM††	0.89	0.26	2.43	1.45 to 4.08

ß=regression coefficient; SE=standard error; CI=confidence interval; *=men versus women; **=no versus yes; †=pT3N1M0 versus pT3N0M0; ††=pT3N2M0 versus pT3N0M0

Discussion

In this study the overall hospital mortality of 3.2% is similar to the results of McCaughan et al.[3], but lower than other reports.[6,7,12-15] En bloc resection had no higher mortality rate (1.9%) than extrapleural dissection (4.1%). Our estimated mean 5-year survival for 121 hospital survivors of 24% is similar to the results of others[5-7,12], but less than those achieved by Patterson et al.[13] and McCaughan et al.[3] The retrospective nature of our study sometimes made it difficult to trace former treatment strategies.

The choice of extrapleural dissection or en bloc resection is an important factor in the treatment of lung cancer with chest wall invasion. Some authors favour en bloc resection of the carcinoma and chest wall[5,6,14], whereas others have found no difference between the two procedures.[3,7,12] However, comparison of these studies is difficult because of differences in patient selection, operative procedures, and statistical analysis. In this series there was no difference in mean 5-year survival between patients undergoing en bloc resection or extrapleural dissection when only the parietal pleura was involved. When invasion of the thoracic wall was proven pre-operatively by pathological examination en bloc resection was planned, otherwise the choice of operative procedure was made peroperatively. When the parietal pleura could be easily dissected from the ribs an extrapleural dissection was carried out, but when there was fixation of the tumour to the thoracic wall or when pathological examination showed positive resection margins en bloc resection was performed. However, 6 patients had positive resection margins at the parietal pleura although the surgeon was certain during the operation that all tumour was removed. This indicates that pathological examination of resection margins should always be carried out peroperatively and that, if there is any doubt about complete resection, an en bloc resection should performed, whenever possible.

As is generally recognized, mediastinal lymph node involvement indicates an unfavourable prognosis.[3,5-7,12-15] Mean 5-year survival for patients with N0

tumours was 36%, compared with 23% and 14% for N1 and N2 tumours, respectively. The difference between N0 and N2 tumours was statistically significant.

The tumour was opened peroperatively in 7 patients and none of these patients lived more than 16 months. The difference in mean 5-year survival between patients with and without intrapleural tumour spill was significant (0% and 32% respectively). In our study, these 7 patients were judged to have had a complete resection but, because of their poor prognosis, we believe that intrapleural tumour spill must be regarded as incomplete resection.

Histological examination showed a higher incidence of squamous cell carcinoma (55.2%). Patients with adenocarcinoma had a better mean 5-year survival than those with squamous cell carcinoma (40% and 26%, respectively), although the difference was not significant. The fact that adenocarcinomas are often located more peripherally and thus cause earlier complaints of chest pain may be a reason for this difference in survival.

Unlike McCaughan et al.[3], other studies reported no relation between depth of chest wall invasion and survival[7,15] and our results are in agreement with this finding. Patients who underwent en bloc resection had no difference in mean 5-year survival when there was tumour involvement in or beyond the parietal pleura.

The indications for radiotherapy in resected T3 lung cancer with chest wall involvement remain unclear. Some authors[13,16] have described a better survival in patients who have radiotherapy, while others have reported no difference.[5,15,17] In this study preoperative radiotherapy was only given to 3 patients so we can not comment on its efficacy. Sixty patients received postoperative radiotherapy, 27 of whom underwent incomplete resection and 33 complete resection. In the latter group no significant relationship was found between survival and postoperative radiotherapy, but it must be borne in mind that this is a non-randomised series.

No relationship was found between operative procedure and local recurrence. Thirteen patients who underwent complete resection had local recurrence: compared with five patients after extrapleural dissection and eight after en bloc resection.

We conclude that complete resection in patients with T3 lung cancer involving the chest wall yields good survival results after either en bloc resection or extrapleural dissection. Both surgical techniques can be performed safely and invasion of the parietal pleura is not a contra-indication to extrapleural dissection.

Mediastinal lymph node involvement, incomplete resection, and intrapleural tumour spill, however, imply an unfavourable prognosis. Postoperative

irradiation, age and depth of chest wall invasion do not influence survival significantly.

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CHAPTER 3

Results of resection of T3 non-small cell lung cancer invading the mediastinum or main bronchus

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Abstract

Background
T3 tumours can be divided into several subgroups. Surgical treatment of T3 tumours with chest wall invasion results in good survival. This study shows the results of resection of T3 non-small cell tumours located in the main bronchus or with invasion of mediastinal structures.

Methods
From 1977 through 1993, 108 patients underwent resection for primary non-small cell carcinomas located in the main bronchus or with invasion of mediastinal structures. A complete resection was performed in 70 patients (64.8%). Actuarial survival time was estimated and risk factors for late death were identified.

Results
Overall hospital mortality was 8.3%. All deaths followed pneumonectomy. Mean 5-year survival was 29% for all hospital survivors, 35% for patients with complete resection, and 18% for patients with incomplete resection ($p=0.03$). In patients with complete resection, mean 5-year survival was 45% for N0 patients and 37% for N1 patients. There were no 5-year survivors in the group of N2 patients. The mean 5-year survival was better (but not statistically significantly better) in patients with tumours located in the main bronchus (40%) than in patients with tumours with invasion of mediastinal structures (25%) ($p>0.05$). Histology, tumour spill, age, sex, and type of operative procedure were not significant prognostic factors.

Conclusion
Patients with tumours located in the main bronchus have a better survival than patients with invasion of the mediastinal structures. Pneumonectomy increases hospital mortality. Incompleteness of resection and mediastinal lymph node involvement influence survival significantly.

Introduction

Pulmonary resection is the treatment of choice for non-small cell bronchogenic carcinoma if there are no distant metastases. Resectability is closely related to the stage of the disease.[1] Whereas stage I and stage II tumours are considered to be resectable[2], the role of resection for stage III tumours remains controversial.

Stage III tumours can be divided into stage IIIA and stage IIIB tumours. Stage IIIA tumours include tumours with limited extrapulmonary extension of the primary tumour, like invasion of the superior sulcus, chest wall, mediastinal structures, pericardium, or diaphragm, or tumours with endobronchial proximity to the main carina. According to the TNM classification, these tumours are staged as T3.[3]

Resection shows good survival results in bronchogenic carcinoma involving the chest wall.[4,5] Our previous study[6] was in agreement with these findings.

The present report concerns 108 patients who underwent resection because of T3 tumours with invasion of the mediastinal structures, pericardium or with localisation in the main bronchus. It is a retrospective study to analyse survival characteristics.

Patients and methods

From 1977 to 1993, 2009 patients with bronchogenic carcinoma had a resection at our hospital. Of this group, 108 patients (5.4%) underwent operation for T3 non-small cell bronchogenic carcinoma with invasion of the mediastinal structures or pericardium, or localisation in the main bronchus at pathologic examination. Patients with distant metastases, synchronous tumours, and recurrences were excluded. Resection was considered as complete when (1) the surgeon was morally certain that all known disease was removed, (2) resection margins were free at pathological examination, and (3) the highest mediastinal lymph node was negative by microscopy. Peroperative tumour spill was scored separately.

Ages ranged from 31 to 82 years with a mean of 60 years. One hundred and three patients were male and 5 were female. Ninety-eight patients (91%) were smokers.

The most common complaints were cough (75%), dyspnoea (47.2%), haemoptysis (39.8%), weight loss (27.8%), thoracic pain (25%), and hoarseness (12%). Sixteen patients (14.8%) presented without symptoms.
A pre-operative diagnosis was obtained in 105 patients (97.2%). Bronchoscopy was diagnostic in 99 patients, and percutaneous needle aspiration biopsy of the lung and sputum cytology were diagnostic in 3 patients each.
Fifty-seven tumours were located on the right side and 51 tumours on the left side. Cervical mediastinoscopy was negative in 98 patients (90.7%) and positive in 5 (4.6%). The latter group was operated on because they only had a positive lymph node at the ipsilateral tracheobronchial angle (n=3) or because they were relatively young (51 and 56 years) (n=2). The type of resection and tumour localisation are shown in Table 3.1. A complete resection was achieved in 70 patients (64.8%), 46 patients with localisation in the main bronchus, 21 patients with involvement of the mediastinal structures, and 3 patients with localisation in the main bronchus and invasion of the mediastinal pleura. Resections were incomplete due to positive resection margins (87%) and positive lymph nodes (13%). A combined heart-lung operation was performed in 2 patients; 1 patient had a pneumonectomy and a coronary artery revascularization and 1 patient had a pneumonectomy and an aortic valve replacement. Four patients had a pneumonectomy and a tracheobronchial reconstruction because of positive resection margins. Peroperative tumour spill occurred in 5 patients (4.6%).
The histologic diagnosis was squamous cell carcinoma in 90 patients (83.3%), adeno-squamous cell carcinoma in 8 patients (7.4%), adenocarcinoma in 5 patients (4.6%) and large cell carcinoma in 5 patients (4.6%).

Table 3.1. Operative procedures and tumour localisation in 108 patients

Procedure	All patients (n=108)	Patients with complete resection (n=70)
Main bronchus		
Pneumonectomy	61	42
Sleeve lobectomy	6	4
Lobectomy	1	0
Mediastinal structures		
Pneumonectomy	21	14
Bilobectomy	1	0
Sleeve lobectomy	3	1
Lobectomy	8	6
Main bronchus and mediastinal structures		
Pneumonectomy	7	3

All patients were staged as T3 because of involvement of the mediastinal structures or pericardium, or localisation in the proximal airway (Table 3.2). In 3 patients with a tumour located in the main bronchus, there was also atelectasis of the complete lung. The pericardium was involved in 8 patients. Of these patients, 5 patients had also tumour involvement of the phrenic nerve. An intrapericardial pneumonectomy was performed in 6 patients, which was complete in 4 patients. Two patients had a lobectomy and partial pericardiectomy.

Table 3.2. Structures involved in T3 tumours*

Structure	Number of patients
Main bronchus within 2 cm of the carina	75
Mediastinal pleura	32
Phrenic nerve	10
Pericardium	8

* Involvement of more structures at the same time was possible

Pathologic TNM classification is shown in Table 3.3. One patient was staged as T3N0M1 because of a metastasis on the pericard. He underwent an incomplete pneumonectomy.

Table 3.3. Pathologic TNM classification and tumour localisation of all patients and patients with complete resection

pTNM	All patients (n=108)	Patients with complete resection (n=70)
Main bronchus		
pT3N0M0	13	12
pT3N1M0	38	28
pT3N2M0	17	6
Mediastinal structures		
pT3N0M0	11	6
pT3N1M0	16	13
pT3N2M0	6	2
Main bronchus and mediastinal structures		
pT3N0M0	1	1
pT3N0M1	1	0
pT3N1M0	2	2
pT3N2M0	3	0

Thirty-five patients (32.4%) received irradiation as adjuvant therapy. Three patients (2.8%) were irradiated pre-operatively: 2 patients because of a large tumour and 1 patient because he was first suspected to have chronic lymphatic leukaemia. Thirty-two patients (29.6%) received radiotherapy postoperatively. Of these patients, 20 patients underwent an incomplete resection. In the group of patients with complete resection, 6 patients were irradiated because of positive mediastinal lymph nodes.
Six patients (5.6%) received postoperative chemotherapy because of an incomplete resection.
Follow-up was complete as of January 1995. Follow-up data were obtained from hospital files and from questionnaires to referring pulmonary physicians and general practitioners. Follow-up about local recurrence or distant metastases was achieved in 95.4 % of the patients.
Survival was estimated from the date of operation, using the Kaplan-Meier survival analysis method.[7] Hospital deaths were excluded. Survival comparisons were analysed by the log rank test.[8] The difference was considered statistically significant when the p-value was less than 0.05. Incremental risk factors affecting survival were evaluated using Cox's proportional hazards model.[9]

Results

Hospital mortality was 8.3% (pneumonectomy 10.1% [9/89], lobectomy 0% [0/19]). Regarding the localisation of the tumour, hospital mortality was 8.8% (6/68) for tumours localized in the main bronchus, 3% (1/33) for tumours with involvement of mediastinal structures, and 28.6% (2/7) for tumours with involvement of the main bronchus and mediastinal structures. Six deaths were due to bronchopleural fistula in the postoperative period, one to sepsis, one to cardiac arrest, and one to adult respiratory distress syndrome.
Of 6 patients with bronchopleural fistula, 5 had a tumour located on the right side and 1 on the left side. In all patients the bronchial stump had been covered with surrounding tissue. The operation was incomplete because of massive residual carcinomatous tissue at the bronchial stump in 1 patient. This was the only patient who had received pre-operative radiotherapy in whom a bronchopleural fistula developed. In another patient with a bronchopleural fistula the operation was incomplete because of positive mediastinal lymph nodes. In 4 patients sutures of 3-0 Vicryl (Ethicon, Somerville, NJ) were used to close the main bronchus. A stapler was used in the remaining 2. For patients 60 years of age or younger, hospital mortality was 7.0% (4/57), compared with 9.8% (5/51) for those older than 60 years.

Estimated mean 5-year survival was 27% for all patients (n=108) and 29% for hospital survivors (n=99).
Complete resection was performed in 64 hospital survivors (64.6%) with a mean 5-year survival of 35%. The remaining 35 hospital survivors underwent an incomplete resection with a mean 5-year survival of 18% (p=0.03) (Figure 3.1). Because of this significant difference in survival between patients with complete and incomplete resection, only the results of hospital survivors with complete resection were studied for the analysis of other prognostic factors.

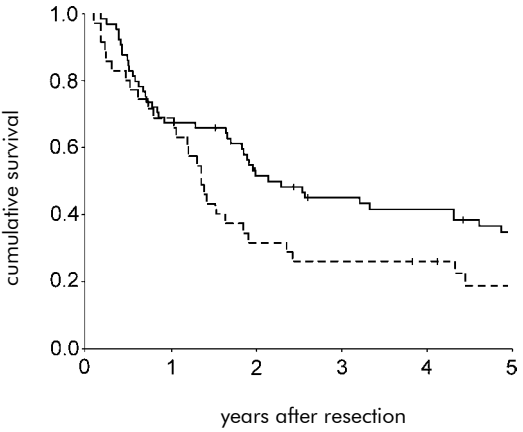

Figure 3.1 Estimated survival in patients with complete resection (——) and incomplete resection (- - -). + = censored cases.

Regarding lymph node involvement, mean 5-year survival was 45% for N0 patients, and 37% and 0% for N1 and N2 patients, respectively. The difference between N0 and N1 disease versus N2 was statistically significant, with a p-value of 0.03 and 0.02, respectively (Figure 3.2).
Regarding T3 classification, mean 5-year survival of hospital survivors with tumour localisation in the main bronchus within 2 centimetres of the carina was 40%. Mean 5-year survival of hospital survivors with tumour involvement of the adjacent mediastinal structures was 25%. The difference between the two groups was not statistically significant.
Patients with squamous cell carcinoma had a better mean 5-year survival than patients with adenocarcinoma, adeno-squamous cell carcinoma, or large cell carcinoma, but the difference was not statistically significant (37% and 22%, respectively, p=0.31).
In the group of patients with complete resection, postoperative radiotherapy did not improve survival. On the contrary, mean 5-year survival of patients who

received radiotherapy was 17%, whereas patients who were not irradiated had a mean 5-year survival of 39% (p=0.01)

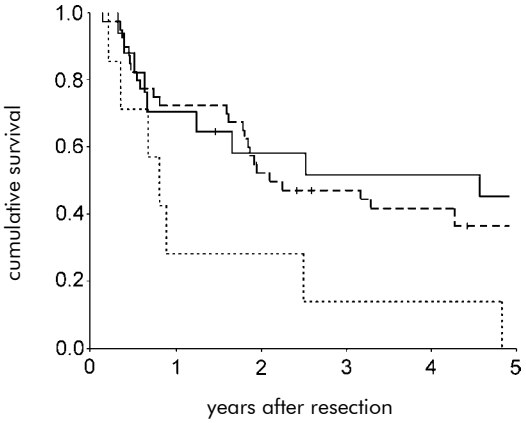

Figure 3.2 Estimated survival after complete resection with lymph node involvement (N1 — —, N2 - - -) and without lymph node involvement (N0 ——). + = censored cases.

Patients younger than 60 years had a better survival than older patients (38% and 31%, respectively). This difference was not significant, but when a new classification into patients younger than 70 years and older was made, the difference was of borderline significance (p=0.05). Sex, tumour spill, and type of operative procedure did not influence survival significantly.
According to the multivariate analysis regarding age, sex, pTNM classification, histology, localisation and tumour spill, only mediastinal lymph node involvement was a significant prognostic factor (Table 3.4).
Distant metastases developed in 25 of 64 hospital survivors with complete resection (39.1%) and 8 patients had local recurrence (12.5%). One patient had combined local and distant recurrence (1.6%).

Table 3.4. Proportional hazards regression model based on 64 patients with complete resection

Variable	ß	SE	Hazard ratio	95% CI
pTNM*	0.31	0.37	1.36	0.66-2.81
pTNM**	1.21	0.50	3.35	1.25-8.99

ß=regression coefficient; SE=standard error; CI=confidence interval; *=pT3N1M0 versus pT3N0M0; **=pT3N2M0 versus pT3N0M0

Comment

Surgical treatment of non-small cell bronchogenic carcinoma is closely related to the stage of the disease.[1] Some selected T3 tumours are potentially resectable. Patients with bronchogenic carcinoma involving the thoracic wall have good survival rate when a complete resection is performed and there are no mediastinal metastases.[4,5] Similar results have been published about tumours located in the main bronchus.[10-14] Although some studies about tumours invading the mediastinum have been published[15-18], the role of resection for carcinomas invading the mediastinal structures remains unclear.

The present study was undertaken to analyse survival characteristics of patients with T3 tumours in the main bronchus or with invasion of mediastinal structures. Comparison with other reports is sometimes difficult due to differences in patient selection, tumour invasion, operative procedure, and statistical analysis.

Hospital mortality was 8.3%. It was closely related to type of operation: pneumonectomy had a higher hospital mortality (10.1%) than lobectomy (0%). This concurs with the results of others.[11,12] Although hospital mortality is high, mean 5-year survival of complete resection by pneumonectomy is still 37%.

Mortality was particular high in patients with a tumour with carinal proximity (8.8%) in contrast to patients with a tumour invading mediastinal structures (3%). Our findings agree with the results published, where hospital mortality for tumours with carinal proximity varies between 6% and 11%[10-12], whereas tumours invading mediastinal structures have a hospital mortality of 3% to 6%[16,18], although it must be noticed that this study included more pneumonectomies in the group of patients with a tumour in the main bronchus.

An important source of postoperative problems was a bronchopleural fistula which developed in 7 patients. Six of them died in the postoperative period. In literature the prevalence of bronchopleural fistula ranged from 2% to 10%.[19] Operative mode (pneumonectomy with bronchoplasty), residual carcinomatous tissue at the stump, preoperative radiotherapy, and diabetes mellitus are significant risk factors.[19] In this study, all patients with bronchopleural fistula had a pneumonectomy and a tumour located in the main bronchus. This stresses the importance of surgical technique in this type of tumour. Only 1 patient was irradiated pre-operatively and had positive resection margins at the bronchus stump. Although age is often correlated with operative mortality, no significant correlation was found in this study.

The estimated mean 5-year survival for 99 hospital survivors was 29%. This is similar to the results of others.[12,13,18] In patients with complete resection the

mean 5-year survival was 35%, whereas patients with an incomplete resection had a mean 5-year survival of 18%.

Regarding the localisation of the tumour, patients with bronchogenic carcinoma located in the main bronchus had a better mean 5-year survival (40%) than patients with a tumour invading mediastinal structures (25%), although the difference was not statistically significant. This was also described by Nakahashi and associates[15], who found a 4-year survival of patients with invasion of the main bronchus of 80%, demonstrating that this subcategory of T3 tumours had a favourable prognosis.

Based on the promising results of chemotherapy in patients with N2 tumours, the use of induction chemotherapy or chemoradiotherapy before resection becomes relevant in bronchogenic carcinoma involving mediastinal structures to improve completeness of resection and survival.

Like other reports[15,16,20], mediastinal lymph node involvement had a poor prognosis. In this study, no patient with mediastinal lymph node involvement survived more than 5 years.

Histologic analysis showed no statistically significant difference in mean 5-year survival between patients with squamous cell carcinoma and adenocarcinoma, adenosquamous cell, or large cell carcinoma, although the first patient group had a better mean 5-year survival (37% versus 22%). This is also described by others[17,20], although Martini and associates[18] found a better survival for patients with adenocarcinoma.

Patients with complete resection who received postoperative radiotherapy had a worse survival than patients who were not irradiated (17% versus 39%). A possible reason for this difference is the fact that 50% (6/12) of patients with complete resection who received radiotherapy had N2 disease, which is associated with a poor prognosis.

Comparing the results of this study with the results of complete resection of T3 bronchogenic carcinoma involving the chest wall[6], patients with a tumour located in the main bronchus had the best prognosis, but the difference was not statistically significant (mean 5-year survival was 40% and 29%, respectively).

In conclusion, complete resection in patients with invasion of mediastinal structures shows moderately good results, whereas patients with involvement of the main bronchus have a superior survival rate. Mediastinal lymph node involvement worsens the prognosis significantly.

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CHAPTER 4

Surgical treatment of Pancoast tumours
A review article

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Summary

Due to its localisation in the apex of the lung with invasion of the lower part of the brachial plexus, first ribs, vertebrae, subclavian vessels or stellate ganglion, a superior sulcus tumour causes characteristic symptoms, like arm or shoulder pain or Horner's syndrome. If rib invasion is the only feature, lyses of the rib must be evident on the chest radiograph, otherwise the tumour can not be defined as a Pancoast tumour. It is important to adequately stage the tumour, because staging significantly influences survival. Survival is better for T3 than T4 tumours and mediastinal lymph node involvement has been found to be a negative prognostic factor. Also Horner's syndrome and incompleteness of resection worsen survival.
The management of superior sulcus tumours has evolved over the past 50 years.
Before 1950 it was considered to be inoperable and uniformly fatal. Shaw and Paulson introduced combined modality treatment and for many years, this combination of radiotherapy and surgery was the treatment of choice with a mean 5-year survival of approximately 30%. Postoperative radiotherapy or brachytherapy does not improve survival in patients with complete or incomplete resection. The tumour can be resected through the classic posterior Shaw-Paulson approach or the newer anterior transcervical approach, introduced by Dartevelle. This method facilitates better exposure of the extreme apex of the lung, brachial plexus and subclavian vessels. Regarding the extent of pulmonary resection, en bloc resection of the involved ribs with a lobectomy is recommended.
Recent multimodality studies, involving chemoradiotherapy and surgical resection, show promising results regarding completeness of resection, local recurrence and survival, provided that appropriate staging has been carried out. However, careful patient selection and adequate perioperative management with protection of the bronchial stump or anastomosis are important to achieve reasonable rates of morbidity and mortality.
As brain metastases remain one of the most common forms of relapse, further studies are needed to examine the role of prophylactic cranial irradiation in patients with complete resection. Also the addition of other chemotherapy agents or biologic agents such as angiogenesis inhibitors or tyrosine kinase inhibitors gives a new perspective in the treatment of Pancoast tumours.

Introduction

Pancoast or superior sulcus tumours produce a characteristic clinical syndrome, which was first described by Edwin Hare in 1838.[1] In 1924 Henry Pancoast, radiologist, called this tumour, located in the apex of the lung and associated with typical complaints "apical chest tumour". In 1932 he changed this name in superior sulcus carcinoma.[2,3] His first impression was that the tumour was extrapulmonary of origin, arising from epithelial remnants of the fifth branchial cleft. However, Tobias recognised that its origin was bronchopulmonary tissue and that it was the localisation of the tumour that made it specific and not its origin.[4] Pancoast's – Tobias syndrome is a constellation of characteristic symptoms that includes pain down the arm and eventually weakness and numbness along the distribution of the eight cervical nerve trunk and first and second thoracic nerve trunks, Horner's syndrome, and radiographic evidence of destruction of the first thoracic rib or vertebral body. It is caused by benign or malignant tumours invading portions of the lower brachial plexus, subclavian vessels, vertebral bodies, parietal pleura, apical ribs and the stellate ganglion.[2,3] The tumour represents less than 5% of all bronchogenic carcinoma and recent reports indicate that its biology is not different from the usual non-small cell lung tumours with its predilection for distant metastases.[5-8] Although Pancoast's syndrome may be the result of different neoplastic, inflammatory, and infectious diseases, the focus of this review will be on the clinical presentation, diagnosis, and treatment of primary non-small cell bronchogenic carcinoma, which causes the vast majority of cases. We will also present the results of surgical treatment of 24 patients who underwent a resection in our hospital because of a superior sulcus tumour.

Clinical presentation and diagnosis

Superior sulcus tumours may occur in three locations and symptoms are related to the location: anterior, in which they invade major blood vessels such as the subclavian artery; middle, in which they mainly invade the brachial plexus; and posterior, in which they invade the stellate ganglion or vertebral bodies. In case of invasion of the brachial plexus, patients often present with pain that begins in the shoulder and scapular region and then extends down to the ulnar aspect of the arm (T1 dermatome) onto the small and ring fingers (C8 dermatome). This pain can be very intensive and often patients are first submitted to the

physiotherapist and neurologist or orthopaedist. With increasing pressure on the nerve roots, muscle atrophy of the ulnar aspect of the hand and loss of the triceps reflex can occur. Because of these aspecific complaints, the time between onset of the symptoms and a correct diagnosis is around 6-10 months.[9-11] In about 20% of the patients tumour invasion of the sympathetic chain and the stellate ganglion causes Horner's syndrome (ipsilateral ptosis, miosis, and anhydrosis).

Specific pulmonary symptoms like cough, dyspnoea, and haemoptysis are mostly absent in the initial stages of the disease due to the peripheral localisation of the tumour. A pathological diagnosis is often difficult to obtain by fiberoptic bronchoscopy.[9,12] The most sensitive procedure for diagnosis is a percutaneous transthoracic needle biopsy with a diagnostic yield of 95%.[9,13,14]

On a chest roentgenogram, the tumour is visible as a small mass or pleural thickening in the apex of the lung with rib and possible vertebral body invasion, although the tumour can be easily missed on a regular chest X-ray. The apical lordotic or slightly oblique views show the apical lesions much better. Computed tomography (CT) and nowadays magnetic resonance imaging (MRI) are the preferred imaging modality for these tumours because they visualise best the relationship of the tumour to adjacent structures like the brachial plexus, subclavian vessels and vertebral bodies.[15]

Regarding histology, non-small cell lung cancer accounts for 90 to 95% of the cases. In current reports, adenocarcinoma is the most common histological diagnosis, followed by squamous cell carcinoma and large cell carcinoma.[16,17] Small cell carcinoma is only rarely associated with this syndrome.[11,18] The differential diagnosis of Pancoast's syndrome includes other primary thoracic neoplasms (mesothelioma, lymphoma, plasmacytoma), infectious processes with organisms such as actinomyces, staphylococcus and echinococcus, neurogenic thoracic outlet syndromes and pulmonary amyloidosis.[7] This wide variety of diseases makes it necessary to make a definitive diagnosis before treatment is started. After the diagnosis of a Pancoast tumour is confirmed, it is important to adequately stage the tumour.

Staging and survival

Because of involvement of the chest wall, these carcinomas are at least staged as T3. Invasion of the vertebral body, or the subclavian vessels upgrades the staging to T4. Staging significantly influences survival. In the study of Rusch and associates actuarial 5–year survival was 46% for stage IIB (T3N0) and 13% for stage IIIB.[19] Both univariate and multivariate analysis showed that T and N status had a significant impact on survival.

In the study of Ginsberg and colleagues, of 22 patients with vertebral body invasion, only 2 survived for 5 years.[17] Other studies support the poor prognosis associated with vertebral body invasion.[14,16] Also tumours with invasion of the subclavian vessel are staged as T4. Dartevelle and co-workers, using the anterior transcervical-thoracic approach, have reported a 30% actuarial 5-year survival in 12 patients.[20] In most studies, however, subclavian vessel involvement is a negative prognostic factor.[14,16,17]

Lymph node status is a very important prognostic factor.[16,21] In the past, mediastinoscopy was not routinely performed in most studies. Because patients with mediastinal lymph node metastases exhibit poor survival, most surgical groups nowadays recommend staging of the mediastinum by mediastinoscopy or positron emission tomography (PET) scan to document the absence of N2 disease, even if the CT or MRI do not demonstrate enlarged lymph nodes.[6,7,22,23] Some series show that patients with supraclavicular lymph node metastases had a better prognosis than patients with N2 disease. Ginsberg and associates found a 5-year survival of 14 % in patients with N3 disease as opposed to 0% in patients with N2 disease.[17] Comparable results were described by Hilaris and co-workers[21], suggesting that tumour involvement of these nodes does not necessarily exclude a curative resection because, in the context of a Pancoast tumour, this form of disease simply represents local contiguous spread.[6]

To exclude metastatic disease, a CT of the liver and adrenal glands or PET scan should be performed. As brain metastases are the most frequent form of distant metastases, the question rises if all patients should have a CT or MRI of the head.[7,24] Bone scans are mostly performed only if indicated by the patient's symptoms.

Treatment and results

The management of superior sulcus tumour has evolved over the last decades and has consisted of surgery alone, radiotherapy alone, pre-and postoperative radiotherapy, or most recently, preoperative chemoradiation.[6,25-27]

Before 1950 the tumour was considered to be inoperable and uniformly fatal. Heburt and Watson reported survival without treatment between 3 and 24 months.[28] In 1953 Chardack and MacCallum reported the first 5-year survival in a patient who initially underwent resection followed by 65 Gy of radiation.[29] Subsequently, Shaw presented a series of 18 patients who were treated by preoperative radiotherapy followed by en bloc resection with up to 51 months survival.[30] And for many years, this combination of radiotherapy and surgery was the treatment of choice.

Radiotherapy alone

Radiotherapy was initiated by Haas and associates in patients with otherwise hopeless thoracic neoplasms. This treatment resulted in good pain relief and improvement of survival.[31] In 1950, Binkley reported the first cure using interstitial brachytherapy.[32]
The doses of radiotherapy used usually ranges between 50 to 70 Gy. In most studies, long-term survival rates are low.[33] This is particularly due to the fact that these studies often include patients with advanced disease and poor performance status. In selected patients, 5-year survival is about 20%, but these results cannot be compared with those of surgical series because of differences in patient selection.[18,33-35]

Combined modality: radiotherapy and surgery

The combination of preoperative radiotherapy with doses between 30 and 35 Gy followed by surgical resection was first reported by Shaw and his colleagues in 1961.[30] Paulson and associates used this approach, updated it on several occasions and found that preoperative radiation including the primary tumour, mediastinum and supraclavicular region facilitated surgical resection and that combined treatment was potentially curative. In their series overall 5-year survival was 31% and for patients with no nodal involvement 44%.[36] In most studies, 5 year survival ranges between 10% and 56% (Table 4.1). Patients with a complete resection had improved 5-year survival rates of 40%.[11,17,37] Results of preoperative radiotherapy followed by surgery in 225 patients in the Memorial Sloan-Kettering Cancer Center published by Rusch and colleagues showed that a complete resection was achieved in only 64% of T3N0 and 39% of T4N0 tumours. Five-year survival was 46% for stage IIB, 0% for stage IIIA and 13% for stage IIIB. Locoregional disease was the most common form of relapse (40%).[19]
Usually, the dose of preoperative radiotherapy ranged between 30 and 35 Gy. Because of a well known dose-response curve in patients with non-small cell lung cancer which suggests that standard treatment is in the range of 50 to 60 Gy, Attar and Miller gave preoperative doses of radiotherapy of 40 to 60 Gy.[33,38] However, both groups noticed an increase of postoperative morbidity and mortality and so lowered the dose to 30 Gy. Fuller and Chambers also used as much as 60 Gy preoperatively, but their study showed no survival advantage.[37] No large phase II or III trials have been reported testing the standard approach of induction radiotherapy in patients with superior sulcus tumours.

Table 4.1. Preoperative radiotherapy followed by surgical resection for patients with superior sulcus tumours

First author	(year)	No. of patients	Complete resection (%)	5-year survival (%)
Attar[33]	(1979)	19	NS	23 (3-year)
Paulson[36]	(1985)	78	NS	31
Devine[35]	(1986)	40	NS	10
Shahian[39]	(1987)	18	50	56
Wright[14]	(1987)	21	76	27
Hilaris[21]	(1989)	82	NS	29
Sartori[16]	(1992)	42	NS	25
Ginsberg[17]	(1994)	124	56	26
Maggi[11]	(1994)	60	60	17.4
Attar[25]	(1998)	28	NS	27
Hagan[8]	(1999)	34	NS	33
Dartevelle[44]	(1999)	70	NS	35
Pitz	(2004)	18	33.3	16.7

NS= not stated

The potential benefits of preoperative radiotherapy include a decrease in the size of the tumour, with improved resectability, and a reduction in the number of viable cells, which theoretically prevents dissemination of the tumour during surgery.[30,36] Surgery is usually performed 2 to 4 weeks after the last radiation.

Shahian and colleagues reported on 18 patients who were treated with preoperative radiotherapy. 14 of these patients also received postoperative radiotherapy because of N2 disease, positive resection margins, or both. Overall 5-year survival was 56%. They believed that this "sandwich" radiation would improve survival.[39] Ginsberg also reported 4 long-term survivors in a group treated with sandwich radiotherapy, but too few patients have received this treatment to assess its outcome and radiobiologically it is not recommended.[17]

The rates of complete resection with preoperative radiotherapy followed by resection have not changed in the last past years (Table 4.1). Any apparent increased survival has probably occurred because of better patient selection due to enhanced detection of unresectable disease or occult metastatic disease with modern radiological imaging.

The role of intra-operative and postoperative radiotherapy is unclear at this time, but most studies have failed to demonstrate any advantage regarding survival for postoperative radiotherapy or intra-operative brachytherapy in the face of incomplete resection or N2 disease. Same results were described in patients with complete resections.[17,21,37]

Surgical technique

Surgical resection remains the treatment of choice for superior sulcus tumours. The goal is to resect the upper lobe with the invaded ribs and transverse processes and all invaded structures such as the lower trunk of the brachial plexus, stellate ganglion and upper dorsal sympathetic chain. The problem is that the apex is a small, rigid, bone encased area which is difficult to access and that surrounding structures are either difficult to resect macroscopically free of tumour (vertebrae) or that resection can leave important deficits (brachial plexus, subclavian vessels). In patients with involvement of the brachial plexus or the spine, a combined thoracic, orthopaedic and neurosurgical approach can improve resectability and local control.[40]

Different surgical approaches have been described. As a general rule, superior sulcus tumours not invading the thoracic inlet are completely resectable through the classic posterior Shaw-Paulson approach.[30] This consists of a posterolateral thoracotomy with a high posterior parascapular incision carried to the base of the neck. This method allows good access to the posterior part, but poorer access to the more anterior structures like the subclavian vessels. Chest wall reconstruction is rarely needed because the defect is covered by the scapula. A newer alternative approach is the anterior transcervical approach, popularized by Dartevelle and colleagues.[20] This method facilitates better exposure of the extreme apex of the lung and cervically based structures (brachial plexus and subclavian vessels). The incision parallels the lower sternocleidomastoid muscle and courses over the manubrium and then turns laterally below the involved clavicle. Resection, division or retraction of the clavicle opens the thoracic inlet. This approach shows lower morbidity than the posterior approach because the posterior chest wall muscles and the shoulder are undisturbed. However, these osteomuscular resections can cause postoperative alterations in the shoulder mobility and cervical posture. To avoid these deformities Grunenwald and colleagues developed a transmanubrial technique, through a manubrial L-shaped transaction and first costal cartilage resection, which allows retraction of an osteomuscular flap including but sparing the clavicle and its muscular insertions.[41] Recently, both Dartevelle and Grunenwald developed a technique which is a combination of a transcervical or transmanubrial and posterior midline approach. This technique makes it possible to resect posteriorly located superior sulcus tumours extending into the intervertebral foramen without intraspinal extension.[40,42,43]

Regarding the extent of pulmonary resection, a lobectomy is recommended.[17,23] Ginsberg and associates reported a survival benefit (lobectomy 60% versus limited resection 33%) and a reduction in local recurrence in patients who underwent a lobectomy.[17]

The reported surgical morbidity ranges from 7 to 38% with surgical mortality generally around 5 to 10%.[9,16,21] Surgical complications include spinal fluid leakage, Horner's syndrome and nerve deficits, haematothorax, chylothorax and prolonged ventilatory support. The postoperative course is usually characterized by atelectasis because of the concomitant extended chest wall resection and phrenic nerve resection.

Invasion of the subclavian vessel is a relative contraindication, but successful surgical resection has been described.[14,20] Absolute surgical contraindications are the presence of extrathoracic metastases, mediastinal lymph node involvement, invasion of the brachial plexus above T1 as supported by sensitive or motor deficits in the nerve distribution of the median and radial nerves or vertebral body invasion with invasion of the spinal canal.[44]

Own results

Between 1977 and 1993, we operated on 24 patients (mean age 53.3 years, range 38 to 71 years) with superior sulcus tumours. The diagnosis was made by the clinical presentation of pain around the shoulder and upper arm, associated with a tumour in the apex of the lung. Duration of the symptoms before diagnosis ranged from 3 to 24 months. The majority of the lesions were either squamous cell carcinoma (n=11) or adenocarcinoma (n=11), 2 patients had a large cell carcinoma. pTNM classification was pT3N0M0 in 19 patients, pT3N1M0 in 2 patients, pT3N2M0 in 1 patient and pT4N0M0 in 2 patients. The patients were divided into 3 groups according to the method of therapy: group I (n=9) preoperative radiation and surgery, group II (n=6) surgery and postoperative radiation, group III (n=9) preoperative radiation followed by surgery and postoperative radiotherapy. Preoperative radiotherapy was delivered to the primary tumour and mediastinum and doses ranged between 30 Gy and 50 Gy. The involved lung was resected by lobectomy in 18 patients and segment or wedge resections in 6 patients. The 6 patients in group II received postoperative radiotherapy to the tumour and mediastinum with doses between 55 to 60 Gy.

Group III comprised 9 patients who had preoperative radiotherapy (range 30 to 40 Gy) followed by surgery and postoperative radiation (range 20 to 30 Gy).

A complete resection was only possible in 6 patients (25%). All these patients were treated with pre-operative radiotherapy. There were no hospital deaths. The median survival for all patients was 1.9 year. The 5-year survival rate was 25%. The median survival for group I was 1.2 year, for group II 1.6 year and for group III 2.2 year. There was no statistical difference in survival between the groups.

By univariate analysis age, sex and cell type were not statistically significant.

Induction chemoradiotherapy and surgery

Because of the reported improved results of combined treatment with chemotherapy and irradiation in patients with stage IIIA and stage IIIB non-small cell lung cancer, it seemed logical to apply such therapy to patients with Pancoast tumours (Table 4.2). The combination of radiotherapy and radiation – sensitizing chemotherapy increases the chance of performing a complete resection. At the current time concurrent treatment is favoured above sequential treatment, but concurrent chemoradiotherapy can be more toxic than sequential and requires close monitoring of the patient.

Table 4.2. Preoperative chemoradiotherapy followed by surgical resection for patients with superior sulcus tumours

First author	(year)	No. of patients	Complete resection (%)	4-year survival (%)
Martinez-Monge[45]	(1994)	18	76	56
Rusch[26]	(2001)	111	92	55, patients with CR* 70 (2-year)
Wright[46]	(2002)	15	93	84

*= complete resection

Martinez-Monge and associates reported on a series of 18 patients with Pancoast tumours treated with cisplatin based chemotherapy followed by simultaneous preoperative chemotherapy and irradiation, after which the patient underwent resection with insertion of brachytherapy catheters. Resectability rate was 76.4% and a complete pathologic response was seen in 70.5%. Local failure rate was only 9% and 4-year actuarial survival was 56%. However, mortality was 16.7%.[45] Same results were described by the Southwest Oncology Group which conducted a prospective phase II North America Intergroup study looking at preoperative chemoradiotherapy.[26] This study included 111 patients with T3-4 superior sulcus tumours without mediastinal lymph node metastases. 102 patients completed the induction treatment of 2 cycles of cisplatin based chemotherapy concurrent with 45 Gy of radiation. Of 95 patients eligible for surgery, 83 underwent a resection, which was complete in 76 (92%). Fifty-four patients (65%) had either a pathologic complete response or minimal microscopic disease. The 2-year survival was 55% for all eligible patients and 70% for patients with a complete resection. Overall treatment mortality was only 4.5%. Assessment of response to induction treatment was difficult. Only 40% of the patients with radiologically stable disease and 27% of the patients with a radiological partial response had significant gross residual tumour at thoracotomy. This shows that radiological response to induction treatment has to

be viewed with caution and usually underestimates the results of treatment. The intent of the study was to treat all patients with two additional cycles of the same chemotherapy regardless of whether a resection was performed, but in the postoperative group, this was only feasible in a small group of patients.
Better results of combined chemoradiotherapy followed by surgery compared to induction radiation are also described by Wright and colleagues.[46] However, surgery has to be considered a high-risk procedure after induction chemotherapy or chemoradiotherapy. Careful patient selection and adequate perioperative management with protection of the bronchial stump or anastomosis are important to achieve reasonable rates of morbidity and mortality.[47,48]
At the moment, a prospective phase II intergroup trial (S0220) is being conducted by the Southwest Oncology Group. In this study, patients will receive induction chemoradiotherapy with cisplatin/etoposide and then go on to receive consolidation taxane cytotoxic chemotherapy in the postoperative setting which appeared to be effective even in tumours previously treated with or resistant to cisplatin.[49]

Recurrence and prognostic factors

Control of locoregional disease remains the major challenge in treating Pancoast tumours. Despite the relative improvement in survival of patients with superior sulcus tumours treated with combined preoperative radiotherapy and operation, there is still a high incidence of local recurrence between 25 and 70%. In the study of Ginsberg of 69 patients with complete resection, two third of the cases had local recurrence.[17] Most frequent sites are the spine, chest wall and lung.[19] However, treatment with combined preoperative chemoradiation seems to lower this incidence of local recurrence.[26,46] In the study of Rusch and associates, local recurrence was only 23%. This concurrent treatment appears to change the most common side of relapse from local to distant. Brain metastases are one of the most common forms of relapse, accounting for 40% to 80% of distant recurrences, especially in patients with poorly differentiated large cell carcinoma and adenocarcinoma.[8,17,21] This raises the question whether patients with a complete resection should be treated with prophylactic cranial irradiation (PCI).[21,26,34] In general, few studies have routinely used PCI in patients with non-small cell bronchogenic carcinoma. Eberhardt and colleagues did not perform a randomised investigation of PCI in their study, but the overall brain relapse was remarkably reduced in the group that received PCI even though no impact on survival was noted.[50] In the study of Stuschke and associates, regarding PCI in locally advanced non-small cell lung cancer after multimodality treatment, this

treatment reduced the rate of overall brain metastases from 54% to 13% ($p<0.0001$).[51] Bone metastases appear to be to second most common side of distant disease.[21,38]

Factors associated with poor prognosis are extension of the tumour into the basis of the neck, mediastinal lymph node involvement, invasion of vertebral bodies or great vessels, presence of Horner's syndrome, and incompleteness of resection. The value of histology per se as a prognostic factor is controversial.[7-9,17,19,36]

Conclusion

After Shaw introduced combined modality treatment for patients with a superior sulcus tumour, this combination of preoperative radiotherapy followed by surgery was the treatment of choice with a mean 5-year survival of approximately 30%. In several studies, it appeared that N2 disease and incomplete resections had an adverse impact on survival and that postoperative radiotherapy or brachytherapy did not improve survival in patients with complete or incomplete resections.

During the 1990s, studies have focused on prognostic factors and adequate staging, on determining the role of brachytherapy and on exploring new surgical techniques that facilitated complete resection. Despite these reports, complete resection rate and 5-year survival were low and locoregional recurrence remained the predominate form of relapse.

These results emphasized the need for improved therapy for superior sulcus tumours. A multimodality approach, involving chemoradiotherapy and surgical resection shows promising results, provided that appropriate staging has been carried out. In the study of Rusch and colleagues cisplatin based chemotherapy with concurrent radiation followed by surgery is feasible and resectability and overall survival were improved. However, careful patient selection and adequate perioperative monitoring are very important, regarding the higher morbidity and mortality rates in some studies after induction chemotherapy.

As brain metastases are one of the most common forms of relapse, the question rises whether patients with a complete resection should be treated with PCI. Given the proven efficacy of this treatment to prevent metastases to the brain in small cell lung cancer, the introduction of PCI into the treatment of non-small cell lung cancer in the curative setting seems promising.

Another approach to diminish the incidence of distant metastases can be the addition of another chemotherapy agent, like docetaxel, or biologic agents such as angiogenesis inhibitors or tyrosine kinase inhibitors.

Therefore, further studies are needed to minimize morbidity and mortality and to examine the best combination of induction chemotherapy and biological agents and the role of prophylactic cranial irradiation.

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CHAPTER 5

Results of surgical treatment of T4 non-small cell lung cancer

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Abstract

Background

Because of location and invasion of surrounding structures, the role of surgical treatment for T4 tumours remains unclear. Extended resections carry a high mortality and should be restricted for selected patients. This study clarifies the selection process in non-small cell T4 tumours with invasion of the mediastinum, recurrent nerve, heart, great vessels, trachea, oesophagus, vertebral body, and carina, or with malignant pleural effusion.

Methods

From 1977 through 1993, 89 patients underwent resection for primary non-small cell T4 carcinomas. Resection was regarded as complete in 34 patients (38.2%) and incomplete in 55 patients (61.8%). Actuarial survival time was calculated and risk factors for late death were identified.

Results

Overall hospital mortality was 19.1% (n=17). Mean 5-year survival was 23.6% for all hospital survivors, 46.2% for patients with complete resection and 10.9% for patients with incomplete resection (p=0.0009). In patients with complete resection, mean 5-year survival for patients with invasion of great vessels was 35.7%, whereas mean 5-year survival for invasion of other structures was 58.3% (p=0.05). Age, mediastinal lymph node involvement, type of operative procedure, and postoperative radiotherapy did not significantly influence survival.

Conclusion

In certain T4 tumours complete resection is possible, resulting in good mean 5-year survival especially for tumours with invasion of the trachea or carina. High hospital mortality makes careful patient selection imperative.

Introduction

Prognosis in carcinoma of the lung is influenced by the stage of the disease and consequently by the therapeutic potential. Surgical resection is the treatment of choice for stage I and stage II non-small cell lung cancer, but its role in stage III disease remains unclear.[1] Our previous studies have shown that complete resection will result in good survival in T3 bronchogenic carcinoma with chest wall involvement[2], and in lung tumours invading mediastinal structures, or the main bronchus.[3] These tumours are classified as stage IIB, or IIIA disease.[4] Stage IIIB non-small cell lung cancer can be divided into primary bronchogenic carcinoma invading adjacent structures (T4), or into tumours with metastases to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) (N3). T4 bronchogenic carcinomas are a heterogeneous group of locally advanced cancers. Generally, these T4 tumours are regarded as unresectable.[5] Treatment is palliative for the majority of the patients, ranging from supportive care to chemotherapy or radiotherapy. However, some studies about extended resection of T4 tumours have been published[6-10]; hospital morbidity and mortality are high but, in selected patients, surgery appears to be beneficial and radical resection of the tumour has a potential for cure in the absence of mediastinal lymph node metastases.
The present report is a retrospective analysis of survival characteristics in 89 patients who underwent resection for T4 tumours with invasion of the mediastinum, recurrent nerve, heart, great vessels, trachea, oesophagus, vertebral body and carina or with a malignant pleural effusion.

Materials and methods

From 1977 through 1993, 2009 patients with bronchogenic carcinoma had a resection at our hospital. Of this group, 89 patients (4.4%) underwent operation for T4 non-small cell lung cancer (NSCLC) with invasion of the mediastinum, recurrent nerve, heart, great vessels (aorta, superior vena cava, proximal main pulmonary vessels (proximal defined as proxim to the pericard or at pericardial reflection)), trachea, oesophagus, vertebral body, or carina, or with malignant pleural effusion at pathologic examination. Patients with distant metastases, synchronous tumours, superior sulcus tumours, a satellite tumour within the same lobe or recurrences were excluded. Resection was considered complete when (1) the surgeon was morally certain that all known disease was removed,

(2) resection margins were histologically free, and (3) the highest mediastinal lymph node was negative by microscopy. Staging procedures included routine blood tests, thoracic computed tomography, ultrasonography of the upper abdomen, bronchoscopy, mediastinoscopy, and pulmonary function tests. Computed tomography of the brain or bone scintigraphy was performed only in case of clinical suspicion of metastatic disease.
Patient characteristics are shown in Table 5.1. Cervical mediastinoscopy was negative in 81 patients (91.0%), not performed in 1 patient (1.1%) and positive in 7 patients (7.9%). These seven patients were operated because they only had one single positive lymph node at the ipsilateral tracheobronchial angle (n=4), or, because they were relatively young (46 and 51 years). In one patient the reason for thoracotomy could not be assessed retrospectively. One patient was pre-operatively diagnosed at bronchoscopy as having a carcinosarcoma in the main right bronchus. No cervical mediastinoscopy was performed. Frozen sections peroperatively showed a squamous cell carcinoma.

Table 5.1. Patient characteristics

	No. of patients
Age (years)	
Mean	61.5
Range	34-78
Sex	
Male	81
Female	8
Smokers	82
Symptoms*	
Cough	65
Dyspnoea	37
Haemoptysis	35
Pain	34
Weight loss	24
No symptoms	10
Side of tumour	
Right	43
Left	46
Preoperative diagnosis	
Bronchoscopy	79
Percutaneous needle aspiration	3
No diagnosis	7

* a patient presented with one or more symptoms

The type of resection is shown in Table 5.2. In 4 patients with bronchogenic carcinoma invading the right side of the mediastinum, a pneumonectomy (n=3)

or lobectomy (n=1) included resection and reconstruction of the superior vena cava by a Goretex graft. Two patients had a lobectomy of the right upper lobe and a bypass of the superior vena cava. One patient had a lobectomy of the left upper lobe followed by a Dacron prothesis of the subclavian artery. In one patient with a pneumonectomy the tumour invaded the chest wall and an en bloc resection of the tumour and the chest wall was performed.

Table 5.2. Operative procedures

Procedure	All patients (n=89)	Patients with complete resection (n=34)	Hospital survivors with complete resection (n=26)
Pneumonectomy	56	19	14
Sleeve pneumonectomy	4	3	3
Carinal pneumonectomy	7	5	4
En bloc pneumonectomy	1	1	0
Pneumonectomy + reconstruction blood vessel	3	2	2
Bilobectomy	1	0	0
Lobectomy	6	2	1
Sleeve lobectomy	5	2	2
Lobectomy + reconstruction/ bypass blood vessel	4	0	0
Sleeve bronchus	2	0	0

A complete resection was achieved in 34 patients (38.2%). Resections were incomplete due to positive resection margins (n=39), positive lymph nodes (n=2), a combination of both (n=12) or malignant pleural effusion (n=2). The histological diagnosis was squamous cell carcinoma in 77 patients (86.5%), adenocarcinoma in 10 patients (11.2%), adenosquamous cell carcinoma in 1 patient (1.1%), and large cell carcinoma in 1 patient (1.1%). Cervical mediastinoscopy was false negative in 27 patients. Fourteen of these 27 patients had positive subaortic or para-aortic lymph nodes (n=11) or positive paraesophageal lymph nodes (n=3).

All patients were staged as T4 because of involvement of the mediastinum, recurrent nerve, heart, great vessels, trachea, oesophagus, vertebral body, or carina, or the presence of malignant pleural effusion (Table 5.3). Invasion of the different great vessels and pTNM staging are shown in Table 5.4 and 5.5.

Radiation therapy was given to 47 patients as adjuvant therapy. One patient with tumour invasion of the pulmonary artery was pre-operatively irradiated. Although he was judged to be inoperable, a palliative pneumonectomy was carried out some months later because of persistent complaints of dyspnoea and the absence of distant metastases. Forty-six patients (51.7%) received

radiotherapy postoperatively. Of these patients, 32 patients had an incomplete resection. In the group of patients with complete resection (n=14), 7 patients were irradiated because they were staged as T4N2, the other 7 patients received radiotherapy because of the bulk of the tumour or localization near great vessels or other major structures. One patient with a T4N2 tumour only received 1.2 Gy radiation because she developed a pericardial effusion. Ten years after the operation she is still alive.
Four patients (4.5%) received postoperative chemotherapy because of incomplete resection.

Table 5.3. Structures involved in T4 tumours*

Structure	All patients (n=89)	Patients with complete resection (n=34)	Hospital survivors with complete resection (n=26)
Great vessels	61	23	17
Mediastinum	32	6	4
Trachea	24	9	8
Heart	15	4	4
Recurrent nerve	13	8	6
Oesophagus	12	3	3
Carina	11	4	4
Vertebral body	2	0	0
Pleuritis carcinomatosa	2	0	0

* = Involvement of more structures at the same time was possible

Table 5.4. Invasion of the different great vessels

Structure	All patients (n=61)	Patients with complete resection (n=23)	Hospital survivors with complete resection (n=17)
Aorta	17	6	3
Superior vena cava	13	4	3
Pulmonary artery	6	4	4
Pulmonary vein	25	9	7

Follow-up was completed as of August 2002. Follow-up data were obtained from hospital files and from questionnaires to referring pulmonary physicians and general practitioners. Follow-up about local recurrence and distant metastases was obtained in 96.6% of the patients.
Survival was estimated from the date of operation, using the Kaplan-Meier survival analysis method.[11] Hospital deaths were excluded. Survival comparisons were analysed by the log rank test.[12] The difference was considered statistically

significant when the p value was less than 0.05. Incremental risk factors affecting survival were evaluated using Cox's proportional hazards model.[13]

Table 5.5. pTNM staging

pTNM	All patients (n=89)	Patients with complete resection (n=34)	Hospital survivors with complete resection (n=26)
pT4N0M0	11	4	3
pT4N1M0	43	22	16
pT4N2M0	35	8	7

Results

Hospital mortality was 19.1% (pneumonectomy 18.3% [13/71], lobectomy 26.6% [4/15]. The mean age of these 17 patients was 64.4 years (51-77 years). Ten patients had undergone a pneumonectomy, 2 a carinal pneumonectomy, 1 an en bloc pneumonectomy, 2 a lobectomy and 2 a lobectomy with reconstruction of the superior vena cava. Of these 17 deceased patients, 13 had invasion of the great vessels (4 left atrium and intrapericardial pulmonary vein, 3 intrapericardial pulmonary vein, 3 aorta, 3 superior vena cava), 2 invasion of the trachea and oesophagus, 1 invasion of the trachea and 1 had tumour involvement of the vertebral column. Hospital deaths were due to cardiac arrest (n=5), sepsis (n=4), respiratory failure (n=3), haemoptysis (n=1), cerebral haemorrhage (n=1) and gastro-intestinal tract bleeding (n=1). Two patients died at home, 1 and 2 days respectively after their discharge from the hospital, but within 30 days of the operation.

Estimated mean 5-year survival was 19.1% for all patients (n=89) and 23.6% for hospital survivors (n=72).

Complete resection was performed in 26 hospital survivors (36.1%) with a mean 5-year survival of 46.2%. The remaining 46 hospital survivors underwent an incomplete resection with a mean 5-year survival of 10.9 % (p=0.0009)(Figure 5.1). Because of this significant difference in survival between patients with complete and incomplete resection, only the results of hospital survivors with complete resection were studied for the analysis of other prognostic factors.

As for the N status, mean 5-year survival was 33.3% for 3 N0 patients, and 43.8% and 57.1% for 16 N1 and 7 N2 patients, respectively (p>0.05).

Regarding the T status, mean 5-year survival for patients with invasion of great vessels (n=14) was 35.7%, whereas mean 5-year survival for patients with invasion of other structures (n=12) was 58.3% (p=0.03) (Figure 5.2). Although patients with involvement of the carina or the trachea had a better mean 5-year

survival (50.9%) than involvement of other structures (44.4%), the difference was not statistically significant.

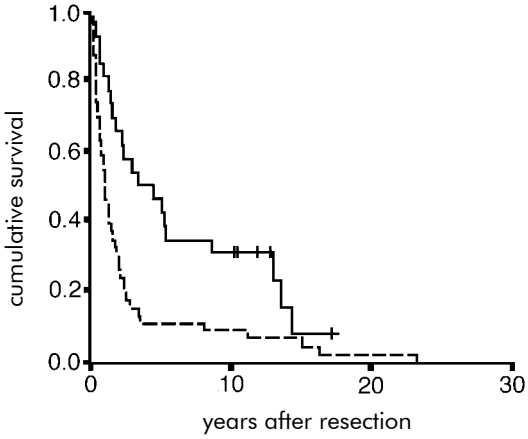

Figure 5.1 Estimated survival in hospital survivors with complete resection (——) and incomplete resection (- - -). + = censored cases.

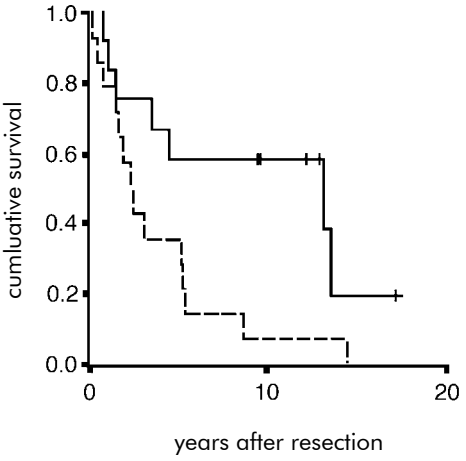

Figure 5.2 Estimated survival after complete resection with invasion of great vessels (- - -) and invasion of other structures (——). + = censored cases.

Of the 26 hospital survivors with complete resection, 24 patients had a squamous cell carcinoma with a mean 5-year survival of 45.8%. One patient with an adenocarcinoma died after 2 years and an other patient is still alive after 10 years.

Mean 5-year survival for patients who underwent a pneumonectomy (n=23) was 43.5%, and for patients post lobectomy (n=3) 66.7% ($p>0.05$). Age and postoperative radiotherapy did not influence survival significantly.
According to the multivariate analysis regarding age, sex, pTNM classification, histology and localization no significant prognostic factors were found in the group of patients with complete resection.
Distant metastases developed in 4 of 26 hospital survivors with complete resection (15.4%), and 1 patient had a local recurrence (3.8%). Three patients had combined local and distant recurrence (11.5%).

Discussion

Prognosis, surgical treatment and long-term survival of non-small cell bronchogenic carcinoma are closely related to the stage of the disease.[1] Stage IIIB non-small cell lung cancer has a 5-year survival rate of about 7%, and results of surgical treatment are poor[4,6,14]; however, some selected T4 tumours are potentially resectable, survival depending on completeness of resection, locoregional tumour invasion and lymph node metastases. These extended resections carry a high mortality and morbidity and make careful patient selection imperative.
Hospital mortality varies between 5% and 20%, increasing after extended resections.[15,16] Our study also shows a substantial hospital mortality of 19.1%. Hospital mortality was related to invasion of the great vessels. Thirteen of 17 hospital deaths had tumour involvement of the aorta, superior vena cava or pulmonary veins. In this subset hospital mortality was 21.3% (13/61).
Resectability of a tumour is influenced by pTNM staging. Our results of surgical treatment of T3 tumours with invasion of the chest wall, or with invasion of the mediastinal structures and/or localization in the main bronchus showed that complete resection was possible in 68.8% and 64.8%, respectively.[2,3]
In T4 tumours, localization and invasion of adjacent structures often make complete resection impossible. A complete resection is vital.[6,15] In our series, mean 5-year survival for complete resections was 46.2%, for incomplete resections 10.9% ($p< 0.05$).
A complete resection could be performed in 34 patients (38.2%). This is higher than described by Martini et al. who had a complete resection rate of 18%. In that study none of the tumours invading the aorta, trachea or spine were resected.[6] However, other studies reported complete resection rates of 72% and 80%, respectively, for tumours invading great vessels or the carina.[10,17] Based on resectability criteria, Grunenwald divided stage IIIB tumours in two subcategories: potentially resectable (invasion of superior vena cava, carina,

lower trachea, left atrium) and definitively non-resectable (malignant pleural effusion, invasion of the oesophagus and vertebrae).[18] Our study supports this classification.

In the past, high postoperative morbidity and mortality and uncertain long-term survival have been associated with carinal surgery for bronchogenic carcinoma.[19] Respiratory failure after noncardiogenic pulmonary oedema or infection in the remaining lung and anastomotic dehiscence with bronchial fistula were the major postoperative problems and the main cause of the high operative mortality, varying from 11% to 27% in large series.[8] However, careful patient selection, much attention to surgical details and careful anaesthetic management can lower the levels of surgical deaths. Recently, a postoperative mortality of 6.6%-15% has been reported and pneumonectomy with tracheal sleeve resection is advocated by several surgeons with 5-year survival approaching 43%.[7,16] In our study, complete resection of tumours with invasion of the trachea or carina was 37.5% and 36.4% respectively, while it was less for tumours with invasion of other structures and it had a favourable prognosis with a mean 5-year survival of 50.9%.

Results of surgery for T4 tumours with invasion of the left atrium or great vessels are poor. Burt et al. reported no 5-year survivors in their series of 18 patients after resection for tumours extending into the vena cava superior[14], while Tsuchiya et al. found only 2 of 101 patients alive after 5 years.[9] However, recent advances in cardiovascular surgery offer possibilities for complete resection in cases of invasion of the great vessels, like aorta and superior vena cava.[10,15] Spaggiari et al. reported extended resections for tumours invading the superior vena cava with 5-year actuarial survival of 29%, with 4 of 25 patients alive at 5 years.[10] Hospital mortality was 12%, and a complete resection was achieved in 20 patients (i.e. 80%). This is high, but Doddoli et al. described the same results for completeness of resection and survival.[17] In our study 37.7% of the patients with invasion of the great vessels had a complete resection (n=14). This conforms to the results of Fukuse et al.[15] There was no difference in completeness of resection between invasion of the aorta, superior vena cava and pulmonary vein. The results of complete resection in the group with invasion of the pulmonary artery were better, but this was a very small group. Mean 5-year survival was 35.7%.

Traditionally, tumours invading vertebrae were considered as unresectable. We had no complete resection in both patients with involvement of the vertebral body. However, recent progress in spinal surgery has opened new possibilities. Induction treatment with total or partial vertebrectomy and pulmonary resection is feasible in selected patients with an estimated 5-year survival of 14%.[20]

In most studies involvement of the oesophagus precludes a complete resection.[6,21] We achieved a complete resection in 3 patients (25%), as only the muscular layer of the oesophagus was involved by the tumour.
Regarding lymph node involvement, mean 5-year survival was worse for N0 patients than for N1 and N2 patients. This finding is contradictory to our previous studies[2,3] in which mediastinal lymph node involvement worsens the prognosis. All 3 N0 patients in this series, however, had involvement of great vessels or the heart. Invasion of these structures carries a worse prognosis.[6] In the group of 16 N1 and 7 N2 patients involvement of great vessels or the heart was present in 9 and 5 patients, respectively. The remaining patients had involvement of the trachea (n=8), carina (n=4), mediastinum (n=4) or oesophagus (n=3). Izbicki et al. also found no statistical significant differences in survival related to lymph node status in T4 tumours.[22] In their study, mean 3-year survival for 6 T4N0, 7 T4N1 and 12 T4N2 patients was 0%, 53% and 16.6%, respectively. This suggests that in T4 tumours local invasion of surrounding structures may be more important for survival than lymph node involvement. But in both studies the number of patients is limited and other studies reported no long-term survivors in patients with T4N2 tumours.[6,15,21]
Because of the poor results of surgical resection alone, multimodality treatment has surfaced as the treatment of choice in patients with stage III NSCLC.[23] However, it is still unclear which treatment modality (surgery, radiotherapy or a combination of both) will result in prolonged survival after neo-adjuvant chemotherapy. Recently, several trials have been conducted showing that some locally advanced, initially unresectable tumours become operable after inductionchemotherapy.[24,25]
Given our own results, and those reported by others[18,19,22] for patients presenting with T4 pathology, pre-operative work-up should establish the possibilities of complete resection using complete available modern imaging technology. If complete resection, with appropriate reconstruction, is feasible, all patients, otherwise fit for surgery, should be operated on. Complete resection resulting in good mean 5-year survival is possible, especially for tumours invading the trachea or carina. Tumours with invasion of the oesophagus, vertebrae and with malignant pleural effusion appear to be unresectable in most cases. The results of inductionchemotherapy make us propose that presently multimodality treatment offers new possibilities to treat patients with T4 disease and a good performance status.

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CHAPTER 6

Surgery as part of combined modality treatment in stage IIIB non-small cell lung cancer

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Abstract

Background
The role of surgery after neo-adjuvant chemotherapy in patients with stage IIIB non-small cell lung cancer (NSCLC) remains unclear.

Methods
A prospective multicenter trial of neo-adjuvant chemotherapy followed by surgery or radiotherapy or both was conducted with 41 patients with stage IIIB NSCLC. End points were toxicity, response, downstaging, complete resectability, and survival. The diagnostic value of repeat mediastinoscopy after neo-adjuvant chemotherapy (three courses of gemcitabine/cisplatin) was also studied.

Results
Response rate after neo-adjuvant chemotherapy was 66% (27/41). Fifteen patients underwent repeat mediastinoscopy, which proved to be inadequate in 6 patients. Two repeat mediastinoscopies were false negative. Resection was performed in 18 patients, of which 10 proved to be radical. Hospital mortality was 2.4% (n=1). Major complications occurred in 6 patients (fistula, empyema, haemorrhage). Histopathologically proven downstaging was seen in 16 patients (39%). Twenty-three patients underwent radiotherapy of whom 14 were diagnosed with stable/progressive disease and 9 patients with partial/complete response. Median survival for all patients was 15.1 months, for non-responders 8.4 months and for responders 16.8 months (p=0.11). Patients with partial/complete response had a mean survival of 21.5 months after resection and 13.0 months after radiotherapy (p=0.0003).

Conclusion
Radical surgery can be performed in 37% (10/27) of the responders resulting in a prolonged survival. Surgery as part of combined modality treatment is feasible in stage IIIB NSCLC. Results of a repeat mediastinoscopy are disappointing and proved to be a not so effective restaging tool because of the high number of incomplete procedures and because it yields false negative results.

Introduction

At presentation, 25 to 35% of all patients with non-small cell lung cancer (NSCLC) have tumours that have not yet metastasised systemically, but are locally too advanced to allow complete resection. Even though it could not cure the majority of patients, radiotherapy used to be the standard treatment in locally unresectable tumours.[1]
Recently, multimodality treatment has become the standard therapy used for these patients.[2] In combined modality treatment, the main goal of chemotherapy is to eradicate micrometastases and mediastinal lymph node metastases, and to diminish the size of the primary tumour.
So far, most clinical trials of neo-adjuvant chemotherapy followed by surgery or radiotherapy or both have focused on patients with stage IIIA N2 disease.[3] In this group, neo-adjuvant chemotherapy did achieve improved survival. However, the role of surgery after neo-adjuvant chemotherapy in patients with stage IIIB disease remains unclear.
In this prospective phase II multicenter trial we evaluated the role of surgery after neo-adjuvant chemotherapy in patients with stage IIIB NSCLC. The diagnostic value of repeat mediastinoscopy after neo-adjuvant chemotherapy for mediastinal staging was also analysed.

Methods

Patients

All patients with stage IIIB NSCLC were eligible: patients were staged as IIIB because of contralateral mediastinal lymph node metastases, or invasion of the mediastinum, heart, great vessels, trachea, oesophagus, vertebral body or carina. N3 nodes, or T4 primary lesions were confirmed either by means of cervical mediastinoscopy, thoracotomy or by anterior mediastinotomy. Further eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; platelet count 100 x 10^9/L; leukocyte count 3 x 10^9/L; normal liver and renal functions; uni- or bidimensionally measurable disease; no active infections; no pregnancy or lactation; no other malignancies except carcinoma in situ of the cervix or basal cell carcinoma of the skin and no malignant pleural effusion or positive supraclavicular lymph nodes. Staging procedures included routine blood tests, thoracic computed tomography (CT), ultrasonography of the upper abdomen, bronchoscopy, mediastinoscopy, and

pulmonary function tests. Computed tomography of the brain and bone scintigraphy was performed only in case of clinical suspicion of metastatic disease.
The study has been approved by the ethics committee in all participating centres. All patients were entered after written consent had been obtained. Multimodality treatment consisted of neo-adjuvant chemotherapy, which was followed by surgery or radiotherapy or both.

Chemotherapy

Neo-adjuvant chemotherapy consisted of three cycles of gemcitabine and cisplatin. Gemcitabine was administered on a weekly basis on days 1, 8 and 15 at a dose of 1000 mg/m ^{2} (intravenously over 30 minutes) for 3 weeks followed by a 1-week rest throughout 28-day cycles. Cisplatin 100mg/m ^{2} (intravenously over 4 hours) was administered on day 2 of each 28-day course. Dose escalations were not allowed during this study. Treatment was stopped in those cases in which the disease progressed or unacceptable toxicity occurred. A complete blood cell count and differential cell count, serum electrolytes, renal and liver function were measured on day 1, 8, and 15 of each cycle. Doses for both gemcitabine and cisplatin were reduced to 75% if the leukocyte count was 2.0 to 2.9 x 10^9/L and/or platelet count was 50 to 99 x 10^9/L. Chemotherapy was not given when the leukocyte count was less than 2.0 x 10^9/L, or the platelet count less than 50 x 10^9/L. The cisplatin dose was reduced to 50% if patients showed peripheral neurotoxicity grade 2. Cisplatin was omitted in case of peripheral neurotoxicity grade 3-4. The dose of cisplatin was reduced to 50% when the creatinine clearance was 40-60 ml/min. Cisplatin was not given in patients with a creatinine clearance less than 40 ml/min.

Tumour assessment

Response to neo-adjuvant chemotherapy was assessed after three cycles of chemotherapy. Restaging procedures included routine blood tests and thoracic CT. Other investigations were performed on indication.
Complete response, throughout this study, was defined as the complete disappearance of all evidence of malignant disease as assessed by CT. Partial response was defined as at least 50% reduction in the product of the two largest perpendicular diameters in bidimensional measurable disease, or at least a 30% reduction of the largest diameter in unidimensional disease. Progressive disease was defined as at least a 25% increase of the product of the two largest perpendicular diameters in bidimensional measurable disease, or the largest diameter in unidimensional disease, or appearance of any new lesion not previously identified. All other patients were considered to have stable disease.

Surgery/radiotherapy

Repeat mediastinoscopy was performed if mediastinal lymph node metastases were present at diagnosis in patients with complete, or partial response. Biopsies were taken at five different levels (Naruke numbers: 2 right and left, 4 right and left, and 7). In case repeat mediastinoscopy showed no mediastinal lymph node metastases, surgical exploration was performed within 4 to 5 weeks after finishing chemotherapy. A pneumonectomy was performed in cases in which the tumour was located in the lower or middle lobe. In case the tumour was located in the upper lobe, a lobectomy was performed. Postoperative radiotherapy was given at a dose of 5640 cGy when resection margins were not free at histopathology, the tumour was not resectable, or ipsilateral mediastinal lymph nodes were found to be positive.
When repeat mediastinoscopy showed mediastinal lymph node metastases, patients were treated with radiotherapy alone at a dose of 5640 cGy with daily fractions of 235 cGy if only ipsilateral nodes were positive, and at a dose of 3900 cGy in 13 fractions if contralateral nodes were involved. Follow-up visits were made every 3 months.

Statistics

Survival was estimated from the date of inclusion, using the Kaplan-Meier survival analysis method.[4] Survival comparisons were analysed by means of the log rank test.[5] The difference was considered statistically significant when the p value was less than 0.05.
The follow-up was complete as of February 1, 2002. Follow-up data were obtained from hospital files and from questionnaires to referring pulmonary physicians and general practitioners.

Results

From January 1997 until September 1999, 41 patients with stage IIIB NSCLC were entered into this trial. Ages ranged from 39 to 73.6 years with a mean of 60.5 years. Thirty-one patients were male. Twenty-six tumours were located on the right side. Cervical mediastinoscopy proved to be positive in 29 patients (70.7%). In this group, eight patients showed positive N2 nodes and 21 positive N3 nodes. Clinical TNM classification is shown in Table 6.1. The histological diagnosis was adenocarcinoma in 17 patients (41.5%), squamous cell carcinoma in 15 patients (36.6%), and large cell carcinoma in 9 patients (21.9%).

Table 6.1. Clinical TNM classification

cTNM	All patients (n=41)
cT2N3	12
cT3N3	4
cT4N0	12
cT4N2	8
cT4N3	5

Induction chemotherapy and response

Thirty-seven patients (90%) received three cycles of gemcitabine and cisplatin. Four patients did not continue treatment after two cycles of chemotherapy because they developed either asthenia (n=3) or microangiopathy with progressive disease (n=1). In all 4 cases early evaluation took place. The patients were further treated with radiotherapy.
The radiological response to neo-adjuvant chemotherapy is presented in Table 6.2. The response rate after neo-adjuvant chemotherapy was 66% (27/41). Two patients showed a complete response.

Table 6.2. Response after induction chemotherapy

Response	All patients (n=41)
Complete response	2
Partial response	25
Stable disease	7
Progressive disease	7

Surgical treatment and radiotherapy

Repeat mediastinoscopy was performed on 15 patients without complications. The results are shown in Table 6.3.

Table 6.3. Results of repeat mediastinoscopy (n=15)

	T4N0	T4N2	T1-3N3	T4N3	Total
Repeat mediastinoscopy	0	2	6	1	9
No repeat mediastinoscopy	8	2*	1	1	12
Inadequate	0	2	3	1	6
Total	8	6	10	3	27

* At presentation mediastinal lymph node metastases in aortic pulmonary window (Naruke no. 5)

Either no biopsies or incomplete biopsies were obtained in 6 patients (40%), owing to fibrosis or adhesions or both. Of all patients with an adequate repeat mediastinoscopy (n=9), 2 had positive nodes. Seven biopsies showed negative results. In 2 patients (28.6%), this result proved to be false negative at thoracotomy. Surgical procedures are shown in Table 6.4.

Table 6.4. Results of surgery (n=20)

Group	No. of patients	Types of Resection	No. of patients
Resection	18	Pneumonectomy	7
		Sleeve pneumonectomy	1
		Bilobectomy	1
		Lobectomy	7
		Lobectomy and chest wall resection	1
		Sleeve lobectomy	1
		Complete resection	10
Unresectable	2		

Surgical pathology for each subset of clinically staged patients is shown in Table 6.5. Histopathological downstaging was proven in 16 patients (39.0%).

Table 6.5. Histopathologically proven downstaging (n=16)

cTNM	No. of Patients	RpTNM	No. of patients
cT2N3	6	RpT0N0	1
		RpT0N1	1
		RpT1N2	1
		RpT2N0	1
		RpT2N2	2
cT3N3	3	RpT1N1	1
		RpT3N0	2
cT4N0	5	RpT0N0	1
		RpT1N1	1
		RpT2N0	2
		RpT2N1	1
cT4N2	1	RpT3N1	1
cT4N3	1	RpT4N2	1

Twenty-three patients (61%) received radiotherapy, 14 patients with stable, or progressive disease (3900 cGy) and 9 patients with partial response (3900 to 5640 cGy). In the latter group, 3 patients underwent a positive repeat mediastinoscopy, 2 patients continued to have a T4 tumour at thoracotomy, and 1 patient showed progression of the tumour before surgery. Resection was not possible owing to insufficient predicted postoperative pulmonary function in 2

patients. One patient showed a suspect lesion on bone-scintigraphy, although metastatic disease could not be proven histologically. This patient was treated with radiotherapy instead of surgery, as there was suspicion of bone metastases. Treatment of the responders in relation to clinical TNM classification is shown in Table 6.6.

Table 6.6. Treatment of responders in relation to cTNM

Treatment	cT2-3N3	cT4N0-2	cT4N3	Total
Surgery	9	8	1	18
Radiotherapy	1	6	2	9
Total	10	14	3	27

Treatment-related complications

Hospital mortality was 2.4% (n=1). The patient had a complete, intrapericardial pneumonectomy without complications. Two days after discharge from the hospital this patient was admitted with septic shock due to purulent pericarditis and an empyema without fistula. The patient died 2 days later. Other complications occurred in 6 patients. Three had a bronchopleural fistula with empyema after pneumonectomy. In 2 patients the resection was incomplete because of residual tumour at the bronchial stump. Haemorrhage occurred in 3 other patients, 2 of whom needed rethoracotomy.

Survival

After a median follow-up of 46 months, 36 patients had died. The estimated median survival for the whole group was 15.1 months [95% confidence interval [CI]=11.2 to 19.1] with an estimated 1-year, 2-year, and 3-year survival of 60%, 25%, and 15%, respectively (Figure 6.1).
Response was found in 27 patients with a median survival of 16.8 months [95% CI =12.7 to 20.8]. The remaining 14 patients had stable, or progressive disease with a median survival of 8.4 months [95% CI =6.9 to 10.0] (p=0.11) (Figure 6.2).
Patients with partial or complete response had a median survival of 21.5 months [95% CI =7.75 to 35.2] if resection was done, and 13.0 months [95% CI =7.7 to 18.3] when treated with radiotherapy (p=0.0003) (Figure 6.3). Of the 10 patients with a complete resection, 5 are still alive. One of these patients had radiotherapy because of local recurrence, the other 4 patients have no disease activity. Five patients died after complete resection: 1 of the complications of the operation, 2 with local recurrence and 2 with distant metastases.

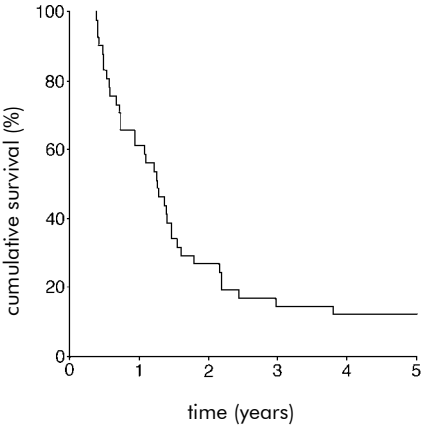

Figure 6.1 Estimated survival of all patients (n=41)

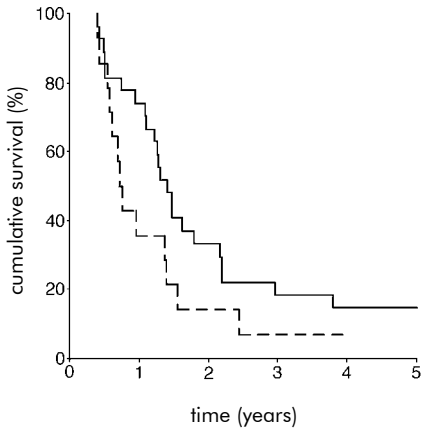

Figure 6.2 Estimated survival of patients with stable/progressive disease (n=14) (- - -) and patients with complete/partial response (n=27) (——).

Patients with T4N0 disease (12/41) had a median survival of 15.1 months [95% CI =12.1 to 18.1] versus a median survival of N2/N3 disease (29/41) of 14.6 months [95% CI =10.3 to 19.00] for the whole group. There is no significant difference in median survival between the T4N0 group and the N2/N3 group (p=0.46). In the group of patients with partial or complete response (27/41), patients with T4N0 disease (8/41) had a median survival of 15.1 months [95% CI =12.7 to 17.6] versus a median survival of the N2/N3 group (19/41) of 17.5 months [95% CI =13.3 to 21.8]. Again there is no significant difference

between the T4N0 group and the N2/N3 group in the group of patients with partial of complete response (p=0.99).
Distant metastases developed in 8 of 27 patients with complete or partial response (29.6%). Brain metastases occurred in 6 (22.2%). Eight patients had local recurrence (29.6%). Two patients had combined local and distant recurrence (7.4%).

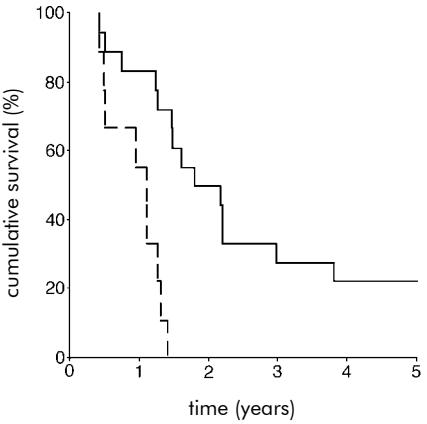

Figure 6.3 Estimated survival in responders treated with surgery (n=18) (——) or radiotherapy (n=9) (- - -).

Comment

Surgery is the treatment of choice in patients with NSCLC but resectability is closely related to the stage of the disease.[6] Whereas stage I and II tumours are considered to be resectable, the role of surgery for stage IIIB NSCLC remains controversial.[7] In the series by Mountain 5-year survival is 7% for clinical T4 and 3% for N3 disease.[8] Death of patients with stage III NSCLC is more often caused by distant metastases rather than local disease, and patients are rarely cured with local treatment modalities alone. Therefore, multimodality treatment has surfaced as the treatment of choice in a selected group of patients with stage III NSCLC.[2,9] However, it is still unclear which treatment modality (surgery or radiotherapy or both) will result in prolonged survival after neo-adjuvant chemotherapy.
Over the years, the optimal chemotherapy has proved hard to define. Meta-analyses has indicated that the chance of survival increases when a platinum-based regimen is being used.[9,11] Numerous combinations of cisplatin and older

drugs have been used with no single mix emerging as the superior combination. Although several single-agents have been producing response rates of 15 to 20%, combination chemotherapy is still considered the standard of care.[12] The combination of cisplatin and gemcitabine has shown significant activity in advanced non-small cell lung cancer with response rates as high as 70% in several phase II studies.[13]

The optimal duration of induction chemotherapy remains controversial as well. The American Society of Clinical Oncology guidelines proposed a duration of 2 to 8 cycles.[2] Crino and associates[14], who studied the gemcitabine/cisplatin regimen as induction chemotherapy in 42 patients with stage IIIA (n=11) and IIIB (n=31), achieved an overall response rate of 62%. Complete resection could be achieved in 10 patients, with tumour downstaging in 9. Similar results have been reported by Van Kooten and colleagues[15] and Abratt and coworkers.[16]

Our study showed a response rate of 66% after induction chemotherapy. Two patients responded completely. Albain and coworkers found in their research an even higher response rate, when using a trimodality approach of concurrent chemotherapy and irradiation followed by surgery in patients with stage IIIA and IIIB NSCLC. Resectability in their case was 80% for the entire IIIB group.[17]

In the past, repeat mediastinoscopy has been considered to be contra-indicated, as it was perceived to be too hazardous to dissect the scarred mediastinum.[18] Between 1976 and 1990, 140 patients underwent repeat mediastinoscopy in our hospital as a routine staging procedure. No mortality occurred. Sensitivity was 74%, and accuracy 94%.[19]

Mediastinal structures become differently affected after neo-adjuvant chemotherapy. The cytotoxic drugs change the normal inflammatory response and adhesions. Additionally nodal tissue can be seriously distorted. During our research, the 15 patients who underwent repeat mediastinoscopy, did not show complications, such as described by Pauwels and associates and Mateu-Navarro and colleagues.[20,21] However, 40 % remained incomplete owing to fibrosis and adhesions. Beside that, 2 out of 7 proved to be false negative. Comparable figures were reported by Pauwels and coworkers (25%), and Mateu-Navarro and associates (40%).[20,21] Hence, this paper argues that repeat mediastionoscopy after neo-adjuvant chemotherapy is a not the most effective restaging tool. The promising results of PET-scanning in staging NSCLC[22,23] make it an attractive alternative for selecting patients with negative mediastinal lymph nodes after neo-adjuvant chemotherapy. A prospective pilot study of FDG-PET-scan after neo-adjuvant chemotherapy in stage IIIA NSCLC of Vansteenkiste showed an accuracy of 100%.[22]

In this study a thoracotomy was performed on 20 patients. In 2 cases the tumour proved to be unresectable. Although 8 patients underwent a pneumonectomy, hospital mortality was low (2.4%). Complications occurred in 6 patients, 4 of

them underwent a pneumonectomy. Three patients suffered from a haemorrhage and 3 had a bronchopleural fistula with an empyema. A complete resection was performed in 10 responders (24.4%). Survival in this group was better than survival among patients with a stable or progressive disease. However, this difference was not significant. For all responders, survival proved significantly better among patients who underwent surgery than among patients treated with radiotherapy.

The brain is a major site of distant metastases.[17] In this study, 6 responders developed brain metastases (22.2%). Few studies have routinely used prophylactic cranial irradiation. Eberhardt and colleagues did not perform a randomised investigation of prophylactic cranial irradiation in their study, but the overall brain relapse was remarkably reduced in the group that received prophylactic cranial irradiation, even though no impact on survival was noted. Large prospective randomised studies are necessary to evaluate the role of prophylactic cranial irradiation.[24]

In conclusion: these data show that radical surgery can be performed in 37% (10/27) of the responders and can result in prolonged survival. Surgery as part of combined modality treatment is feasible for patients with stage IIIB NSCLC. Results of repeat mediastinoscopy are disappointing and proved to be a not so effective restaging tool because of the high number of incomplete procedures and because it yields false negative results.

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CHAPTER 7

Summary and concluding remarks

Summary

Surgery is the treatment of choice for patients with stage I and II non-small cell lung cancer (NSCLC). However, the role of surgery in the treatment of stage III NSCLC remains unclear. The aim of this thesis was to evaluate results of resection of different subtypes of T3 and T4 NSCLC and to analyse the characteristics and prognosis of each subgroup. Also, results of surgery in patients with stage IIIB NSCLC treated with induction chemotherapy, and the role of repeat-mediastinoscopy were discussed.

Chapter 1

The introduction provides an overview of general aspects of NSCLC, like epidemiology, carcinogenesis, histology, clinical features, and diagnosis. Accurate staging is important as it determines treatment pathways. For stage I and II NSCLC surgical treatment is evidence based, whereas for stage III disease there is no "standard" therapy. Treatment may include combinations of induction chemotherapy, radiotherapy and surgery. To patients with stage IV NSCLC surgery only offers trauma, and thus, they should be treated with either palliative chemotherapy or best supportive care. Survival is closely related to the stage of the disease.
The chapter focuses on patients with T3 and T4 NSCLC. T3 tumours comprise a heterogeneous group, including tumours with invasion of the chest wall, mediastinal structures, or diaphragm, Pancoast tumours, tumours with involvement of the main bronchus within 2 cm of the carina, and tumours associated with atelectasis or obstructive pneumonitis of the entire lung. These tumours are suitable for surgical treatment if no metastases are present. Prognosis depends on the completeness of the resection and the presence of lymph node metastases. Characterisation of the primary tumour as T4 includes invasion of the mediastinum, heart, great vessels, trachea, oesophagus, vertebrae, carina, or the presence of malignant pleural or pericardial effusion, or satellite tumour nodule(s) within the same lobe as the primary tumour. Thus, T4 tumours also encompass heterogeneous subgroups, invading other vital structures. Surgical treatment is limited to highly selected patients.

Chapter 2

This chapter is an analysis of the results of en bloc resection or extrapleural dissection in 125 patients with chest wall involvement. An important factor in the

treatment of lung cancer with chest wall invasion is the question whether an extrapleural dissection, or en bloc resection has to be performed in patients with a tumour adjacent to the parietal pleura. In this series, no difference was found in mean 5-year survival between both operative procedures when only the parietal pleura was involved. When the surgeon could finger-dissect the parietal pleura from the ribs, such an extrapleural dissection was carried out (n=73). When adherence of the tumour to the thoracic wall precluded digital dissection, an en bloc resection was performed (n=52). A complete resection was achieved in 86 patients (68.8%). Hospital mortality was 3.2%, with no significant difference between en bloc resection and extrapleural resection. In most patients, resection consisted of a lobectomy (n=86) and the number of resected ribs ranged from one to four. Mean 5-year survival was 24% for all hospital survivors, 29% for hospital survivors with complete resection and 11% for hospital survivors with an incomplete resection ($p<0.001$). The difference in mean 5-year survival for hospital survivors between N0 and N2 tumours was statistically significant (36% and 14%, respectively). The tumour was opened peroperatively in 7 patients, all of whom died within 16 months. It was concluded that both operative procedures yield good survival results. Incompleteness of resection, intrapleural tumour spill, and N2 involvement influenced survival adversely. No relation was found between survival and age, depth of chest wall invasion and postoperative radiotherapy in patients with complete resection.

Chapter 3

This chapter evaluates the retrospective results of resection of 108 patients with centrally located T3 tumours. Patients were divided into 3 subgroups. The first group included 33 patients with a T3 tumour due to invasion of mediastinal structures, like mediastinal pleura, phrenic nerve, or pericardium. In the second group (n=68), tumours were staged as T3 because they were located in the main bronchus less than 2 cm of the carina. The last group included patients with a combination of both tumours (n=7). A complete resection was performed in 70 patients (64.8%). In the subgroups analysed in this study, most tumours were squamous cell carcinomas (83.3%) and resection mostly consisted of a pneumonectomy (82%). Only a few patients had a sleeve lobectomy. Overall hospital mortality was 8.3% (n=9), 10% for pneumonectomy and 0% for lobectomy. Most of the hospital deaths were due to bronchopleural fistula. Mean 5-year survival was 29% for all hospital survivors, 35% for hospital survivors with complete resection, and 18% for hospital survivors with incomplete resection ($p=0.03$). Regarding T3 subgroups, tumours located in the main bronchus had a more favourable prognosis with a mean 5-year survival of 40%, but the difference between this subgroup and hospital survivors with T3 tumours due to mediastinal

involvement (mean 5-year survival 25%) was not statistically significant. Incompleteness of resection and mediastinal lymph node involvement were significant adverse prognostic factors. No patient with N2 disease survived more than 5 years.

Chapter 4

This chapter is a review of the clinical characteristics, diagnosis, tumour staging, treatment and survival of superior sulcus, or, Pancoast tumours. Due to their location in the apex of the lung and invasion of surrounding structures (brachial plexus, first ribs, stellate ganglion, subclavian vessels, or vertebrae) these tumours cause specific symptoms, like pain in the arm or shoulder or Horner's syndrome. Pancoast tumours can be staged as a T3 or T4 tumour, depending on invasion of adjacent structures. Survival is better for the first group. Incompleteness of the resection, mediastinal lymph node involvement and Horner's syndrome have been found to be a negative prognostic factor. The classic treatment for these tumours, introduced by Shaw and Paulson, has been preoperative radiotherapy followed by surgery, with a mean 5-year survival of approximately 30%. Surgery usually consists of en bloc resection of the involved ribs with a lobectomy. Common surgical techniques used to approach the tumour are the classic posterior Shaw-Paulson approach or the newer anterior transcervical technique introduced by Dartevelle.
Recent results of combination of chemoradiotherapy and surgical resection suggest that this combined modality treatment offers the best survival results for Pancoast tumours, but careful patient selection and adequate peri-operative monitoring are essential, regarding the higher rates of mortality and morbidity after neo-adjuvant therapy.

Chapter 5

T4 tumours encompass heterogeneous subgroups and the role of extended resections for these tumours invading vital structures remains doubtful. However, good survival results after extended resection have been described in selected patients. In this chapter results of 89 patients who underwent resection for primary non-small cell T4 carcinomas were analysed. It was shown that a complete resection was possible in 38.2% of the patients (n=34). Mean five-year survival was 46.2% for hospital survivors with complete resection and 10.9% for hospital survivors with an incomplete resection ($p<0.05$). Most complete resections were achieved in patients with invasion of the carina, trachea, or great vessels. Surgery mostly consisted of pneumonectomy (n=71). Hospital mortality was high (19.1%), which highlights the importance of careful patient selection. Best survival results were described for patients with tumours located in the trachea or

carina, with a mean 5-year survival of 50.9%. Patients with invasion of the great vessels had a lower survival rate of 35.7%. In this study no relation was found between mediastinal lymph node metastases and survival, but the number of patients was limited. Also age, operative procedure, and postoperative radiotherapy did not significantly influence survival.

Chapter 6

Recently, multimodality treatment has become the recommended therapy for patients with locally advanced tumours. In this chapter, results of a prospective multicentre trial of neoadjuvant chemotherapy followed by surgery or radiotherapy or both in 41 patients with stage IIIB non-small cell lung cancer were evaluated. Response to neoadjuvant chemotherapy was shown in 27 patients (66%). It was reported that radical surgery with acceptable hospital mortality could be performed in 37% of the responders (n=10) and that survival was better for these patients than for responders treated with radiotherapy (21.5 versus 13.0 months). Major complications occurred in 6 patients (fistula, empyema, haemorrhage). Histopathological downstaging was proven in 16 patients (39%). The diagnostic value of repeat mediastinoscopy after neoadjuvant chemotherapy for mediastinal staging was also analysed. Fifteen patients underwent repeat mediastinoscopy which proved to be inadequate in 6 patients and false-negative in 2.
It was concluded that surgery as part of combined modality treatment is feasible in stage IIIB NSCLC. Results of repeat mediastinoscopy are disappointing due to the number of incomplete procedures, caused by fibrosis and adhesions, and because it yields false negative results.

Concluding remarks

The data presented in this thesis confirm that surgery is the treatment of choice for patients with a T3 tumour. The most important goal of surgical therapy is a complete resection, as an incomplete resection predicts poor survival. Regarding the several subgroups of T3 tumours in our studies, a complete resection was achieved in 68.8% of tumours with chest wall invasion, and in 64.8% of centrally located T3 tumours. Review of the literature reveals that most of the articles studying T3 NSCLC concern tumours with chest wall invasion or superior sulcus tumours. Only a few reports have also focused on other subgroups, like tumours with mediastinal involvement and tumours located in the main bronchus less than 2 cm of the carina. Results of these limited data suggest that patients with chest wall invasion are a favourable subgroup. This is explained by a higher chance to achieve a complete resection. To ensure complete resection, surgery of T3 tumours usually consists of en bloc resection of the tumour and involved structures. In patients with centrally located tumours and superior sulcus tumours resections with wide margins are more difficult to perform due to the presence of vital structures in the mediastinum or the apex of the lung.

In tumours invading the parietal pleura or chest wall the choice of operation (en bloc resection of the tumour and chest wall or extrapleural resection) is based on pre- and intraoperative assessment. Peroperatively, pathological examination of resection margins is recommended to assess completeness of resection. In case of doubt, an en bloc resection should be performed, as incomplete resections, even if only microscopic disease, and intrapleural tumour spill offer the patient no curative benefit. Patients with tumours located in the main bronchus within 2 cm of the carina are generally treated with a pneumonectomy or sleeve lobectomy. As hospital mortality increases in a pneumonectomy, a sleeve lobectomy should be considered as an alternative treatment in more patients.

Another important factor regarding survival of resected T3 tumours is the presence of mediastinal lymph node metastases. It is generally known that nodal disease confers a poor prognosis and that survival decreases with increasing nodal stage. Our studies showed that in all three T3 subgroups, N2 disease is highly unfavourable. Similar results have been published for Pancoast tumours. Therefore, distinction between N0-1 and N2 disease is essential, as patients with mediastinal lymph node metastases are no candidates for primary resection, but for treatment with induction chemotherapy. This stresses the importance of appropriate staging of the tumour preoperatively by radiological investigation (CT / PET scanning) and histological assessment of mediastinal lymph nodes by mediastinoscopy.

In our studies, mean 5-year survival for several subgroups of patients with resected T3 NSCLC varies between 24 % and 40%. Superior survival was reported for patients with tumours located in the main bronchus, although the difference was not significant. Some authors published similar results, whereas others demonstrated a survival benefit for tumours with chest wall invasion. However, it is difficult to compare these studies because patient selection and the method of reporting are not consistent. Large comparative studies between several T3 subgroups are needed to answer the question if there is a subgroup with a favourable prognosis.

In recent years, several trials have been conducted to examine the role of induction chemotherapy or chemoradiotherapy in patients with stage IIIA and stage IIIB disease. Results of these studies are encouraging by showing high response rates and an increase in the number of complete resections. For that reason it seemed logical to apply this combined treatment to patients with Pancoast tumours. The available data suggest that in these patients a tri-modality approach, involving induction chemoradiotherapy followed by surgical resection, achieves the best survival. The usefulness of this approach in other T3 tumours will need further investigation and patients should be enrolled in trials to investigate if survival improves by combined modality treatment. Until now, adjuvant therapy (radiotherapy or chemotherapy) has not shown survival benefit in patients with complete resection.

The historical difference between T3 and T4 tumours is the determination of resectability. Generally, stage IIIB NSCLC is defined as an unresectable disease. However, T4N0-1 disease has been shown to be biologically different from N3 disease, and although surgery for T4 tumours remains a difficult question, some patients with a T4 tumour can indeed be candidates for resection. Although several reports have demonstrated the technical feasibility of resection of T4 structures, few data are published about long-term survival. The largest experience and the best results for long-term survival are described in patients with T4 tumours invading the carina and trachea. Even though recent progress in cardiovascular and spinal surgery has opened new possibilities for patients with invasion of great vessels, heart or vertebrae, surgical treatment of these tumours mostly results in limited survival. Also invasion of the oesophagus mostly precludes a complete resection. Aggressive surgical resection in T4 tumours has been associated with high hospital mortality rates of 15-20%. Regarding this increased mortality and the limited survival, it is important to accurately stage and select patients, and refer them to a centre with experience in performing extended resections.

Several trials of combined modality treatment have demonstrated that this therapy should be the first choice for patients with T4 disease and good performance status. The aims of induction chemotherapy prior to resection or

radiotherapy are to improve local control by downstaging the primary tumour and nodal metastases and to eradicate systemic micrometastases. Many options are currently available with regard to the optimum chemotherapeutic regimen as induction chemotherapy. Platinum-based chemotherapy has become the most effective and widely used.

It remains an important issue to demonstrate histopathological downstaging, as patients with persistent N2/N3 disease do not benefit from surgical resection. Repeat mediastinoscopy does not seem a useful tool for restaging of the mediastinum after induction therapy due to false negative results and incomplete procedures. This stresses the need to search for other restaging techniques. Positron emission tomography is a promising modality in lung cancer staging. However, only few data exist about the role of PET in restaging after induction chemotherapy. Its accuracy has not been determined in prospective trials and further studies are needed to define this issue. Recently, other techniques have been developed for evaluating mediastinal lymph nodes. It is expected that both transoesophageal and transbronchial endoscopic ultrasound guided fine needle aspiration will prove to be valuable for the restaging of mediastinal lymph nodes.

Although surgical treatment can achieve effective local control, many patients who have previously undergone a complete resection of the primary tumour, develop distant metastases. As brain metastases are one of the most common forms of relapse, the question has been raised whether patients with a complete resection should be treated with prophylactic cranial irradiation (PCI) to improve the control of distant metastatic disease and survival. At this moment, limited data about the routine use of PCI in patients with NSCLC suggest that the overall brain relapse will reduce.

Over the last decade, the use of new chemotherapeutic agents, used single or in combination, appears to have improved survival in patients with NSCLC. Recently, taking into consideration the comparable survival results of many phase III trials, progress seems to have reached a plateau. Progress in understanding the molecular biology of NSCLC has lead to the identification of new pharmacologic agents. These include angiogenesis inhibitors, tyrosine kinase inhibitors, which block signal transduction, and immunotherapy. These agents are currently being tested in phase I and II trials. Whether a combination of these agents with traditional therapeutic strategies, such as surgery, radiotherapy, and cytotoxic chemotherapy will result in better survival needs to be defined.

CHAPTER 8

Samenvatting

Samenvatting

Jaarlijks wordt wereldwijd bij 1,2 miljoen mensen de diagnose longkanker gesteld en overlijden 1,1 miljoen mensen aan deze ziekte. Hiermee is longkanker de meest voorkomende vorm van kanker en een belangrijke doodsoorzaak. De incidentie is het hoogst in Noord-Amerika en Europa. De laatste jaren komt longkanker steeds meer bij vrouwen voor terwijl het aantal mannen met longkanker daalt. De belangrijkste verklaring voor deze tendens is een verandering in het rookgedrag. Er bestaat een direct verband bestaat tussen roken en het ontwikkelen van longkanker, daar door rook veroorzaakte prikkels kunnen leiden tot veranderingen in het genetische materiaal van een cel. Hierdoor treedt een ongeremde deling van cellen op, hetgeen leidt tot de vorming van een tumor.

De meeste patiënten presenteren zich met klachten zoals hoesten, kortademigheid, bloed ophoesten, pijn en heesheid. Het probleem bij longkanker is dat deze klachten meestal pas in een laat stadium optreden waardoor een curatieve behandeling vaak niet meer mogelijk is. Als gevolg daarvan is de prognose ongunstig, met een gemiddelde 5-jaarsoverleving van 15%.

Als er verdenking bestaat op de aanwezigheid van een longtumor wordt verder onderzoek verricht. Voor het stellen van de diagnose longkanker is weefselonderzoek nodig. Dit weefsel wordt meestal verkregen door middel van een bronchoscopie of longpunctie. Aanvullende beeldvormende diagnostiek bestaat uit röntgenfoto's, computertomografie (CT scan), magnetic resonance imaging (MRI scan), echografie en positron emission tomografie (PET scan). Een mediastinoscopie is bij veel patiënten noodzakelijk om mediastinale lymfkliermetastasen aan te tonen dan wel uit te sluiten. Het doel van bovenstaande onderzoeken is om de tumor adequaat te stadiëren aan de hand van de TNM-classificatie. Deze beschrijft de grootte en plaats van de tumor en de mate van ingroei in de omringende weefsels (T) en de aanwezigheid van metastasen in de mediastinale lymfklieren (N) en/of metastasen elders in het lichaam (M).

Longkanker kan worden onderverdeeld in 2 hoofdgroepen: het kleincellige type en het niet-kleincellige type. Het kleincellige type longkanker is een zeer agressieve vorm van longkanker, die frequent metastasen vormt en die daarom meestal behandeld wordt met chemotherapie al dan niet in combinatie met radiotherapie. Bij ongeveer 80% van de patiënten is sprake van een niet-kleincellige longtumor. De behandeling en prognose van dit type longtumor is sterk afhankelijk van het stadium van de ziekte op het moment van presentatie.

Dit stadium wordt bepaald door de TNM-classificatie. Voor patiënten met een stadium I en II tumor (longtumoren zonder lymfklieraantasting of met alleen metastasen in hilaire of intrapulmonale lymfklieren) is chirurgische resectie van de tumor met het omringende longweefsel de aangewezen behandeling, mits de cardiopulmonale reserves voldoende zijn. Voor patiënten met een stadium III tumor (aanwezigheid van metastasen in mediastinale lymfklieren of ingroei van de tumor in belangrijke omringende structuren) is er geen standaard therapie. Behandeling bestaat uit een combinatie van chemotherapie, chirurgie en radiotherapie. Patiënten met een stadium IV tumor (metastasen elders in het lichaam) komen in aanmerking voor palliatieve behandeling. Deze is gericht op het remmen van de ziekte en op vermindering van de klachten en bestaat uit chemotherapie of radiotherapie. Daarnaast bestaat de mogelijkheid te kiezen voor een afwachtend beleid.

Dit proefschrift omvat een aantal studies waarin de resultaten van chirurgische behandeling van diverse subgroepen van T3 tumoren (stadium II/III) en T4 tumoren (stadium III) worden besproken. Doel van het onderzoek was om verschillende subgroepen met elkaar te vergelijken en te bepalen welke factoren van belang zijn voor de prognose. In de studies is een resectie als compleet beschouwd als 1) de chirurg er macroscopisch zeker van was dat hij de gehele tumor verwijderd had, 2) de snijvlakken vrij waren van tumorweefsel bij pathologisch-anatomisch onderzoek en 3) de hoogste gebiopteerde mediastinale lymfklier negatief was.
Daarnaast worden de resultaten gepresenteerd van chirurgische behandeling van patiënten met een stadium IIIB niet-kleincellige longtumor die behandeld zijn met inductie-chemotherapie. Hierbij wordt tevens de rol van de remediastinoscopie besproken.

T3 tumoren

Bij ongeveer 10% van de patiënten die een operatie ondergaan in verband met longkanker blijkt sprake te zijn van een T3 tumor. De groep van T3 tumoren bestaat uit longtumoren met ingroei in de thoraxwand, mediastinale structuren of het diafragma, Pancoast tumoren, tumoren die gelokaliseerd zijn in de hoofdbronchus op een afstand van minder dan 2 cm van de hoofdcarina en tumoren met een atelectase of obstructiepneumonie van de gehele long. De behandeling van deze groep tumoren bestaat in principe uit chirurgie.

Hoofdstuk 2 beschrijft de resultaten van en bloc resectie en extrapleurale resectie bij 125 patiënten met een T3 tumor met ingroei in de thoraxwand. Belangrijk bij de behandeling van deze tumor is de vraag of er bij ingroei in de pleura parietalis standaard een en bloc resectie (verwijdering van longkwab

inclusief deel van de thoraxwand) verricht moet worden of dat bij sommige patiënten een extrapleurale resectie (verwijdering longkwab inclusief pleura parietalis) voldoende is.
In deze studie werd bij patiënten met ingroei in de pleura parietalis geen verschil gevonden in vijfjaarsoverleving tussen beide ingrepen. Als het voor de chirurg mogelijk was om de pleura parietalis met zijn vingers van de ribben los te maken voerde hij een extrapleurale resectie uit (n=73), maar indien de tumor gefixeerd was aan de thoraxwand kwam de patiënt in aanmerking voor een en bloc resectie (n=52). Bij ruim 68% van de patiënten werd een complete resectie verricht. De vijfjaarsoverleving bedroeg 23% voor alle patiënten. Hierbij is een significant verschil in overleving gevonden tussen patiënten met een complete ingreep en een niet-complete resectie. Ook de aanwezigheid van metastasen in mediastinale lymfekleren en het peroperatief openen van de tumor waardoor er "tumorspil" optreedt, beïnvloeden volgens deze studie de overleving negatief. Er is geen verband gevonden tussen overleving en leeftijd, diepte van ingroei in de thoraxwand en postoperatieve radiotherapie bij patiënten met een complete resectie.

Hoofdstuk 3 analyseert de resultaten van chirurgische behandeling van een groep van 108 patiënten met een centraal gelokaliseerde T3 tumor. De patiënten zijn onderverdeeld in patiënten met een T3 tumor ten gevolge van ingroei in mediastinale structuren, zoals de pleura mediastinalis, nervus phrenicus en het pericard, en patiënten met een tumor die gelokaliseerd is in de hoofdbronchus op een afstand van minder dan 2 cm van de hoofdcarina. Het percentage complete resecties bedroeg 64,8% en bij de meerderheid van de patiënten werd een pneumonectomie verricht. Deze ingreep ging gepaard met een toename van de ziekenhuissterfte, waarbij het optreden van een bronchopleurale fistel de meest voorkomende oorzaak van overlijden was. De vijfjaarsoverleving bedroeg 27% voor alle patiënten. Ook bij deze subgroepen van T3 tumoren zijn een niet-complete resectie en de aanwezigheid van metastasen in mediastinale lymfklieren als belangrijke prognostische factoren te onderscheiden. Patiënten met een tumor gelokaliseerd in de hoofdbronchus hadden een betere overleving dan patiënten met een tumor met ingroei in de mediastinale structuren, maar het verschil was niet statistisch significant.

Hoofdstuk 4 geeft een overzicht van de klinische kenmerken, diagnostiek, stadiëring, behandeling en overleving van sulcus superior tumoren, ook wel Pancoast tumoren genaamd. Door hun lokalisatie in de top van de long met ingroei in de omringende structuren (plexus brachialis, eerste rib, sympathische grensstreng) veroorzaken deze tumoren specifieke klachten, zoals pijn in de schouder en arm en het syndroom van Horner. Afhankelijk van deze ingroei

wordt de tumor gestadieerd als een T3 of T4 tumor, waarbij T3 tumoren tot een betere overleving leiden. Zowel het niet-compleet zijn van de resectie, de aanwezigheid van positieve mediastinale lymfklieren en het syndroom van Horner hebben een negatieve invloed op de overleving. De standaard-behandeling van deze tumor bestaat uit preoperatieve radiotherapie gevolgd door chirurgie, waarbij de klassieke posterieure benadering volgens Shaw-Paulson of de nieuwere anterieure transcervicale benadering volgens Dartevelle de meest gebruikte technieken zijn. Hierbij wordt meestal een lobectomie van de bovenkwab verricht, soms met thoraxwand resectie. De gemiddelde vijfjaarsoverleving bedraagt ongeveer 30%. Recente resultaten van een gecombineerde behandeling bestaande uit inductiechemoradiotherapie gevolgd door chirurgie zijn veelbelovend en suggereren dat deze gecombineerde behandeling de beste overleving geeft voor patiënten met een Pancoast tumor. Gezien de toename van de ziekenhuismorbiditeit en mortaliteit tijdens deze behandeling zijn hierbij een strenge patiëntenselectie en adequate peri-operatieve begeleiding van essentieel belang.

T4 tumoren

De groep van T4 tumoren bestaat uit longtumoren met ingroei in het mediastinum, hart, grote bloedvaten, trachea, oesofagus, wervellichaam of carina, tumoren met maligne pericard-of pleuravocht en tumoren met een metastase in dezelfde kwab als de primaire tumor. De rol van chirurgie bij de behandeling van deze groep van tumoren is onduidelijk. Hoewel het merendeel van de T4 tumoren beschouwd wordt als inoperabel, zijn bij geselecteerde patiënten goede resultaten beschreven na een uitgebreide chirurgische ingreep. De vraag is echter welke patiënten tot deze geselecteerde groep behoren.

In hoofdstuk 5 worden de resultaten weergegeven van chirurgische behandeling van 89 patiënten met een T4 tumor. In tegenstelling tot de groep van T3 tumoren was het aantal complete resecties bij T4 tumoren veel lager en bedroeg 38,2%. Patiënten met ingroei in de carina, trachea en grote bloedvaten hadden de meeste kans op een complete resectie, waarbij meestal een pneumonectomie werd verricht. De ziekenhuissterfte was hoog en bedroeg 19,1%, hetgeen het belang van zorgvuldige patiëntenselectie benadrukt. De 5-jaarsoverleving was 19,1% voor alle patiënten. Wederom is er een significant verschil in overleving gevonden tussen patiënten met een complete en een niet-complete resectie De beste overlevingsresultaten zijn beschreven voor de patiënten met een tumor in de trachea of carina, terwijl patiënten met ingroei in de grote vaten de kortste overleving hadden. In deze studie is geen verband gevonden tussen overleving en de aanwezigheid van mediastinale lymfklier-metastasen, maar de studie

betrof slechts een kleine groep patiënten. Leeftijd, soort operatieve ingreep en postoperatieve radiotherapie hadden geen significante invloed op de overleving.

Tegenwoordig is multimodale behandeling, bestaande uit inductiechemotherapie gevolgd door radiotherapie of chirurgie, de aanbevolen therapie voor patiënten met stadium IIIB tumoren. Het doel van de chemotherapie is hierbij om de locale controle te verbeteren door "downstaging" van de tumor en lymfklieruitzaaiïngen en om micrometastasen uit te roeien. Inductiechemotherapie bestaande uit een platinum bevattende combinatie wordt momenteel het meest effectief geacht en daardoor ook het meest gebruikt.

In hoofdstuk 6 worden de resultaten beschreven van een prospectieve multicenter studie waarin 41 patiënten met een stadium IIIB niet-kleincellige longtumor behandeld werden met inductiechemotherapie gevolgd door chirurgie, radiotherapie of een combinatie van beide. Het responspercentage van de behandeling met de inductiechemotherapie bedroeg 66%. Bij 37% van de responders (n=10) werd een complete ingreep verricht. 1 patiënt is postoperatief overleden. Responders die geopereerd werden hadden een betere overleving dan responders die behandeld werden met radiotherapie. Belangrijke complicaties bij diegenen die geopereerd werden waren fistelvorming, empyeem en bloeding. Histopathologische downstaging trad op bij 39% van de patiënten. Deze gegevens tonen aan dat chirurgische behandeling na inductiechemotherapie haalbaar is bij patiënten met een stadium IIIB niet-kleincellige longtumor.
In deze studie is tevens gekeken naar de diagnostische betekenis van de remediastinoscopie als middel voor mediastinale lymfklierstadiëring na inductiechemotherapie. De resultaten van dit onderzoek zijn echter teleurstellend door het aantal inadequate procedures ten gevolge van verbindweefseling en verklevingen, en het daardoor voorkomen van vals negatieve resultaten.

Conclusie

De studies in dit proefschrift bevestigen dat chirurgie de aangewezen behandeling is voor patiënten met een T3 tumor. Een operatie heeft echter alleen zin als de tumor volledig verwijderd kan worden. Bij T3 tumoren bestaat de ingreep daarom meestal uit een en bloc resectie van de tumor met de omringende structuur. T3 tumoren met ingroei in de thoraxwand zijn hierbij een gunstigere subgroep omdat hun perifere lokalisatie met afwezigheid van andere belangrijke omringende structuren de kans op het verrichten van een complete resectie vergroot.
Een belangrijk punt met betrekking tot de prognose van longtumoren is de aanwezigheid van metastasen in mediastinale lymfklieren. Ook dit is bevestigd

in onze T3 studies. Het is daarom van groot belang om patiënten adequaat te stadiëren en pre-operatief een onderscheid te maken tussen N0-1 en N2 ziekte, aangezien deze laatste groep patiënten geen kandidaat is voor primaire behandeling met chirurgie, maar in aanmerking komt voor behandeling met inductiechemotherapie.
Vergelijking van de 5-jaarsoverleving tussen de verschillende subgroepen toont geen significant verschil. Ook andere studies laten geen eenduidige subgroep met een gunstigere prognose zien. Hierbij moet vermeld worden dat het echter moeilijk is om deze studies met elkaar te vergelijken omdat patiëntenselectie en onderzoeksmethoden nogal verschillen. Om deze vraag te beantwoorden zijn grote vergelijkende studies tussen de diverse subgroepen nodig.
Ook dient verder onderzoek verricht te worden naar de rol van trimodale behandeling. Gezien de veelbelovende resultaten van die therapie bij patiënten met een Pancoast tumor rijst de vraag of deze combinatie van inductiechemoradiotherapie gevolgd door chirurgie ook geschikt is voor andere T3 tumoren en dan vooral de centraal gelokaliseerde tumoren.
In het verleden is er een duidelijk verschil gemaakt tussen T3 en T4 tumoren wat betreft de mogelijkheid voor chirurgische resectie. Diverse studies hebben de technische haalbaarheid van resectie van T4 tumoren met omringende structuren aangetoond, maar er zijn weinig gegevens bekend over een langdurige overleving. Daarnaast gaan deze uitgebreide operaties meestal gepaard met een hoge mortaliteit. Daarom is het van groot belang patiënten accuraat te stadiëren en ze te verwijzen naar een centrum met expertise in het uitvoeren van deze uitgebreide operaties. De beste resultaten worden beschreven voor T4 tumoren met ingroei in de trachea of carina.
Gezien de gunstige resultaten van inductiechemotherapie is dit tegenwoordig de aanbevolen behandeling voor patiënten met een T4 tumor. Daarbij is het aantonen van "downstaging" door de inductiebehandeling erg belangrijk, aangezien patiënten met persisterende metastasen in mediastinale lymfklieren geen geschikte kandidaten zijn voor chirurgische behandeling.
Resultaten van remediastinoscopie voor restadiëringsonderzoek van het mediastinum zijn teleurstellend ten gevolge van vals negatieve resultaten, c.q. het voorkomen van inadequate procedures. Daarom moeten we op zoek gaan naar andere restadiëringsmethoden. Positron emission tomografie (PET) scan speelt een belangrijke rol bij stadiëringsonderzoek. Op dit moment zijn er echter weinig gegevens bekend over de rol van PET in restadiëring na inductiebehandeling. Op dat terrein is verder onderzoek nodig. Andere in ontwikkeling zijnde technieken om mediastinale lymfklieren te stadiëren zijn endoscopische oesofageale en bronchiale echografie met naaldbiopsieën.
Hoewel chirurgische resectie kan leiden tot effectieve lokale controle, ontwikkelen veel patiënten op den duur metastasen op afstand, waarvan

hersenmetastasen de meest voorkomende zijn. Daarom is de vraag gesteld of deze patiënten behandeld moeten worden met profylactische hersenbestraling om de overleving te verbeteren. Op dit moment zijn hierover slechts beperkte gegevens bekend, maar die suggereren inderdaad dat profylactische hersenbestraling het ontstaan van hersenmetastasen bij patiënten met een niet-kleincellige longtumor kan verminderen.
De afgelopen jaren heeft het gebruik van nieuwe chemotherapeutische middelen, gebruikt als monotherapie of in combinatie, de overleving bij patiënten met een niet-kleincellige longtumor verbeterd. Recent lijkt hierin echter, gezien de vrijwel identieke resultaten van de diverse fase III studies, een plateau bereikt te zijn. Vooruitgang in de moleculaire biologische kennis van niet-kleincellige longtumoren heeft geleid tot het ontwikkelen van nieuwe farmacologische middelen, zoals angiogenese remmers, tyrosine kinase remmers en immuuntherapie. Deze worden momenteel onderzocht in fase I en II trials. Of een combinatie van deze middelen met de traditionele behandelmogelijkheden zoals chirurgie, radiotherapie en chemotherapie, zal leiden tot een betere overleving zal uit verder onderzoek dienen te blijken.

Dankwoord

Dankwoord

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Curriculum vitae

Curriculum vitae

De auteur van dit proefschrift werd geboren op 13 juni 1967 te Heerlen. In 1985 behaalde zij haar Gymnasium-$ diploma aan de Scholengemeenschap Sint Michiel te Geleen.
Aansluitend studeerde zij geneeskunde aan de Universiteit Utrecht, waar zij in december 1992 haar artsexamen behaalde.
Van maart 1993 tot juli 1995 is zij werkzaam geweest als AGNIO longziekten in het Sint Antonius Ziekenhuis in Nieuwegein. In juli 1995 startte zij met haar vooropleiding interne geneeskunde in het Diakonessenhuis te Utrecht (opleider dr. J.B.L.Hoekstra). De opleiding tot longarts vond plaats in het Sint Antonius Ziekenhuis te Nieuwegein, (opleiders achtereenvolgend dr. R.G.J.R.A. Vanderschueren en dr. J.M.M. van den Bosch) en een half jaar in het Universitair Medisch Centrum Utrecht (opleider prof. dr. J-W. J. Lammers).
Sinds januari 2001 is zij werkzaam als longarts in het Laurentius Ziekenhuis te Roermond.