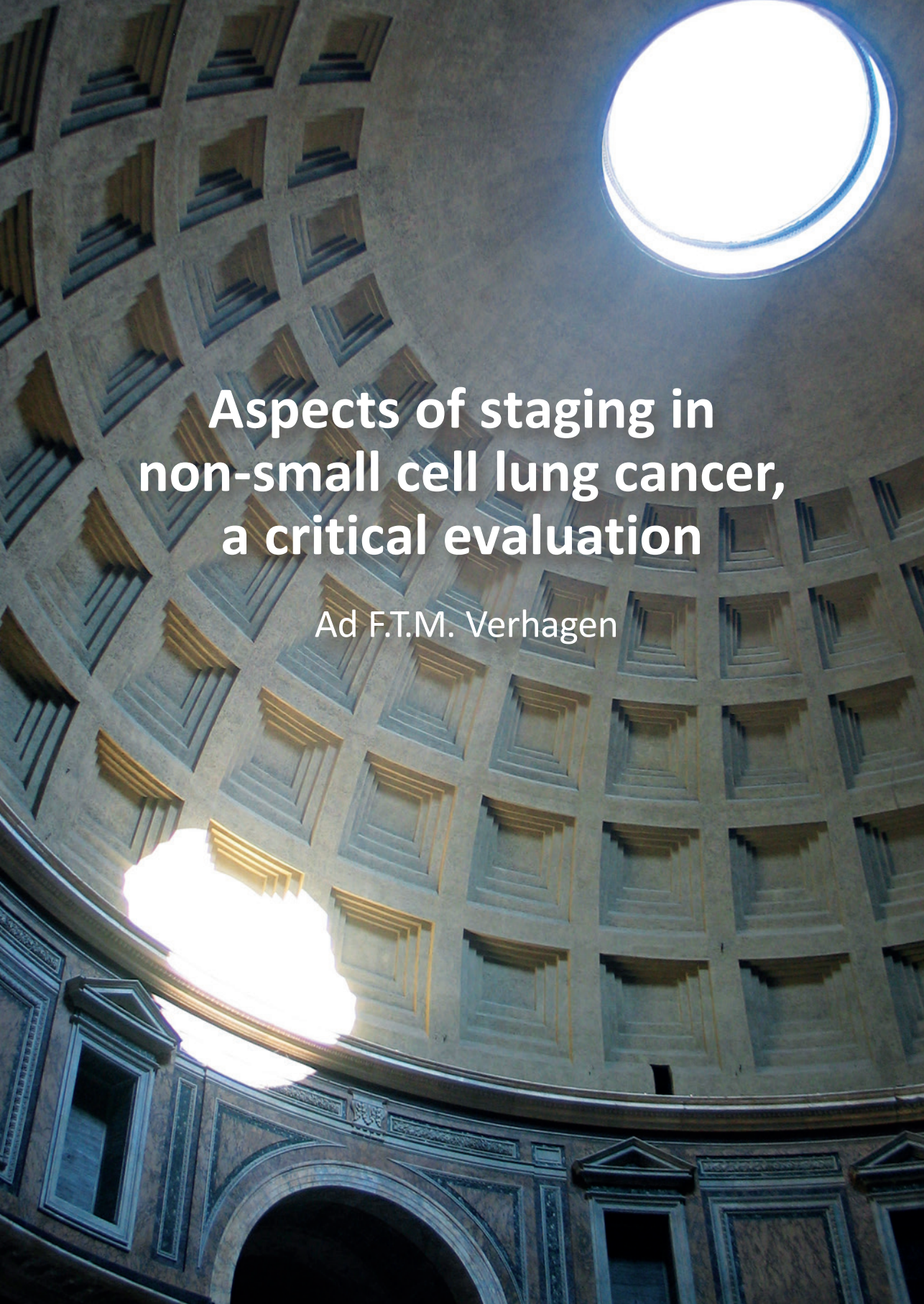

Aspects of staging in non-small cell lung cancer, a critical evaluation

Ad F.T.M. Verhagen

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Contents

Chapter 1

General introduction and outline of the thesis.

Introduction.

Lung cancer accounts for a huge disease burden worldwide: it is the leading cause of cancer in the entire population, representing 12.7% of all newly diagnosed malignant diseases and responsible for 18.2% of all cancer related deaths (1).

Also in The Netherlands lung cancer is frequently diagnosed: in 2011, in almost 12000 patients a lung carcinoma was detected. It was more frequently diagnosed in men (7,100 pts., being 13.5% of all cancers diagnosed in men) than in women (4,600 pts., being 9.5% of all cancers diagnosed in women), although the incidence among women is still slowly increasing (2).

Treatment of patients with lung cancer is based on both local therapeutic modalities, like surgery or radiotherapy, and several forms of systemic therapy, sometimes in combination, as well as providing best supportive care.

Despite improvements in diagnostic procedures and therapeutic regimens, the overall prognosis of patients with lung cancer remains poor (3). Nevertheless, there is a clear prognostic difference between patient subgroups, depending on the extent of the disease, which is based on clinical aspects, like tumour size and the presence or absence of lymphatic and/or haematogenous metastases (4). Besides these anatomic parameters, the histological type, specific tissue characteristics (5) and both molecular- and genomic characteristics, are also important prognostic factors.

Staging in lung cancer comprises multiple diagnostic procedures to determine the extent of the disease at the time of presentation, as well as during and after treatment. Accurate staging is a multidisciplinary responsibility of all physicians involved in the diagnosis and treatment of patients with lung cancer. This is essential to select the appropriate therapy for an individual patient, but also to have an indication of the prognosis and to compare results of treatment between distinct patient groups (6).

The staging algorithm is not static, but evolving over time, and is dependent on available techniques and performance.

When these techniques reveal no sign or symptom of distant metastasis, the mediastinal lymph nodes are crucial in the staging process and will determine the contribution and sequence of treatment modalities.

The aim of this thesis is to contribute to the evolution of the staging process in patients with non-small cell lung cancer, by a critical evaluation of four different aspects, with special focus on the mediastinum.

Development of a lung cancer staging system.

TNM classification.

As early as the 18th century the concept of staging was introduced by a Scottish surgeon, John Hunter, who divided tumours into “movable” and “not only movable” as a criterion for resection (7). But it was only in the 1940’s that a systematic method to describe the stage of cancer was introduced by Pierre Denoix, a French oncologic surgeon. He presented a “uniform technique for clinical classification”, which was based on the anatomic extent of a carcinoma and defined by three parameters: a “T”, concerning the extent of the primary tumour, an “N”, recording the presence or absence of lymph node metastases and an “M”, describing distant metastases. This method was adopted by the Union Internationale Contre le Cancer (UICC), an organisation founded in 1933 by cancer researchers worldwide to share their knowledge, now called the Union for International Cancer Control (UICC), based in Geneva. In the 1950’s this organisation established a Committee on Clinical Stage Classification and Applied Statistics to “extend the general technique of classification to cancer at all sites” (8). In the 1960’s they published nine brochures, proposing a classification for 23 tumour sites. The first edition of a comprehensive TNM classification of malignant tumours was published in 1968. Since then new editions have been published, containing extensions and changes to previous versions, but by users in different parts of the world local variations in the rules of classification were introduced (9). Despite this, worldwide agreement on cancer staging was reached in the 1980’s and secured by the publication in 1997 of the 5th edition of the “TNM classification of malignant tumours” by the UICC (10), simultaneously with- and identical to- the “Cancer Staging Manual” by the American Joint Committee on Cancer (AJCC) (11).

Subsequent to the TNM classification, the concept of stage grouping was proposed, actually by the AJCC, to facilitate analysis and improve transparency. Patient cohorts with different TNM subsets, but nevertheless a comparable survival, were grouped together in the same stage group, while survival rates for each stage group had to be distinctive (9).

TNM in lung cancer staging.

With regard to lung cancer, a first staging system according to the TNM principles, was proposed by Clifton F. Mountain in the 1970’s, but in 1986 he published the “new international staging system” (12). This was adopted by both the UICC and the AJCC and published in the 4th edition of both staging manuals (13,14). Unfortunately, in this system the end results of TNM subsets within stage groups diverged. Furthermore, greater specificity with respect to the end results, of especially the TNM subsets in stage I, II and IIIa, was needed. As a result, a revised version of the staging system, based on a larger patient cohort, was published by Mountain in 1997 (15).

Additionally, a new system for regional lymph node classification was proposed, since local differences appeared in classifying lymph nodes, as a result of two different systems that were in use: the lymph node map developed by Naruke and adopted by the AJCC (16), and a slightly different scheme approved by the American Thoracic Society (17). Both systems were unified into a new, so called “Mountain-Dresler American Thoracic Society (MD-ATS)” lymph node map (18).

The revisions in this latest staging system were based on analysis of 5,319 patients, primarily treated in a single hospital, the University of Texas M.D. Anderson Cancer Center in the USA. Most of these patients were treated surgically.

Serious doubts about the representativeness of these data with regard to medically treated patients, as well as patients treated in other hospitals in other parts of the world, led to the initiative of the International Association for the Study of Lung Cancer (IASLC), in 1998, to develop an international lung cancer database, from a large number of patients, in all stages of the disease, from all over the world. Analysis would have to lead to validated revisions of the staging system (19).

The current, 7th, edition of the staging system.

As a result of this initiative, data from 68,463 patients with non-small cell lung cancer and an additional 13,032 patients with small cell lung cancer, originating from 20 countries in four continents, were analysed. The analysis led to reclassification of the “T” and the “M” components with regard to lung cancer, in the current 7th edition of the TNM classification of malignant tumours (20). The “N” component remained unchanged, although the concept of nodal zones was introduced. Seven different zones were defined, 1 cervical-, 4 mediastinal- and 2 intrapulmonary zones, each consisting of closely related nodal stations (21).

Because of the reclassification of the T and M components, changes were also proposed for the stage grouping of lung cancer. Based on these proposals, for each stage in the current TNM classification there is a clear relation between stage and survival, as well as a significant separation of survival curves between stages (22).

According to the TNM principles, in the 1980’s a distinction was made between a classification based on clinical findings only, defined as cTNM, and a TNM classification also based on postoperative pathologic examination, pTNM. According to the current stage groupings, the survival rates of the pathological stages exceed the survival rates of the corresponding clinical stages at every stage.

In conjunction with the 7th edition of the TNM staging system, a new lymph node map was again proposed. Despite the development of the MD-ATS lymph node map, the former Naruke map was still used by Asian, especially Japanese, physicians. This hampered the interpretation of treatment results in the lung cancer database. To overcome the discrepancies and to facilitate future analysis, a new IASLC lymph node map has become part of the current staging system, providing precise anatomic

definitions for all lymph node stations and including the grouping of separate stations into seven zones (23).

The redefined anatomic boundaries of lymph node stations can be easily applied to clinical staging, among others by CT scanning. Nevertheless, the redefinition of boundaries between intrapulmonary- and mediastinal lymph node stations, and the distinction between left- and right sided stations, will have an impact on clinical practice, both in determining the correct stage and optimal therapy. For example, the lower border of the paratracheal- and the upper border of the hilar lymph nodes are now defined by the caudal margin of the azygos vein. As a result, hilar lymph nodes have become easily accessible for invasive mediastinal staging by mediastinoscopy. Furthermore, the border between left- and right sided lymph nodes has moved from the midline to the left margin of the trachea, whereas the area of the subcarinal lymph nodes has been extended caudally.

The current staging system only encloses anatomical parameters, although descriptors exist to indicate histopathological grading (G), lymphatic- (L) or venous invasion (V) and descriptors to indicate special circumstances, like classification of multiple primary tumours (m), staging following multimodality therapy (y), recurrent disease (r), or at autopsy (a) (19). Moreover, for the first time, the 7th edition of the staging system is also applicable to small cell lung cancer and carcinoid tumours. Nevertheless, in patients with non-small cell lung cancer, histology appeared to have only limited influence on prognosis and thus was not included as a staging parameter (24).

Future developments.

Analysis of the IASLC database revealed additional non-anatomic parameters, like performance status, age and gender, as significant prognostic factors. These are not taken into account yet, but may be included in the next version of the staging system, although they do not refer to the extent of the process (25). Also functional- or metabolic data, which have become available only after the inclusion period of the current database, as a result of the widespread use of ^{18}FluoroDeoxyGlucose-Positron Emission Tomographic (FDG-PET) scanning in the work-up of patients with lung cancer, will probably have an impact on the next staging system.

Finally, the amount of data, based on molecular- and genomic characteristics of the primary tumour, are rapidly increasing and, once validated with regard to prognosis, are expected to play an important role in future staging systems. The next, 8th , version of the UICC lung cancer staging manual, for which patient data are prospectively collected between 2009 and 2012, is intended to be published in 2016 (26).

Staging methods.

Clinical evaluation.

Determining the anatomical extent of lung cancer starts by the interpretation of symptoms and signs of a patient. Common complaints like coughing and haemoptysis are not specific, but pain referring to the skeleton, or neurologic disorders may be a first sign of distant metastases. In the same way, pain of the chest wall can result from a tumour invading the pleura or beyond, and fever may be a sign of post-obstruction atelectasis or pneumonia, once the diagnosis of a tumour is established. Furthermore, physical examination may reveal enlarged supra-clavicular lymph nodes, suspicious of metastatic involvement. Nevertheless, additional investigation will be necessary to confirm the diagnosis and demonstrate the extent of the disease.

Laboratory tests are, in general, of little help with regard to the detection of a lung carcinoma or identification of metastases. Only in the case of extensive bone metastases an elevated serum calcium concentration will be found. Also results from liver function tests are seldom abnormal, unless numerous metastases are present. However, anaemia at presentation is a poor prognostic factor and seems to correlate with metastatic disease (27).

Imaging.

Once a lung carcinoma is considered, chest radiography is routinely performed to detect a tumour, determine the site and, roughly, extent of the process. Nevertheless in about 20 % of patients with lung cancer, a tumour is not seen on chest X-ray, in the majority due to superimposed structures or additional alterations, for example as a result of pneumonia (28). Also the size, density and ill-defined margins of a lesion are important factors that contribute to detection error (29).

A diagnostic Computed Tomographic (CT) scan of the chest should therefore be performed when a carcinoma is suspected, not only to establish a tumour , but also to gather information about the size of the process, the anatomic location within the lung, the relationship with surrounding structures and to screen for additional nodules or parenchyma disorders, as well as pleural collections.

Furthermore, enlargement of both hilar- and mediastinal lymph nodes has to be assessed on the mediastinal setting of a CT scan. In general, lymph nodes with a short axis of more than 1 cm. are considered enlarged, being suggestive of metastatic involvement.

In conjunction with imaging of the chest, a CT scan of the upper abdomen provides information about the liver and adrenal glands, both being sites of preference for metastatic disease. Overall, a CT scan provides essential information to stage a lung carcinoma, both with regard to the T, N and M parameters.

Even with a CT scan, a tumour may be missed due to the size and characteristics of a nodule, or failure to distinguish a nodule from an adjacent structure or atelectasis (30).

Moreover, with regard to mediastinal lymph node staging, the accuracy of CT scan is low, since size is the main criterion for malignancy. In mediastinal lymph nodes with a size of 10 to 15 mm, the prevalence of metastatic involvement is still 30%, increasing to 67% in lymph nodes over 15 mm (31). In a meta-analysis of 43 studies, concerning 7,368 patients, the pooled sensitivity and specificity of CT scan for mediastinal lymph node metastases was 55% and 81% respectively, with a negative predictive value of 83% (32). These numbers are insufficient for an optimal assessment and thus, historically, a mediastinoscopy had to be performed to improve the reliability of mediastinal staging.

Since the mid 1990's FDG-PET scanning has emerged as a valuable staging tool, which is based on the increased glucose uptake of malignant cells, in this way providing metabolic information. Addition of the metabolic information of FDG-PET to the anatomic information provided by CT scan has improved the reliability of the staging process, both with regard to the detection of distant metastases and with regard to the mediastinal lymph nodes.

In extrathoracic staging up to 30 % unexpected metastases are found by the use of FDG-PET, in addition to conventional imaging by CT scan (33). Furthermore, FDG-PET proved to be more effective in detecting bone metastases than MRI or bone scintigraphy (34).

With regard to the mediastinal lymph nodes, the addition of FDG-PET improved the accuracy of non-invasive staging (35), probably diminishing the need for a mediastinoscopy. Nevertheless, the poor spatial resolution of FDG-PET is a disadvantage, which is only partially solved by the fusion of FDG-PET and CT in a single scan, a so-called integrated PET-CT scan (36).

To assess the additional value of FDG-PET in detecting extrathoracic metastases and to compare the accuracy of FDG-PET in mediastinal lymph node staging to cervical mediastinoscopy, was the aim of the study in chapter 2.

Endoscopy.

To confirm the diagnosis of lung cancer, suspected on chest radiography, CT- and/or FDG-PET scan, bronchoscopy is indicated, possibly providing tissue for histological assessment or the yield of bronchial washing and brushing for cytology. Moreover, in case of a centrally located tumour, the endobronchial extent of the process can be assessed. This may help to define the T status and gives insight to the potential type of resection.

The sensitivity of bronchoscopy for the confirmation of lung cancer in central lesions is high, 88%, but diminishes in peripherally located tumours to 63% and 34%, depending on their size (over- and under 2 cm in diameter, respectively). The yield of

the procedure may be increased by navigation bronchoscopy or radial endobronchial ultrasound-guided lung biopsy, but these methods are not yet widely used (37).

In addition to establishing a diagnosis and determining the type of resection, recently endoscopic techniques have emerged in hilar and mediastinal lymph node staging and have become an important method in determining the N status as part of the staging procedure.

Initially Endoscopic Ultrasound guided-Fine Needle Aspiration (EUS-FNA) was introduced, being a method to puncture and aspirate mediastinal lymph nodes by an oesophageal endoscope, using ultrasound to detect lymph nodes and guide a hollow needle (38). In addition to assessment of the mediastinal lymph nodes, the left-, but also right adrenal gland are accessible by this method, making it possible to prove a metastatic lesion in a suspicious adrenal gland on FDG-PET and/or CT scan (39,40).

Because the oesophagus is running down in the mediastinum behind, but also somewhat on the left side of the trachea, this technique is less suitable for the assessment of lymph nodes on the right side of the trachea. Visibility by ultrasound is hampered by the interfering air. Nevertheless, lymph nodes in the lower mediastinum, in the pulmonary ligament and paraoesophageally, which cannot be reached by mediastinoscopy, are accessible on both sides. Therefore this technique seems primarily complementary to surgical staging of the mediastinum by cervical mediastinoscopy.

However, also Endobronchial Ultrasound guided-Transbronchial Needle Aspiration (EBUS-TBNA) has become available, making use of a bronchoscope to detect and aspirate lymph nodes under real-time guidance by ultrasound. By this technique the same mediastinal lymph nodes can be reached as by mediastinoscopy, moreover also hilar- and even interlobar lymph nodes are accessible (41,42).

A major advantage of both techniques is their minimally invasive character, making it possible to perform them under conscious sedation, without anaesthesia, in an outpatient clinical setting. However, pathologic assessment of the yield of both procedures is only possible by cytology instead of histology, and there is some doubt about the completeness of the mediastinal examination. Furthermore, the sample obtained by needle aspiration is non-diagnostic in a significant number of cases (43). Consequently, the use of Rapid On-Site Evaluation (ROSE) of the aspirate is advised to increase accuracy, by repeating the needle passes and aspiration of a lymph node, until a representative sample is obtained (44). Despite this, endosonography, being the combination of EBUS-TBNA and/or EUS-FNA, has become the first line diagnostic procedure in a growing number of hospitals, when invasive mediastinal lymph node staging is indicated. Whether endosonography can completely replace mediastinoscopy in primary lung cancer staging is still a matter of debate (45). To assess the additional value of cervical mediastinoscopy in routine clinical practice, in patients with suspected or proven non-small cell lung cancer, after a negative result of endosonography, was the goal of the study in chapter 3.

Surgical staging.

In the absence of distant metastases, pre-operative surgical staging of the mediastinum by mediastinoscopy, has proven to be a valuable method to select patients who might benefit most from an intended curative resection (46).

The technique was described by Carlens, in 1959, as a procedure "for inspection and tissue biopsy in the superior mediastinum" (47). Since then the procedure has appeared to be accurate, with a low complication rate and is still considered the gold standard in mediastinal lymph node staging (48). To ensure a high reliability of mediastinoscopy, minimal requirements have been defined (49), although in daily practice they are not always met (50,51). The yield of the procedure is dependent on the thoroughness of the mediastinal exploration and seems related to the experience of the surgeon.

Although mediastinoscopy was initially used to select appropriate candidates for surgical treatment, based on the absence of mediastinal lymph node metastases, its role has changed over time. Since two randomized trials, both published in 1994, demonstrated a survival benefit of chemotherapy prior to surgery, over surgery alone, in patients with resectabel non-small cell lung cancer and ipsilateral mediastinal lymph node metastases, cervical mediastinoscopy became important, not only to demonstrate, but also to discriminate between ipsilateral and contra-lateral mediastinal lymph node involvement (52,53).

Following this combination treatment of systemic and local therapy, the question raised whether the same local control with regard to the primary tumour site could be achieved by radiotherapy instead of surgery. In two landmark trials, designed to define the role of surgery in patients with ipsilateral mediastinal lymph node metastases, overall survival curves of treatment arms with- and without surgery were not significantly different (54,55), resulting in chemo-radiotherapy as the standard of care. However, subgroup analysis showed that in patients with a good response to induction therapy, leading to clearance or so-called down staging of the mediastinal lymph nodes, the surgical arm led to a favourable outcome. As a result of these studies among others (56), the concept of re-staging was introduced. Restaging, or reassessment of the mediastinal lymph nodes to prove down staging after chemo- and/or radiotherapy, can theoretically be performed by the same modalities as primary staging: by imaging, endosonography and/or (repeat) mediastinoscopy. The reliability of both imaging techniques and endosonography in restaging appears to be low. Although a repeat mediastinoscopy is technically possible, this method too has a lower yield compared to an initial procedure (57). Therefore, the highest accuracy in both initial staging and restaging may be achieved by the use of endosonography first, to prove ipsilateral lymph node involvement, followed by the use of a primary mediastinoscopy to evaluate the result of induction therapy in patients with locally advanced lung cancer. However, in cases of an unexpected negative result of

endosonography, in patients suspected to have mediastinal lymph node involvement, mediastinoscopy is still indicated to reduce the false-negative rate (see chapter 3).

This is in agreement with the recent update of the European guidelines on pre-operative staging: apart from the addition of FDG-PET as an imaging modality, endosonography, if available, is suggested the primary staging tool for tissue confirmation, both in cases of only hilar suspicion, a central tumour, or a tumour over 3 cm in diameter, and in cases of positive mediastinal lymph nodes on imaging techniques. However, especially in these latter patients, confirmation of a negative result by mediastinoscopy is recommended (58).

In early stage lung cancer, without mediastinal lymph node involvement by clinical staging, surgical resection is regarded as the standard of care. The goal of surgery is to perform a complete resection, providing the best outcome for an individual patient. The type of resection is mainly dependent on the T stage of the tumour. In case of a T1 or T2 tumour (20), confined to a single lobe, in general a lobectomy is the treatment of choice (59). However, in case of a central location, with tumour invading the pulmonary artery or main bronchus, a sleeve resection or pneumonectomy may be needed. In case of a T3 tumour with invasion of the chest wall or other surrounding tissue, or a T4 tumour, supposed to be resectable, an "en-bloc" resection of the originating lobe or lung, together with the invaded structure, leading to negative resection margins, should be performed. Yet, a prerequisite for a complete resection is confirmation of the clinical stage during surgery, since unexpected findings may be encountered for each of the stage descriptors. Therefore the pre-operative staging process has to be continued during surgery, assessing both the primary tumour and remaining lung parenchyma, to determine the type of resection. Moreover, special attention has to be paid to the intrapulmonary- and mediastinal lymph nodes, since unforeseen lymphatic dissemination may be present despite a thorough pre-operative work-up (60). Nodal metastases themselves may influence the type of parenchyma resection, for example in case of extra-nodal growth. Yet, in addition to the pulmonary resection, a systematic nodal dissection should primarily be performed to accurately determine the pathologic stage and, ideally, consists of a meticulous excision of both lobar-, interlobar-, hilar- and all ipsilateral mediastinal lymph node stations.

To determine completeness of resection, a definition has been proposed by the IASLC and has been adopted by the UICC (61). This definition not only includes a free resection margin at the vascular-, bronchial- and parenchyma margins or pleural surface, but also minimal requirements with regard to lymph node dissection. Moreover, the European Society of Thoracic Surgeons (ESTS) guidelines for intraoperative lymph node staging have been published (62). According to these guidelines a systematic nodal dissection is recommended and should consist, on the right side, of an en-bloc resection of the upper- and lower paratracheal lymph nodes,

any visible lymph nodes in front of the superior vena cava and behind the trachea, as well as lymph nodes in the subcarinal space, next to the oesophagus and in the pulmonary ligament. On the left side, dissection of the sub- and para-aortic lymph nodes, the lower paratracheal lymph nodes and also the lymph nodes in the subcarinal space, next to the oesophagus and in the pulmonary ligament should be performed. Besides these mediastinal lymph nodes, the hilar, interlobar and pulmonary lymph nodes should be dissected. However, based on two large surveys concerning surgical care in the United States, it is questionable whether these guidelines have been adopted by the surgical community (51,63). To assess the extent of mediastinal lymph node dissection, routinely performed during lung cancer surgery, and hereby the completeness of resection according to the guidelines of the ESTS, was the goal of the study in chapter 4.

Pathologic assessment.

Pathology plays an essential role at multiple phases in the staging algorithm. In patients with a suspicious lesion on chest X-ray, confirmation of a primary lung carcinoma by examination of the yield of bronchoscopy is a first step. Furthermore, confirmation of distant metastasis in case of clinical suspicion on tumour dissemination is necessary. In the absence of distant metastasis the focus of clinical staging is oriented towards the mediastinum. Depending on the indication for pre-operative mediastinal lymph node staging, cytological assessment of the yield of endosonography will be performed, in some cases followed by histological examination of lymph node biopsies taken by mediastinoscopy.

During surgery confirmation of malignancy may still have to be performed and additional frozen section analysis to assess the resection margin may be indicated, especially in central tumours, if an extended resection is feasible (64).

Finally, the pTNM stage is determined by pathological examination of the surgical specimen. Based on the size of the tumour, associated atelectasis or pneumonitis, invasion of pleura, chest wall, bronchus, vessels, nerves or surrounding organs, as well as the presence of co-existing tumour nodules, the T stage is recorded. In the current staging system, the M stage can only rarely be determined from the surgical specimen (only in case of pleural or pericardial tumour nodules), however, the N stage is critical to define completeness of resection in addition to assessment of the hilar- and pleural- or parenchyma resection margin.

Examination of lymph nodes, both taken during mediastinoscopy and during surgery, is traditionally performed by assessment of haematoxylin and eosin stained slides, taken at two levels of formalin fixed and paraffin embedded lymph nodes.

However, by this method micrometastases and isolated tumour cells may be overlooked, potentially leading to understaging. Since lymph node involvement is a strong prognostic factor and key to the application of (neo-)adjuvant therapy, accurate

assessment is critical. By serial sectioning and the use of immunohistochemistry or molecular techniques as real-time polymerase chain reaction, micrometastases may be detected in up to 30% of histologically negative lymph nodes (65). Nevertheless, the clinical impact of this “occult” lymph node involvement remains unclear (66).

To assess the clinical impact of lymphatic micrometastases, by determining whether recurrent disease was associated with the presence of lymphatic isolated tumour cells and/or micrometastases at the time of the lung resection, was the goal of the study in chapter 5.

Aim of the thesis.

Determining the optimal treatment for each individual patient with a non-small cell lung cancer, is the main goal of staging. Over the last decades, not only therapeutic regimens have changed and are still changing, but also new techniques and insights into lung cancer staging have become available.

The aim of this thesis is to scrutinize the role and performance of four techniques used in mediastinal lymph node staging:

Firstly, FDG-PET. Over the last 15 years, this technique has become widely available and adopted, but what is the accuracy of FDG-PET with regard to the mediastinal lymph nodes? Does it replace invasive mediastinal staging? To what extent?

Secondly, endosonography. This technique has emerged as an attractive first line method for invasive mediastinal lymph node staging. But is there still a place for cervical mediastinoscopy, if endosonography appears to be negative?

Thirdly, as part of an intended curative resection, a systematic lymph node dissection is recommended to obtain optimal loco-regional staging. However, what is routine performance during lung cancer surgery?

Finally, pathologic assessment of the mediastinal lymph nodes, both taken pre-operatively and during surgery, is critical in treatment planning. What is the clinical impact of occult lymph node involvement, detected by immunohistochemistry, in addition to conventional examination techniques?

Each of these questions is relevant, as they are encountered in daily practice when treating patients with non-small cell lung cancer.

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Chapter 2

FDG-PET in staging lung cancer. How does it change the algorythm?

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Summary

Background: In patients with lung cancer FDG-PET may be used both to detect extrathoracic metastases (ETM) and for mediastinal lymph node staging (MLS), potentially reducing the need for mediastinoscopy.

We assessed the added value of FDG-PET in detecting ETM and focused on the reliability of FDG-PET and mediastinoscopy for MLS.

Patients and methods: In 72 consecutive patients with non-small cell lung cancer, the impact of adding FDG-PET to full conventional clinical staging was prospectively analyzed. The predictive value of FDG-PET findings and tumor location for pathologic mediastinal lymph node status were assessed in a logistic regression analysis.

Results: Unexpected extrathoracic metastases were detected by FDG-PET in 15% of patients. In MLS overall negative- and positive predictive values were 71% and 83% for FDG-PET and 92% and 100% for mediastinoscopy. However, the negative predictive value of FDG-PET was only 17% in case of FDG-PET positive N1 nodes and/or a centrally located primary tumor, whereas it was 96% in case of FDG-PET negative N1 nodes and a non-centrally located primary tumor.

Conclusion: By incorporating FDG-PET in clinical staging 15% of patients with lung cancer are upstaged due to unexpected extrathoracic metastases. In case of a negative mediastinal FDG-PET, mediastinoscopy can only be omitted in the presence of a non-centrally located primary tumor and without FDG-PET positive N1 nodes.

Introduction

To determine the appropriate therapy in patients with lung cancer, accurate staging is mandatory. Both detection of extrathoracic metastases (ETM) and, when there is no sign of distant metastases, assessment of mediastinal lymph node involvement are essential.

For detection of extrathoracic metastases a wide variety of diagnostic procedures is available, such as CT-scan, bone scintigraphy and MRI.

In mediastinal lymph node staging (MLS) the reliability of CT scan is low [1]. Therefore, in the work-up for a thoracotomy a cervical mediastinoscopy is still considered the gold standard, providing a high negative- and positive predictive value and a low morbidity and mortality rate [2,3]. However, it remains an invasive procedure and not every surgeon feels comfortable performing it.

In the last decade increasing evidence on the utility of positron emission tomography (PET) using fluor-18-fluorodesoxyglucose (FDG) to detect both extra-thoracic metastases and mediastinal lymph node involvement has become available. In contrast to the anatomic information provided by CT scan, FDG-PET capitalizes on the increased glucose uptake of malignant cells, thus providing complimentary diagnostic information. The positioning of FDG-PET in the diagnostic work-up of lung cancer patients depends on its reliability to detect both extrathoracic- and lymph node metastases.

Several reports [4,5], using FDG-PET in MLS, suggest that the need for mediastinoscopy in patients potentially eligible for a curative resection is reduced.

Particularly the high negative predictive value of a mediastinal FDG-PET would make a mediastinoscopy redundant.

The aim of this study was to assess the added value of FDG-PET in detecting extrathoracic metastases and to compare the reliability of FDG-PET in MLS to that of mediastinoscopy in patients with non-small cell lung cancer.

Patients and methods

Patients.

From July 2000 until March 2001 we studied 72 consecutive patients (60 man, 12 women; mean age 62 years, range 18-87 years) with suspected or proven primary non-small cell lung cancer at the University Medical Center Nijmegen. The final histological diagnosis was squamous cell carcinoma (n=35), adenocarcinoma (n=19), undifferentiated non-small cell carcinoma (n=16), and carcinoid (n=2, 1 typical, 1 atypical).

All patients underwent full conventional clinical staging, consisting of history taking and physical examination, laboratory investigations, X-chest, bronchoscopy,

CT-scan of the chest and upper abdomen, and, only in case of symptoms, bone scintigraphy and/or CT-scan of the brain (Fig. 1). When there was no evidence of distant metastases, cervical mediastinoscopy (n=50) and, in case of a carcinoma in the left upper lobe, parasternal mediastinoscopy (n=14) was performed in every patient, except for those patients with a peripheral T1 lesion without hilar or mediastinal lymph nodes larger than 1cm. in shortest axis on CT-scan (n=6). At cervical mediastinoscopy multiple biopsies were taken of at least lymph node station 4R, 4L and 7 [6]. An average number of 3.4 lymph node stations was biopsied. Patients were staged according to the revised International System for Staging Lung Cancer [7].

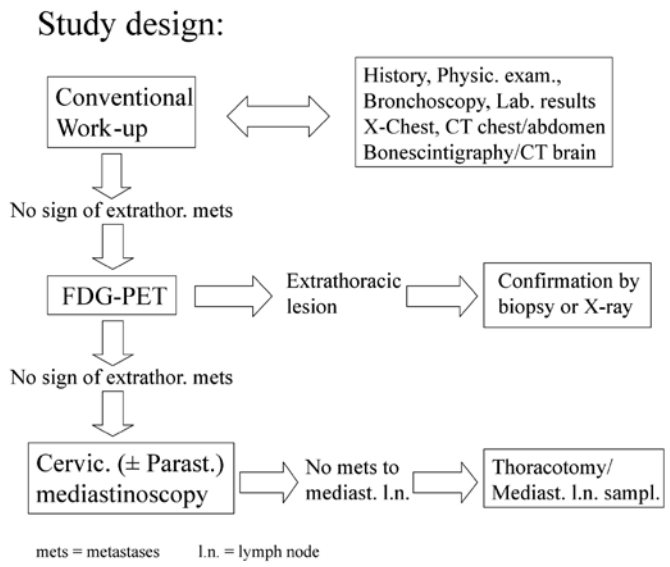

Figure 1. Study design.

FDG-PET.

In case conventional screening was negative for supraclavicular lymph node involvement or distant metastases, patients underwent FDG-PET scanning in the week before mediastinoscopy. A dedicated, rotating half-ring PET-scanner (ECAT-ART, Siemens/CTI, Knoxville, Tn, USA) was used for data acquisition. Prior to FDG-injection, patients were fasting for at least 6 hours. Intake of sugar-free liquids was permitted. Immediately prior to the procedure, patients were hydrated with 500 ml of water. One hour after intravenous injection of 200-220 MBq FDG (Mallinckrodt Medical, Petten, The Netherlands) and 20 mg furosemide, emission images or emission and

transmission images of the area between proximal femora and the base of the skull were acquired (10 minutes per bedposition). When only an emission study was recorded, the images were not corrected for attenuation and reconstructed using filtered backprojection (Butterworth filter with a cut-off frequency of 0.4 Nyquist). When an emission and transmission study were recorded, the images were corrected for attenuation and reconstructed using the Ordered-Subsets Expectation Maximization (OSEM) algorithm. Reconstructed images were displayed in coronal, transverse and sagittal planes. All images were read by two experienced nuclear medicine physicians. Standard uptake values were not calculated.

When FDG-PET suggested supraclavicular lymph node involvement or extra-thoracic metastases, confirmation was obtained by needle biopsy or correlative imaging by X-ray or MRI.

FDG-PET was considered positive for mediastinal involvement when lesions were detected in any mediastinal lymph node station, not separating ipsilateral (N2) from contralateral (N3) lymph nodes. The decision to perform mediastinoscopy was not influenced by the mediastinal status on FDG-PET.

All patients without lymph node involvement at mediastinoscopy underwent thoracotomy during which mediastinal lymph node sampling was performed. An average of 3.2 lymph node stations was explored.

To assess the influence of the location of the primary tumor on the result of mediastinal FDG-PET evaluation, all tumors were classified as centrally-, intermediately- or peripherally located. A central tumor was located into the inner 1/3 of the lung parenchyma (adjacent to the mediastinum) on a transverse image on the CT-scan. An intermediate or peripheral tumor was located in outer 2/3 of the parenchyma.

Statistical analysis.

The reliability of FDG-PET in MLS was assessed using mediastinoscopy and/or thoracotomy as the gold standard. Sensitivity, specificity, negative- and positive predictive values were calculated by cross tabulation. Posterior probabilities of mediastinal lymphnode involvement were calculated in case of positive and negative test results.

The value of N1 status and N2 status according to FDG-PET, and location of the primary tumor (central, intermediate or peripheral) in predicting pathologic mediastinal lymph node status was explored in a logistic regression analysis.

Difference in proportions of a false negative FDG-PET for MLS between patients with positive hilar nodes and/or a central location of the primary tumor and patients with negative hilar nodes and an intermediate or peripheral location was assessed using Fisher's exact test.

A P value of less than 0.05 was considered to indicate statistical significance. Statistical analysis was carried out with SPSS software.

Results

Findings by FDG-PET.

Of the 72 patients extrathoracic metastases were detected in 5 patients by conventional diagnostic methods and one patient was considered irresectable due to tumor invasion into the vertebral column on CT-scan (T4). Therefore, no FDG-PET was performed in these patients.

In the remaining 66 patients FDG-PET revealed previously unexpected metastases in 10 patients (15%): in 8 patients extrathoracic metastases (M1), in 2 patients supraclavicular lymph node involvement (N3). In another patient an FDG-accumulating lesion at the base of the tongue proved to be a second primary carcinoma. In 4 additional patients FDG-positive lesions suggestive of metastasis could not be confirmed by conventional methods and were therefore ignored.

Of 56 patients without any sign of tumor dissemination beyond the mediastinum, FDG-PET was positive in the mediastinum in 18 patients and negative in 38 patients.

In 13 patients both FDG-positive mediastinal ànd hilar (N1) lymph nodes were found, in 5 patients only FDG-positive mediastinal lymph nodes.

Only positive hilar lymph nodes (N1) were found in 8 out of 56 patients.

Findings by mediastinoscopy.

48 out of the 56 patients without tumor dissemination beyond the mediastinum underwent cervical- and when indicated also parasternal mediastinoscopy (n=14), which was positive for mediastinal lymph node metastases in 22 patients and negative in 26 patients. In 2 of these mediastinoscopy-negative patients unexpected N2 disease was found during thoracotomy.

In 2 additional patients with a carcinoma in the left upper lobe only cervical mediastinoscopy was performed, which turned out to be negative. Parasternal mediastinoscopy was omitted because of previous coronary bypass surgery. At thoracotomy in both patients lymph nodes in the aorto-pulmonary window proved to be positive, whereas subcarinal and paratracheal nodes were negative.

Six patients with a peripheral tumor clinically staged T1N0M0 directly underwent thoracotomy, without mediastinoscopy. FDG-PET did not show any pathologic uptake except in the primary tumor. Their pathologic stage also proved to be T1N0M0.

Comparison of FDG-PET to mediatinoscopy.

Of 38 patients with a “FDG-PET negative” mediastinum, mediastinoscopy was positive in 8 patients, while at thoracotomy tumor-positive N2 nodes were found in 3 additional patients. Histologically these 11 patients with a false-negative FDG-PET had squamous cell carcinoma (n=8), adenocarcinoma (n=2) and an atypical carcinoid (n=1).

Of 18 patients with FDG-PET positive lesions in the mediastinum, mediastinoscopy was positive in 14, but negative in 4 patients. Thoracotomy proved a positive paratracheal lymph node in one of these latter 4 patients (Fig. 2).

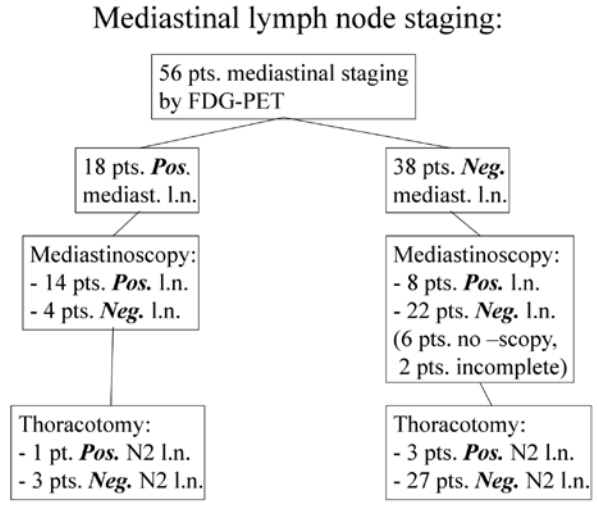

Figure 2. Result of mediastinal lymph node staging by FDG-PET and mediastinoscopy.

Based on the findings at mediastinoscopy and thoracotomy, the overall sensitivity and specificity of FDG-PET with regard to the mediastinum were 58% and 90%. The negative predictive value was 71%, the positive predictive value 83%. The likelihood ratio for mediastinal lymph node involvement in case of a “FDG-PET positive” mediastinum was 5.77, with a posterior probability of mediastinal lymph node metastases of 0.83. The likelihood ratio in case of a “FDG-PET negative” mediastinum was 0.47, with a posterior probability of lymph node metastases of 0.29.

Based on findings at thoracotomy, both sensitivity and negative predictive value of mediastinoscopy in 48 patients were 92%. Specificity and positive predictive value were 100% by definition. When mediastinoscopy was negative, the likelihood ratio for mediastinal lymph node metastases was 0.08. With a prior probability of mediastinal lymph node metastases of 0.5, the posterior probability was 0.07. In case of a positive mediastinoscopy the posterior probability was by definition 1.0.

False-negative FDG-PET.

Of the 11 patients with a false-negative result of FDG-PET for mediastinal involvement, 6 patients showed positive hilar (N1) nodes on PET scan (Fig. 3). Review of the

pathology report showed micrometastases in mediastinal (N2) nodes in all 6 of them. Four other patients had a central location of the primary tumor (adjacent to the mediastinum) on CT scan (Fig. 4). In a logistic regression model not only N2 status

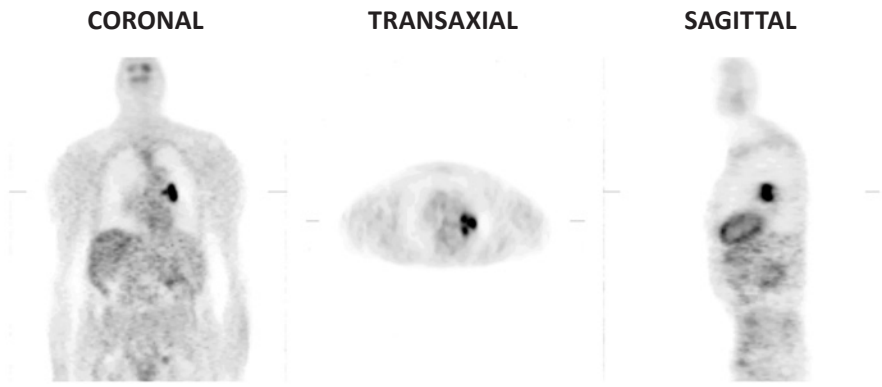

Figure 3. FDG-positive N1 nodes, but negative N2 nodes.
At histology, micrometastases were found in N2 nodes.

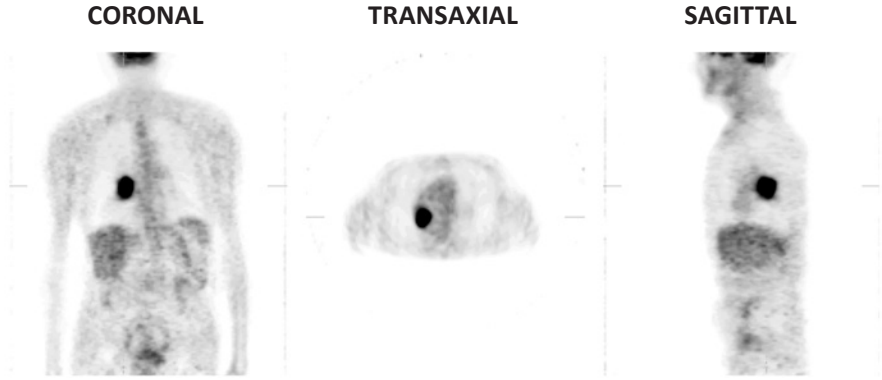

Figure 4. Central primary NSCLC, adjacent to the mediastinum, obscuring histologically proven N2 metastases.

according to PET, but also N1 status (p=0.001) and central location (p=0.04) had an independent predictive value with regard to the pathologic N2 stage. When the group of 38 patients with a negative mediastinum on FDG-PET was divided into a group of 12 patients with positive hilar nodes and/or a central location and a group of 26 patients with negative hilar nodes and an intermediate or peripheral location, mediastinal FDG-PET was false-negative in 10 out of 12 patients in the first group, which was significantly different from only 1 false-negative result out of 26 in the second group (Fisher's exact test, p<0.001) (Table 1).

Sensitivity and specificity of FDG-PET in the first group of patients, with FDG-positive hilar nodes and/or a central location, were 57% and 50%. The negative predictive value was only 17%, the positive predictive value 87%.

In the second group of patients, with FDG-negative hilar nodes and a non-central location, sensitivity and specificity of FDG-PET were 67% and 96%, with a negative predictive value of 96% and a positive predictive value of 67%.

Table 1. Histological mediastinal lymph node status in patients with a negative mediastinal FDG-PET scan (n=38).

	Histological positive mediastinal lymph nodes	Histological negative mediastinal lymph nodes	Total
FDG-PET negative N1 nodes and non-central tumor	1	25	26
FDG-PET positive N1 nodes and/or central tumor	10	2	12
Total	11	27	38

Discussion

In our study FDG-PET scan improved clinical staging of lung cancer patients by detecting unexpected extrathoracic metastases in 15% of patients without any evidence of metastases after conventional staging, thus avoiding futile mediastinoscopy and eventually thoracotomy. This is in accordance with previous publications [8,9]. Routine use of FDG-PET in staging lung cancer may thus lead to a further reduction of patients presenting with metastases within a few months after a "curative" treatment. Of note, conventional staging performed according to the guidelines of the American Thoracic Society and the European Respiratory Society

[10] revealed metastases in 7% (5 of 72) of patients. This is less than expected, but it may reflect the referral pattern to our center, since approximately half of our population consisted of patients who were considered to be surgical candidates by the referring hospital.

Conventionally, when there is no evidence of distant metastases, accurate MLS is the next step in clinical staging, since mediastinal lymph node involvement significantly reduces the benefit of surgery as a single therapy [11,12].

Whether or not FDG-PET should be used as a routine procedure in MLS, replacing mediastinoscopy, is still a matter of debate [13]. On the one hand, a particularly high negative predictive value of mediastinal FDG-PET (up to 97%) is reported [4,5,14]. This led to the recommendation to omit mediastinoscopy in case of a negative mediastinal FDG-PET [15,16].

On the other hand, two important points need to be addressed. First, failure to distinguish involved lymph nodes from activity in the primary tumor on FDG-PET has been reported earlier [8]. Consequently, negative interpretation of mediastinal FDG-PET in patients with centrally located tumors may lead to understaging, because of the primary tumor obscuring the mediastinal lymph nodes [17,18,19]. This is in agreement with our results. Second, we observed that 6 out of 8 patients with FDG-positive N1 nodes but FDG-negative N2 nodes, had microscopic involvement in N2 nodes, ranging in size from a few cells to a few millimeters. Such small volume disease is beyond detectability of any currently available imaging technique. Thus, FDG-PET positive hilar lymph nodes are predictive for microscopic involvement of mediastinal lymph nodes.

The present study convincingly shows that the negative predictive value was only 17% in case of FDG-PET positive N1 nodes and/or a centrally located primary tumor, whereas it was 96% in case of FDG-PET negative N1 nodes and a non-centrally located primary tumor. These conditions clearly identify the limitations of FDG-PET for MLS and strongly support the continued use of mediastinoscopy in the first group of patients. Conversely, the true-negative result of mediastinal FDG-PET in 25 out of 26 patients with a non-centrally located primary tumor and without any FDG-PET positive lymph nodes, makes FDG-PET very reliable in this specific patient group, resulting in a significant reduction in the need for mediastinoscopy, in our series of 46% (26 out of 56 patients undergoing MLS). In the future, fusion of the CT scan with FDG-PET into one study may be helpful to improve the diagnostic accuracy of these imaging procedures.

Although the reliability of a positive mediastinal (N2 or N3) FDG-PET was high in our series (15 histologic positive patients out of 18 FDG-PET positive), we feel that mediastinoscopy should still be performed in these patients to confirm nodal metastases histologically. Otherwise, a potentially curative operation may be withheld from patients due to FDG-uptake in inflammatory lymph nodes, being a

known pitfall. In this patient group FDG-PET should be used for guidance during mediastinoscopy with a potential increase in sensitivity. Moreover, mediastinoscopy may also be indicated to make a distinction between stage IIIa and stage IIIb.

Conclusion

By incorporating FDG-PET in the preoperative work-up of all patients with potentially resectable non-small cell lung cancer, 15% of patients are upstaged due to detection of unexpected extrathoracic metastases, thus avoiding futile mediastinoscopy and eventually thoracotomy.

With strict criteria, FDG-PET reduces the number of mandatory mediastinoscopy procedures by 46% without an increase in unexpected N2 involvement at thoracotomy. However, mediastinoscopy should not routinely be omitted in patients with apparently a negative mediastinal FDG-PET, but with a centrally located primary tumor and/or FDG-positive hilar lymph nodes: the primary tumor may obscure positive mediastinal lymph nodes and positive hilar lymph nodes are predictive for mediastinal micrometastases.

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Chapter 3

Mediastinal staging in daily practice: endosonography, followed by cervical mediastinoscopy. Do we really need both?

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Abstract

Objective: In patients with lung cancer, endosonography has emerged as a minimal invasive method to obtain cytological proof of mediastinal lymph nodes, suspicious for metastases on imaging. In case of a negative result, it is currently recommended to perform a cervical mediastinoscopy additionally. However, in daily practice, a second procedure is often regarded superfluous.

The goal of our study was to assess the additional value of a cervical mediastinoscopy, after a negative result of endosonography, in routine clinical practice.

Methods: In a retrospective cohort study, the records of 147 consecutive patients with an indication for mediastinal lymph node staging and a negative result of endosonography, were analysed. As a subsequent procedure, 124 patients underwent a cervical mediastinoscopy and 23 patients were scheduled for an intended curative resection directly. The negative predictive value (NPV) for both diagnostic procedures was determined, as well as the number of patients who needed to undergo a mediastinoscopy to find one false negative result of endosonography (NNT). Clinical data of patients with a false negative endosonography were analyzed.

Results: When using cervical mediastinoscopy as the gold standard, the NPV for endosonography was 88.7%, resulting in a NNT of 8.8 patients. For patients with FDG-PET positive mediastinal lymph nodes, the NNT was 6.1. Overall, a futile thoracotomy could be prevented in 50% of patients by an additional mediastinoscopy. A representative lymph node aspirate, containing adequate numbers of lymphocytes, did not exclude metastases.

Conclusion: In patients with a high probability of mediastinal metastases, based on imaging, and negative endosonography, cervical mediastinoscopy should not be omitted, not even when the aspirate seems representative.

Introduction

In patients with lung cancer, precise clinical staging is mandatory to provide the appropriate therapy. In the absence of distant metastases, mediastinal lymph node staging is essential to select patients for an intended curative treatment. Assessment of the mediastinum is primarily based on a combination of computed tomography (CT) scan and ^{18}fluoro-2-deoxyglucose positron emission tomography (^{18}FDG-PET). However, despite an improved accuracy of these imaging modalities over the last decade [1], invasive staging remains necessary in case of mediastinal lymph node enlargement, PET positive mediastinal- and/or hilar lymph nodes and/or a centrally located tumor [2,3]. For a long time, cervical mediastinoscopy has been considered the gold standard in mediastinal staging, given the high negative predictive value if well performed [4]. During the last decade, esophageal ultrasound-guided fine needle aspiration (EUS-FNA), followed by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), has emerged as a minimally invasive alternative, reducing the need for a cervical mediastinoscopy as a first line staging procedure. Especially by combining both techniques, nearly all mediastinal lymph node stations are accessible, thus making it possible to perform cytological analysis of mediastinal lymph nodes considered suspicious on imaging. When, nevertheless, the result of endoscopic staging appears negative, a subsequent mediastinoscopy is currently recommended to exclude mediastinal lymph node metastases in patients with clinical suspicion [2]. But, since the sensitivity of EBUS-FNA seems to exceed that of mediastinoscopy [5,6], the need for surgical confirmation may be diminished. Accordingly, in daily practice an additional mediastinoscopy is frequently regarded overdone. However, recently only the combination of endosonography followed by mediastinoscopy was shown to be more accurate in mediastinal nodal staging than mediastinoscopy alone, reducing the rate of futile thoracotomies by more than half. Yet 11 patients had to undergo a cervical mediastinoscopy to find one positive result after negative endosonography [7].

The goal of our study was to assess the additional value of a cervical mediastinoscopy in patients with suspected or proven non-small cell lung cancer, after a negative result of endosonographic mediastinal staging, in routine clinical practice.

Materials and methods

In a retrospective cohort study, medical records of 147 consecutive patients with suspected or proven non-small cell lung cancer and a negative result of combined endosonographic mediastinal staging between January 2009 and August 2012 were analyzed.

All patients were clinically staged based on a diagnostic CT scan of the chest and upper abdomen, followed by an integrated PET/CT scan, according to the current Dutch guidelines.

When there was no sign of distant metastasis, endoscopic mediastinal lymph node staging was performed in case of enlarged- and/or FDG-PET positive hilar- and/or mediastinal lymph nodes, and/or a centrally located tumor. Lymph nodes with a short axis > 1 cm were considered enlarged, a tumor was considered central if located in the inner 1/3 of the lung parenchyma on a transverse image on CT scan. Since patients were referred from different hospitals, lymph nodes were considered FDG-PET positive, when clearly stated in the report of nuclear medicine of the referring hospital. In case of only a mild increased uptake by hilar- and/or mediastinal lymph nodes and thus a dubious suspicion, FDG-PET was considered negative.

Endosonographic mediastinal staging, with the availability of both EUS-FNA and EBUS-TBNA, using Pentax EG3870UTK and EB1970UK scopes (Pentax Medical, Hamburg / Tokyo) in combination with a Hitachi EUB 7000HV ultrasound scanner (Hitachi Medical Corp. Japan), was performed as an outdoor clinic procedure under conscious sedation. All procedures were performed by 2 experienced pulmonologists. The choice for one or both modalities was made by the performing pulmonologist, based on the location and side of the primary tumor, as well as the location of the suspicious mediastinal lymph nodes. Although sometimes aspirated, lymph nodes smaller than 5 mm were regarded unsuitable for assessment. In all patients FNA was performed using 22G needles (Medi-Globe and Cook). Rapid on site evaluation (rose) was available in all cases to assess the yield of the procedure and was performed by an analyst of the department of pathology. The definitive diagnosis was based on cytological and immunocytochemical analysis of the obtained slides and cell-block specimens.

After a negative result of endosonography with regard to the mediastinal lymph nodes, 124 patients were scheduled for a cervical mediastinoscopy, 23 patients directly underwent an intended curative resection. In these patients mediastinoscopy was omitted due to patient factors (laryngectomy, previous cervical radiotherapy, struma).

A cervical mediastinoscopy was performed using a video-mediastinoscope (Karl Storz GmbH, Tuttlingen Germany) in all patients. Performance was based on the recommendations of the ESTS [2], with multiple biopsies taken of at least the lower paratracheal lymph nodes on both sides, as well as the subcarinal lymph nodes, regardless of their size.

In case of a thoracotomy, a complete resection was performed according to the definition of the International Union Against Cancer (UICC), including a lymph node dissection of at least three mediastinal stations, always including the subcarinal station [8].

The negative predictive value (NPV) of endosonography was calculated, using cervical mediastinoscopy as the gold standard, as well as using the combination of cervical mediastinoscopy and, when performed, thoracotomy as the gold standard. The NPV of mediastinoscopy was calculated using thoracotomy as the gold standard. Furthermore, the number of patients who had to undergo a subsequent mediastinoscopy to detect one false negative result of endosonography (Number Needed to Treat, NNT) was determined. The analysis was based on an intention to treat.

Finally, clinical data of patients with a false negative result of endosonography were analyzed. Statistical analyses were performed using SPSS 18.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

Imaging

Of all 147 patients included in this study with an indication for invasive mediastinal staging, the tumor was located centrally in 52 patients (35%). In 80 patients (54%) lymph nodes in at least one station appeared to be enlarged on CT scan and FDG-PET demonstrated positive lymph nodes in 96 patients (65%): hilar lymph nodes only in 38 patients, mediastinal lymph nodes only in 21 patients and both in 37 patients.

Endosonography

As a result of these findings on imaging studies, patients were scheduled for endoscopic mediastinal staging. An EBUS-TBNA was performed in 88 patients (60%), an EUS-FNA in 29 patients (20%) and both modalities were used in 30 patients (20%). In 147 patients a total of 259 lymph nodes were aspirated (mean of 1.8, range 0-5). In 124 patients both mediastinal- and hilar lymph nodes were examined, with a mean of 1.5 (range 1-4) mediastinal lymph nodes aspirated. In 5 patients, only hilar lymph nodes were aspirated. In the remaining 18 patients, no aspiration was performed.

In addition to the aspirated lymph nodes, 231 lymph nodes in 147 patients (mean 1.6, range 0-4) were inspected. The size of the aspirated lymph nodes , mean 8.6 mm (range 2-23), was different from the inspected ones, with a mean size of 5.2 mm (range 1.8-40) ($p<0.001$). When aspirated, on average 2.5 samples (range 1-6) per lymph node were taken. In 109 out of 124 patients, the yield of at least one mediastinal lymph node was considered representative by pathology, based on the relative amount of lymphocytes present in at least one aspirate.

Cervical mediastinoscopy

As a next step procedure 124 patients underwent a cervical mediastinoscopy, while in 23 patients a thoracotomy was performed directly (Fig.1).

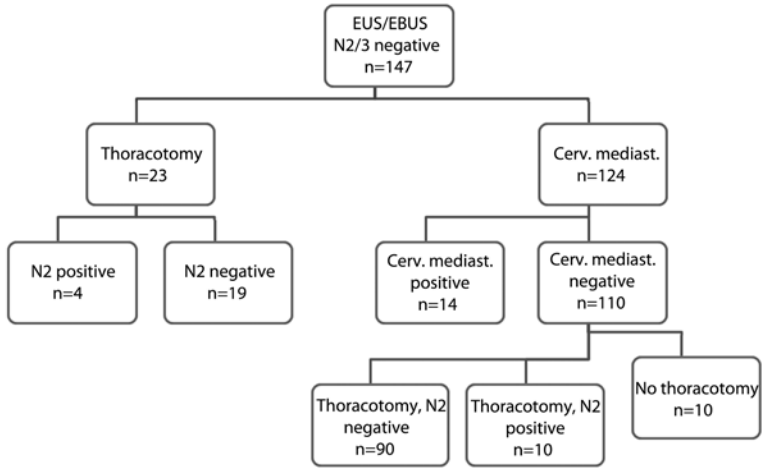

Figure 1. Flow chart of patients with suspected locally advanced lung cancer, after tumor negative mediastinal endosonography, n = 147 pts.

Assessment of the mediastinum by mediastinoscopy was in accordance with the recommendations of the ESTS in 98.5 % of patients. The mean number of mediastinal lymph node stations biopsied was 4.0 (range 1-5, standard deviation 0.69). In 77 patients 4 stations were biopsied, in 26 patients 5 stations, in 19 patients 3 stations, in one patient 2 stations and in the remaining patient one station.

Mediastinoscopy demonstrated positive lymph nodes in 14 out of 124 patients (11%), revealing positive ipsilateral (N2) nodes in 11 patients and positive contralateral (N3) nodes in 3 patients (Table 1). Of 4 patients with only positive intrapulmonary lymph nodes found by endosonography, mediastinoscopy was positive in one.

Table 1. Upstaging based on lymph node involvement, n = 147 pts.

	After endosonography, n = 147 pts.	After cerv. mediast., n = 124 pts. *	After thoracotomy, n = 123 pts. **
N0/N1	147	110	109
N2	-	11	14
N3	-	3	-

* 23 pts. did not undergo a cerv. mediastinoscopy.
** 24 pts. did not undergo a thoracotomy (14 pts. because of a positive mediastinoscopy).

Thoracotomy

In 100 of the remaining 110 patients an intended curative resection was performed, including a mediastinal lymph node dissection of at least 3 mediastinal stations. 10 Patients did not undergo a resection: in 6 patients because of poor condition or patients preference for a different therapy, in 2 patients because of an irresectable tumor and in the last 2 patients the suspected tumor was proven to be a benign lesion. Despite endosonography followed by cervical mediastinoscopy, unexpected mediastinal lymph node metastases were found in 10 out of 100 patients (10%) who had undergone a resection.

In 23 patients mediastinoscopy was not performed. In 4 of these patients mediastinal lymph node metastases were detected by thoracotomy.

Predictive value

Using only the result of cervical mediastinoscopy as the gold standard, the NPV for endosonography was 88.7%. When using both cervical mediastinoscopy and/or thoracotomy as the gold standard this NPV was 80.9%.

For a cervical mediastinoscopy, with a thoracotomy as the gold standard, the NPV was 90%, although the sensitivity was only 58 % in this cohort with a prevalence of N2 disease of 21 %.

As mediastinoscopy was positive in 14 out of 124 patients, the NNT was 8.8 patients.

When only patients with a high probability of mediastinal metastases were considered, based on FDG-PET positive mediastinal lymph nodes in contrast to only hilar suspicion or a central tumor, mediastinoscopy was positive in 9 out of 55 patients, resulting in a NNT of 6.1 patients (Table 2).

By adding cervical mediastinoscopy to the clinical work-up, in this series a futile thoracotomy could be prevented in 14 out of 28 patients (50%).

Analysis of false negative endosonography

In 28 patients the result of mediastinal staging by endosonography was false negative. Of these patients, mediastinal lymph nodes were enlarged on CT scan in 15 patients and 21 patients demonstrated positive lymph nodes on FDG-PET (mediastinal lymph nodes in 12 patients and hilar nodes only in 9 patients). Five patients had to undergo invasive mediastinal staging because of a centrally located tumor.

In 4 patients no lymph nodes were aspirated during endosonography. In the remaining 24 patients, 39 mediastinal stations were investigated (average 1.6, range 1-3), in combination with 9 intrapulmonary lymph node stations. After cytopathological analysis, the yield of endosonography was considered representative (i.e. containing mature as well as immature lymphocytes), in 25 out of 39 investigated mediastinal lymph node stations. In 18 out of 24 patients the yield of at least one mediastinal station was considered representative.

Table 2. Reliability of endosonography and cervical mediastinoscopy in mediastinal staging.

All patients, n = 147 pts.	NPV	NNT
Endosonography, n=147		
CM gold standard	88.7%	8.8
CM and/or thoracotomy gold standard	80.9%	
Cervical mediastinoscopy, n=124		
Thoracotomy gold standard	90%	10
High probability based on FDG-PET*, n = 55 pts.		
Endosonography, n=55		
CM golden standard	83.6%	6.1

CM = cervical mediastinoscopy, NPV = Negative Predictive Value
NNT = Number Needed to Treat, to find one false negative result of the diagnostic procedure.
*Patients with ^{18}FDG-PET positive mediastinal lymph nodes.

In 14 out of 28 patients, the false negative result of endosonography was identified by mediastinoscopy. In these patients, the mean number of mediastinal lymph node stations aspirated by endosonography was 1.5 (range 0-3), as compared to 3.9 (range 1-5) biopsied by mediastinoscopy. The lower paratracheal lymph nodes (station 4) were responsible for most of the failures of endosonography, followed by the subcarinal lymph nodes (station 7) and upper paratracheal lymph nodes (station 2) (Table 3). In 2 patients 2 mediastinal stations were positive by mediastinoscopy and 3 stations in another 2 patients.

In 7 out of these 14 patients, metastases were found in lymph node stations despite assessment by endosonography, in only one of them the yield was considered not representative by the pathologist. In 5 patients, metastases appeared in lymph node stations not examined by endosonography; in the remaining 2 patients, no lymph nodes had been aspirated (Table 4).

In the remaining 14 out of 28 patients unexpected N2 disease was found by thoracotomy: in 10 patients after negative results of both endosonography and cervical mediastinoscopy, in 4 patients after negative endosonography only. Also in this group of patients endosonography failed most frequently in the lower paratracheal lymph nodes (station 4), followed by the subaortic lymph nodes (station 5) and subcarinal lymph nodes (station 7) (Table 3). In 2 patients, no lymph node aspirates were taken during endosonography; in 6 patients metastases were found in lymph node stations also aspirated by endosonography, with a representative yield in

Table 3. False negative mediastinal endosonography: analysis of lymph node stations, n = 28 pts.

Mediastinal lymph node station.	Positive by cerv. mediast., n = 14 pts.	Positive by thoracotomy, no cerv. mediast., n = 4 pts.	Positive by thoracotomy, despite cerv. mediast., n = 10 pts.	Total F.N. result endosonography, n = 28 pts.
2 R	2	-	-	2
2 L	2	-	-	2
4 R	7	1	4	12
4 L	5	-	1	6
5	-	1	3	4
6	-	-	-	-
7	4	1	2	7
8	-	-	1	1
9	-	1	-	1

R = right, L = left, F.N. = false negative.

Table 4. False negative mediastinal endosonography: analysis of yield of endosonography, n = 28 pts.

	Detected by cerv. mediast., n=14 pts.	Detected by thoracotomy, n=14 pts.	Total
Metastasis in: aspirated LN station ánd representative.	6	3	9
Metastasis in: aspirated LN station, not representative.	1	3	4
Metastasis in: non-aspirated LN station.	5	6	11
No LN station aspirated.	2	2	4
Total	14	14	28

LN = Lymph Node.

3 of them. In the remaining 6 patients, metastases were found by thoracotomy in lymph node stations not aspirated during endosonography (Table 4).

In 10 out of these 14 patients also mediastinoscopy was false negative. In 3 patients, because of positive subaortic- and in one patient because of a positive paraesophageal lymph node, both being out of the reach for a cervical approach. In 6 patients lymph node stations were positive despite a biopsy at the time of mediastinoscopy.

Discussion

Treatment planning in patients with a non-small cell lung carcinoma depends on strict and reliable staging. Especially the mediastinal lymph nodes are crucial in determining the contribution and sequence of treatment modalities. For this, EUS- and EBUS-FNA have proven their value and are attractive methods, because of their minimally invasive character [7]. But it is unclear if a negative result has to be double checked by a cervical mediastinoscopy, being the gold standard in clinical staging. The goal of this study was to assess the additional value of a mediastinoscopy after a negative result of endosonography in patients with suspected or proven lung cancer in our routine clinical practice. This study shows that the NPV for endoscopic staging was 80.9%, considering surgical staging by cervical mediastinoscopy and/or thoracotomy as the gold standard, and 90% for a cervical mediastinoscopy. But more important, we found that in every 8.8 patients one futile thoracotomy could be avoided by performing an additional mediastinoscopy. This reduced the number of futile thoracotomies by 50%.

Comparable studies, publishing results of both techniques, are limited. In a recent study of patients with a high clinical suspicion of nodal disease, who underwent EBUS-TBNA followed by mediastinoscopy, the NNT was 3.6 patients [9]. The ASTER trial, a randomized controlled trial comparing mediastinoscopy to combined endoscopic staging followed by mediastinoscopy, demonstrated a NNT of 11 patients [7]. In a prospective trial, performing both EBUS-TBNA and mediastinoscopy under general anesthesia in all patients, similar results were achieved for both techniques, suggesting that mediastinoscopy could be replaced by endobronchial staging [10].

These differences in NNT may be explained by patient selection and performance of either technique. It is therefore important to determine factors that may identify patients who benefit most from an additional mediastinoscopy after negative endosonopraphy.

Firstly, the probability of mediastinal metastases. Based on the criteria of the European Society of Thoracic Surgeons [2], all patients in our study had an elevated risk of mediastinal metastases, necessitating for invasive staging. In a sub analysis of the ASTER trial, according to the risk of mediastinal metastases, no additional value of a mediastinoscopy was demonstrated in patients with a normal mediastinum

based on CT and PET imaging, since the pre-test probability was already low. However, in patients with an abnormal mediastinum, a number of 7 patients who needed an additional mediastinoscopy to avoid one futile thoracotomy, was found [11]. In our study, the prevalence of mediastinal metastases, after a negative result of endosonography, was still 19 % and overall we found a NNT of 8.8 patients, to make an additional mediastinoscopy valuable. Yet, in patients with an abnormal mediastinum, thus by excluding patients with only a centrally located tumor or clinical suspicion because of only hilar lymph nodes, this number dropped to 6.1 patients.

Secondly, the completeness of endoscopic staging. Combined endosonography has the advantage that nearly all mediastinal lymph node stations are accessible and the diagnostic yield of the combination of EUS-FNA and EBUS-TBNA is probably higher than of either technique alone [12]. Nevertheless, in our study, both endoscopic modalities were used in only 20% of patients and the mean number of aspirated mediastinal lymph nodes was 1.5. In contrast to a complete mediastinal investigation, in daily practice performance of endosonography seems to be guided by suspicion on imaging, both with regard to the technique and subsequent aspiration of lymph nodes, and should therefore be classified as selective sampling [13]. For mediastinoscopy, minimal requirements to ensure a high negative predictive value have been defined [2]. Yet, the yield is dependent on the experience of the surgeon and the thoroughness of the mediastinal assessment, as illustrated when more extensive surgical procedures are performed, which demonstrate an even higher NPV [14,15].

However, these procedures are not widely used. In this series on average 4 mediastinal lymph node stations were biopsied. When a comparable examination of the mediastinum is performed by endosonography, equivalent reliability may be achieved [10,16]. However, performance of endosonography is not only dependent of the operator, but also strongly influenced by the condition, and, in particular, comfort of the patient. From this aspect, performance under general anaesthesia creates ideal conditions for endosonography, in contrast to conscious sedation, allowing for a more complete examination of the mediastinum, but diminishes one of the advantages of endosonography in an outdoor clinical setting. Furthermore, in our study the false negative result of endosonography is not only explained by an incomplete examination, since in 7 patients, lymph nodes also aspirated during endosonography appeared positive by mediastinoscopy and in another 6 patients by thoracotomy.

Thus, thirdly, representativeness of the yield of endosonography is an important aspect in determining the need for a mediastinoscopy. A representative sample is supposed to contain lymphocytes in various stages of differentiation, and is a prerequisite for a reliable procedure [17], but also when this criterion was met we found metastases in aspirated lymph node stations in 9 out of 28 patients with a false negative endosonography. This indicates a sampling error, probably as a result of

aspiration of a negative lymph node in an otherwise positive lymph node station, or even negative lymphoid tissue in a positive lymph node due to micrometastases. Furthermore, also by pathologic assessment micrometastases may be missed in a representative aspirate. The same is possible for a mediastinoscopy, but less likely, since the yield of a mediastinoscopy in terms of the amount of tissue, if well performed, is huge in comparison to the yield of endosonography and pathologic assessment is based on histology instead of cytology. For instance, the chance to detect isolated tumor cells in, or micrometastases near the marginal sinus of a lymph node, is higher in a histological biopsy than in a FNA specimen.

Finally, in assessing the need for an additional mediastinoscopy, the consequence of minimal mediastinal disease is another consideration. Since patients with mediastinal lymph node involvement form a heterogeneous group, using endosonography to rule out multilevel or bulky N2 disease and accept the possibility of minimal residual disease only found by thoracotomy, may be an option. Surgical treatment, then followed by adjuvant chemo- and radiotherapy in case of unexpected minimal N2 disease, can be an alternative to induction- or even definitive chemo-radiotherapy for these patients with minimal mediastinal involvement.

The retrospective nature of this study is a limitation when comparing the potential reliability of endosonography and mediastinoscopy in mediastinal nodal staging, but makes it possible to compare the performance of both techniques in daily practice. Considering additional diagnostic procedures in the work-up of patients with lung cancer, the burden for the patient should be balanced against the benefit, therefore local expertise in- and performance of each technique are important aspects to take into account.

In conclusion, in patients with non-small cell lung cancer and an indication for mediastinal staging, performing a cervical mediastinoscopy after a negative result of endosonography reduced the number of futile thoracotomies by 50%. Overall, on average 8.8 patients had to undergo an additional mediastinoscopy to find one false negative result of endosonography, but when only patients with suspicious mediastinal lymph nodes on FDG-PET are taken into account this NNT diminished to 6.1 patients.

Thus, in patients with a high probability of mediastinal metastases, a cervical mediastinoscopy should not be omitted after a negative result of endosonography, not even when the aspirate seems representative, based on the presence of an adequate number- and maturation of lymphocytes.

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Chapter 4

Completeness of lung cancer surgery: is mediastinal dissection common practice?

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Abstract

Objectives: In patients with early stage non-small cell lung cancer surgery offers the best chance of cure when a complete resection, including mediastinal lymph node dissection, is performed. A definition for complete resection and guidelines for intraoperative lymph node staging have been published, but it is unclear whether these guidelines are followed in daily practice.

The goal of this study was to evaluate the extent of mediastinal lymph node dissection routinely performed during lung cancer surgery, and hereby the completeness of resection according to the guidelines of the European Society of Thoracic Surgery (ESTS) for intraoperative lymph node staging.

Methods: In a retrospective cohort study the extent of mediastinal lymph node dissection was evaluated in 216 patients who underwent surgery for lung cancer with a curative intent in 4 different hospitals, 3 community hospitals and one university hospital. Data regarding clinical staging, the type of resection and extent of lymph node dissection were collected from both the patient's medical record and the surgical- and pathology report. Based on histology, location and side of the primary tumor, the extent of mediastinal dissection was compared to the ESTS guidelines for intraoperative lymph node staging.

Results: According to the surgical report interlobar- and hilar lymph nodes were dissected in one third of patients. A mediastinal lymph node exploration was performed in 75% of patients, however subcarinal lymph nodes were dissected in less than 50% of patients and at least 3 mediastinal lymph node stations were investigated in 36% of patients. In 35% of the mediastinal stations explored, lymph nodes were sampled instead of a complete dissection of the entire station. A complete lymph node dissection according to the guidelines of the ESTS was performed in 4% of patients. Despite an incomplete dissection unexpected mediastinal lymph nodes were found in 5% of patients.

Conclusion: In daily practice, the intended curative resection for lung cancer cannot be considered complete in the majority of patients, because of an incomplete lymph node dissection according to the current guidelines of the ESTS.

Introduction

In early stage non-small cell lung cancer (NSCLC), surgery offers the best chance of cure when a complete resection is performed and a 5-year survival rate up to 75 % may be expected [1].

The completeness of a resection is based on both pathological assessment of the bronchial-, vascular- and parenchymal resection margin of the surgical specimen, and the extent of a mediastinal lymph node dissection [2].

Already in the 6th , but also in the 7th edition of the TNM-system for staging lung cancer [3,1], a different survival was observed for patients after clinical- versus pathologic staging, favouring the second in the same stage group. Thus, although progress has been made in pre-operative staging by the use of FDG-PET and EUS- or EBUS-FNA eventually followed by mediastinoscopy, a dissection of both peripheral-, hilar- and mediastinal lymph nodes is mandatory for accurate staging and optimizing therapy [4]. However, in a large survey of more than 11.000 NSCLC patients treated surgically, only 57.8% of patients underwent any kind of mediastinal lymph node dissection [5]. Furthermore, the extent, with regard to the number of mediastinal stations explored, remains unclear and different techniques were used in removing lymph nodes.

In 2006, guidelines for intraoperative lymph node staging in lung cancer surgery have been published by the European Society of Thoracic Surgery (ESTS) [6], but it is unclear if these guidelines have been implemented in daily practice.

The goal of our study was to evaluate the extent of mediastinal lymph node dissection routinely performed during lung cancer surgery, and hereby the completeness of resection according to the Guidelines of the ESTS for intraoperative lymph node staging.

Materials and methods

In a retrospective cohort study the extent of mediastinal lymph node dissection was evaluated in patients who underwent an intended curative resection for early stage NSCLC. Patients from 4 different hospitals were included, 3 community- and one university hospital. Operations were performed by general surgeons with an additional certification for thoracic surgery, and cardio-thoracic surgeons, each in 2 hospitals, which is representative for the general practice in The Netherlands. In 3 hospitals a training program in thoracic surgery is provided.

All patients who underwent a lung resection for NSCLC in 2007 were extracted from the surgical database of each hospital. Only patients who were judged to be candidates for a curative resection after clinical staging were included in this study.

Data regarding clinical staging by means of CT-scan, FDG-PET, EUS-/EBUS-FNA and mediastinoscopy were collected from the patient's medical record. Mediastinal lymph nodes with a short axis of more than 1 cm on CT-scan were considered enlarged, mediastinal FDG-PET was considered positive if noted by nuclear medicine.

The surgical report was used for collecting data about the type of resection and extent of lymph node dissection. Finally, the pathology report was used to check the presence of lymph nodes in each dissected station, as well as the result of histological assessment.

In patients who had undergone induction chemo-radiotherapy, data concerning restaging were used.

Based on histology, location and side of the primary tumor, the extent of mediastinal dissection was compared to the ESTS guidelines for intraoperative lymph node staging [6]. For a tumor on the right the upper- and lower paratracheal lymph nodes (station 2R and 4R), and visible nodes anterior of the superior caval vein or posterior to the trachea (station 3), are supposed to be resected, as well as the inferior mediastinal lymph nodes, which are located subcarinal (station 7), paraesophageal (station 8) and in the pulmonary ligament (station 9). For a tumor on the left, the same inferior mediastinal lymph nodes should be removed, in addition to the subaortic-, para-aortic- and lower paratracheal lymph nodes (station 5, 6 and 4L). A systematic dissection of all the mediastinal tissue containing lymph nodes is recommended and the highest mediastinal node should be labelled.

In case of a peripheral squamous cell carcinoma, smaller than 3 cm., a lobe-specific lymph node dissection is justified when the interlobar- and hilar lymph nodes appear to contain no metastases. Three mediastinal lymph node stations have to be dissected, depending on the lobar location of the tumor, but always the subcarinal nodes. At least 6 lymph nodes have to be removed.

Since the surgical procedures were performed in 2007, lymph node mapping was performed according to the Mountain-Dresler lymph node classification [7].

Results

In a combined series from 4 hospitals 216 patients underwent an intended complete resection for NSCLC in 2007, representing 14% of all lung cancer resections in the Netherlands in one year.

Clinical staging

Pre-operatively all patients had undergone a CT-scan of the chest, as well as a whole body FDG-PET. By imaging 85 patients (39%) appeared to have suspicious mediastinal lymph nodes: in 25 patients (11%) enlarged mediastinal lymph nodes were seen on

CT-scan only, in 15 patients (7%) at least one mediastinal lymph node station appeared to be positive on FDG-PET without lymph node enlargement on CT, while both modalities were positive in 45 patients (21%). Of all patients with suspicious lymph nodes by imaging, 28 patients underwent EUS- or EBUS-FNA, but these procedures weren't standard of care at that time.

A cervical mediastinoscopy was performed in 84 patients (39%), because of enlarged and/or PET positive mediastinal lymph nodes in 72 patients (33%) and due to a centrally located tumor in 12 patients (6%).

Twenty-four patients had undergone induction chemo-radiotherapy due to positive mediastinal lymph nodes at initial staging.

Surgery

A lobectomy was the standard procedure and was performed in 182 out of 216 patients (84%), in 179 patients by means of a thoracotomy. Three patients underwent a video assisted lobectomy. In 27 patients (13%) a pneumonectomy had to be performed and 7 patients (3%) underwent a sub-lobar resection due to poor pulmonary function: a segmentectomy in 2 patients and a wedge resection in 5 patients.

According to the surgical report, interlobar lymph nodes were dissected in 74 patients (34%) and hilar lymph nodes in 67 patients (31%). Any kind of mediastinal lymph node dissection was performed in 161 patients (75%).

In total 414 mediastinal lymph node stations were explored during surgery in 216 patients, a mean of 1.9 station per patient, ranging from zero to 6. No mediastinal lymph node station at all was dissected in 55 patients, whereas 6 stations were dissected in only 4 patients (Fig. 1). There were clear differences between the participating hospitals, the number of patients without any mediastinal dissection ranged from 3% in one clinic to 44% in another. Accordingly, the mean number of dissected mediastinal lymph node stations per patient ranged from 0.8 to 3.9 per clinic.

However, no difference could be found depending on the surgeon specialty. In 83 patients operated by additionally certified general surgeons the mean yield was 2.0 mediastinal stations dissected per patient, which was comparable to a mean yield of 1.8 mediastinal stations per patient in 133 patients operated by cardio-thoracic surgeons.

Of all 216 patients, according to the ESTS guidelines, a complete lymph node dissection should have been performed in 189 patients: because of a resection on the right in 101 patients and on the left in 88 patients. In 27 patients a peripheral squamous cell carcinoma of less than 3 cm. was present for which a lobe-specific lymph node dissection is thought to be sufficient, in 9 patients on the right and in 18 patients on the left side.

Of patients with a right sided tumor the lower paratracheal lymph nodes were dissected most frequently, in 55 out of 101 patients (54%), followed by the subcarinal

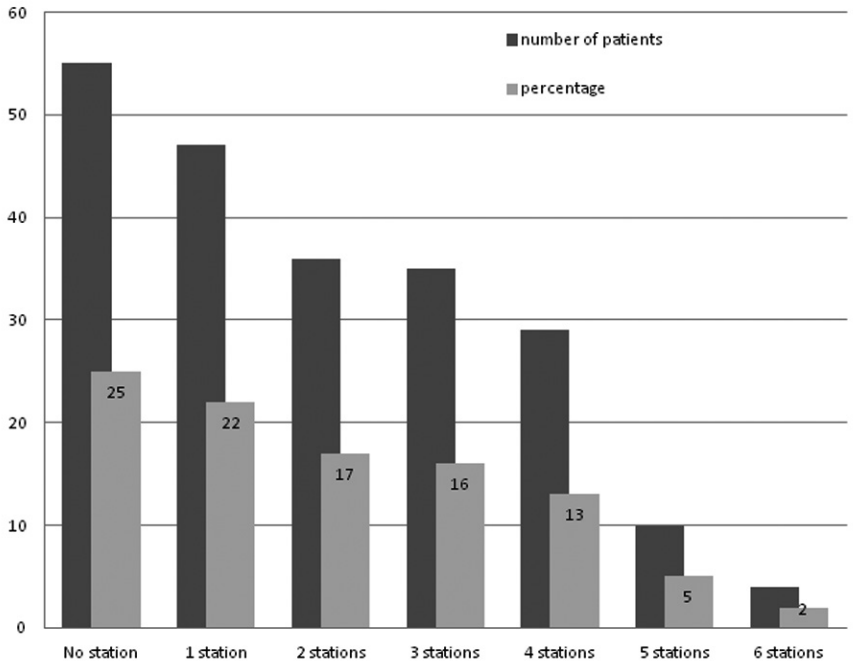

Figure 1. Number of mediastinal lymph node stations* sampled or dissected per patient, n=216.

* according to Mountain-Dresler [7].

lymph nodes, in 48 out of 101 patients (47%) (Fig. 2). Lymph nodes in front of the superior caval vein or behind the trachea were dissected in only one patient. On the left the subaortic nodes were dissected most frequently, in 48 out of 88 patients (54%), followed again by the subcarinal lymph nodes in 33 out of 88 patients (38%) (Fig. 3). The upper paratracheal lymph nodes were dissected in 4 patients. In patients with a lobe specific dissection, the subcarinal lymph nodes were dissected in just more than half of patients, in 5 out of 9 patients (56%) on the right and in 10 out of 18 patients (56%) on the left side (Fig. 4).

Of 85 patients with suspicious mediastinal lymph nodes on CT-scan and/or FDG-PET, no mediastinal dissection was performed in 21 patients (25%).

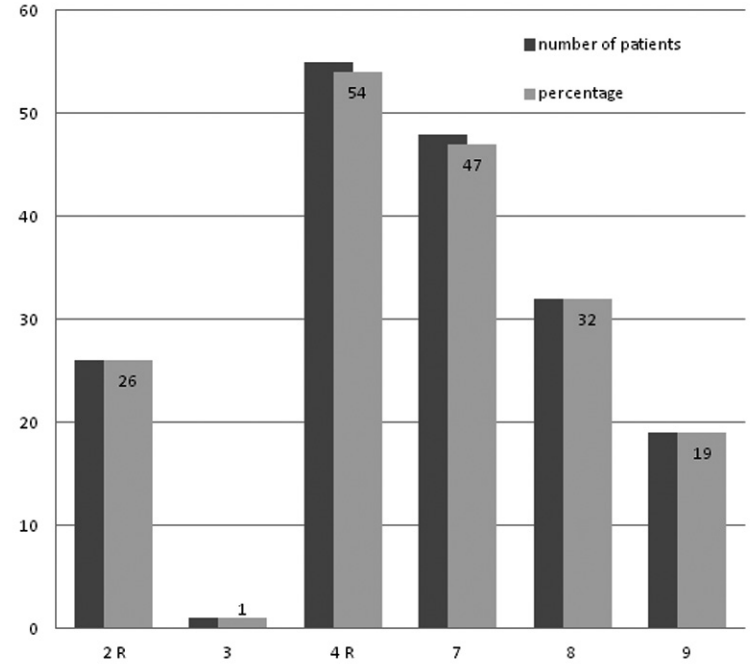

Figure 2. Frequency of dissection per mediastinal lymph node station* in right sided tumors, n=101.

* according to Mountain-Dresler [7], R=Right.

Pathologic assessment

Histological examination of the resected tumors revealed an adenocarcinoma in 117 patients, a squamous cell carcinoma in 79 patients, an undifferentiated large cell carcinoma in 9 patients, a carcinoid in 10 patients and a small cell carcinoma in one patient.

Assessment of the resection margins revealed a microscopic incomplete resection in 5 patients.

In 169 patients (78%) the peripheral, intrapulmonary lymph nodes were described in the pathology report.

With regard to the mediastinal lymph node stations, based on the pathology report no distinction could be made between sampling and dissection, however multiple fragments of lymphatic tissue or an unidentified number of lymph nodes were found in 144 of 414 mediastinal stations, suggesting sampling rather than dissection.

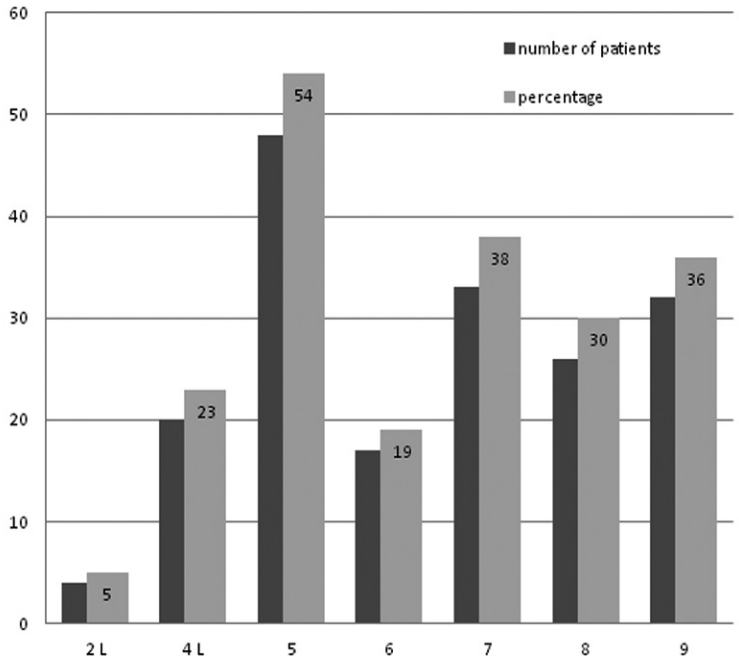

Figure 3. Frequency of dissection per mediastinal lymph node station* in left sided tumors, n=88.

* according to Mountain-Dresler [7], L=Left.

Based on pathologic assessment, 31 patients (14%) were upstaged because of lymph node involvement that was not identified during pre-operative work-up. In 20 patients (9%), clinically staged N0, positive interlobar- or hilar lymph nodes were found and 11 patients (5%) appeared to have unexpected mediastinal metastases. Ultimately, in only 8 patients (4%) a complete lymph node dissection of interlobar-, hilar- and all mediastinal stations according to the recommendations of the ESTS guidelines was performed.

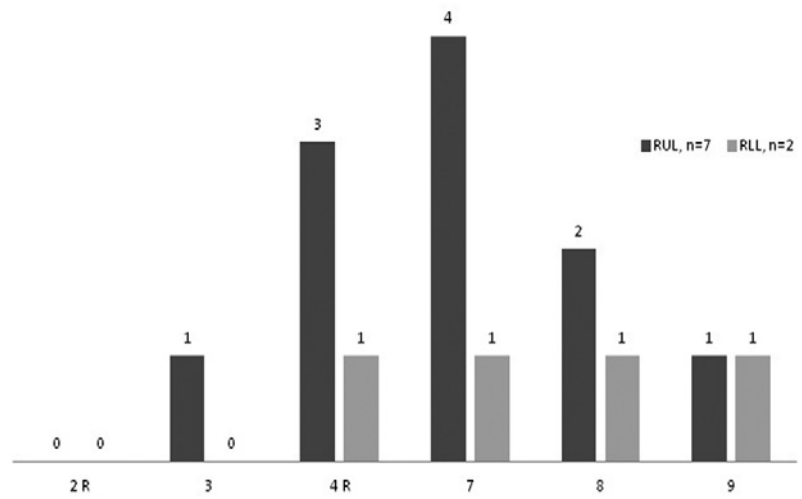

Figure 4a. Frequency of dissection per mediastinal lymph node station*, in case of a right sided, lobe-specific dissection.

* according to Mountain-Dresler [7], R=Right, RUL=Right Upper Lobe, RLL=Right Lower Lobe.

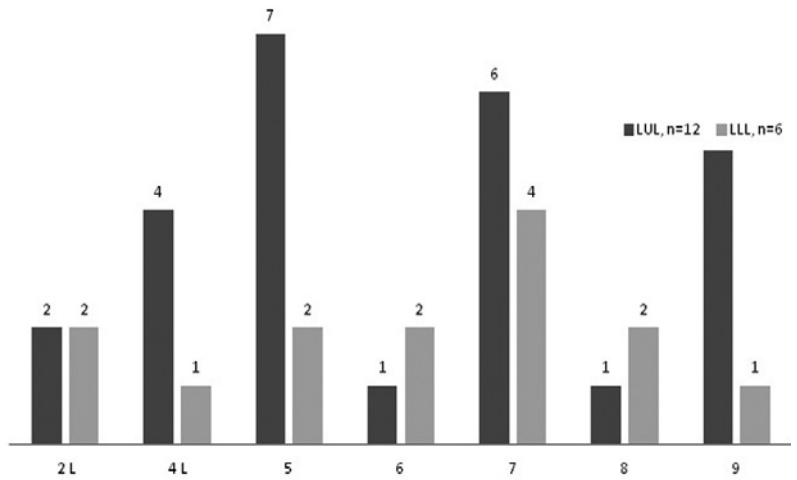

Figure 4b. Frequency of dissection per mediastinal lymph node station*, in case of a left sided, lobe-specific dissection.

* according to Mountain-Dresler [7], L=Left, LUL=Left Upper Lobe, LLL=Left Lower Lobe.

Discussion

In this study, we show that a vast difference exists between a complete mediastinal lymph node dissection as recommended in the current ESTS guidelines and performance in daily practice.

The number of patients that underwent any form of mediastinal lymph node dissection in our study is higher than has been reported in two large surveys concerning surgical care in lung cancer patients [5,8]. Adherence to the guidelines, however, appears far from ideal: in only 4% of patients a complete lymph node dissection was performed.

Preceding the ESTS guidelines a proposed definition of complete resection has been published [2], which has been adopted by the International Union Against Cancer in the 7th edition of the TNM Classification of Malignant Tumors [9]. Based on this definition a resection can be considered complete when only 6 lymph nodes are removed, 3 from mediastinal stations, but always including the subcarinal lymph nodes, and 3 from hilar-, interlobar- or peripheral stations. But even by these criteria the resection in more than 50% of patients in our study was not complete, but should be qualified as “uncertain”, since the subcarinal lymph nodes were not removed in these patients. Moreover, in only 36% of the patients at least 3 mediastinal lymph node stations were explored.

The extent of mediastinal staging is considered a process measure of quality [10], that may be dependent of the surgeon specialty [11]. In contrast to a recently presented study [12], we did not find a different yield of mediastinal dissection between patients operated by general surgeons, with an additional certification for thoracic surgery, and cardio-thoracic surgeons. However, the extent of mediastinal dissection varied considerably between the participating hospitals in this study. Although we didn’t intend to make a comparison, it is illustrative of the controversy that still remains with regard to a mediastinal dissection.

A survival benefit for patients undergoing a complete mediastinal dissection would be the strongest argument in favour of this procedure. Yet, apart from several observational studies [13,14,15], only one randomised controlled trial demonstrates a better prognosis for patients after a systematic mediastinal lymph node dissection as compared to lymph node sampling [16].

In contrast, two other randomised trials [17,18] have been published which did not show a prognostic advantage, but finally a meta-analysis concerning these three studies still reports a survival benefit after a follow-up of 4 years, when a complete dissection was performed [19].

Despite this report, it is questionable whether a survival benefit in the future will ever be proven [4]. Also in the recently published ACOSOG Z0030 trial, a complete dissection of mediastinal lymph nodes did not improve survival in comparison to

systematic sampling, despite an additional yield of mediastinal lymph node metastases of 4% [20,21]. Therefore improving staging should be considered the merit of a lymph node dissection and hereby identifying patients who may benefit from adjuvant therapy.

Clinical staging has already improved over the last decade by the implementation of FDG-PET, and a widespread availability of EUS- and EBUS-FNA will probably lead to a further reduction of futile thoracotomies. Since the yield of a mediastinal dissection, of course, is dependent of the pre-operative evaluation, this may diminish the need for an additional evaluation. But even after precise clinical staging, including mediastinoscopy in case of a negative result of EUS- and/or EBUS-FNA performed in dedicated centres, positive mediastinal lymph nodes can be identified in 7% of patients who have undergone a systematic lymph node dissection [22]. Moreover, in general practice the accuracy of pre-operative evaluation will probably be less than reported by dedicated centres.

In our study all patients underwent FDG-PET in addition to a CT-scan and a mediastinoscopy was performed in 72 out of 85 patients with enlarged and/or PET positive lymph nodes. Despite an incomplete lymph node dissection, positive mediastinal lymph nodes were found in 5 % of patients, emphasizing the need for a complete dissection in every patient.

From the surgical report it remained unclear which criteria were used to perform or omit a mediastinal lymph node dissection in our entire patient cohort, as well as in the group of patients with clinically suspicious lymph nodes. Also the reason to explore a certain lymph node station was rarely described. Of the 75% of patients in whom any mediastinal dissection was performed, on the right side the lower paratracheal lymph nodes were dissected most frequently and on the left side the subaortic lymph nodes, followed on both sides by the subcarinal lymph nodes. The reason for this may be that both the lower paratracheal- and the subaortic lymph nodes are most easily accessible and under direct vision of the surgeon, whereas for the other mediastinal stations additional exploration is needed. Furthermore, the border with adjacent lymph node stations is not always clear during surgery, despite their definition in the latest edition of the current staging manual [9], so that dissected lymph nodes may not always have been labelled as separate stations. For example, the border between the lower- and upper paratracheal lymph nodes on the right and on both sides the border between the pulmonary ligament and paraesophageal lymph nodes can be difficult to identify. Since no differences in survival seem to exist among patients with lymph node metastases to separate stations confined to a single zone [23,24], this may be an argument to define a complete resection based on exploration of mediastinal zones instead of distinct stations.

In the guidelines of the ESTS different techniques are described concerning intraoperative lymph node assessment. In a large part of the patients in our study

lymph node sampling instead of a dissection seems to have been performed, since only lymph node fragments were found by pathology rather than mediastinal fat tissue containing lymph nodes. A lymph node dissection is often considered time consuming and causing additional morbidity, but the impact of both aspects appeared to be modest in the randomized ACOSOG Z0030 trial and not responsible for a prolonged length of stay [25].

The question can be raised whether the participating hospitals in this study are representative for the real world, but patients were included from the 4 largest hospitals from a national cancer registry in the centre and eastern part of our country. In the Netherlands, on average only 25 lung cancer resections are performed per clinic per year, while the number of operations in the participating hospitals ranged from 35 to 72 in one year. Also in the United States the median number of lobectomies for lung cancer performed per year per participant was only 31, according to the Society of Thoracic Surgeons database [8]. Furthermore, 3 out of the 4 hospitals in this study are approved as a training facility, what makes it unlikely to perform worse than average.

In conclusion, despite an exploration of the mediastinal lymph nodes in 75 % of patients who underwent an intended curative resection for lung cancer, based on the current guidelines resection was far from complete in the majority of patients, both with regard to the surgical technique- and the extent of lymph node dissection, as well as the reporting.

Efforts should be made to increase the implementation of guidelines in general practice, to improve the quality of surgical care in lung cancer patients.

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Chapter 5

The clinical value of lymphatic micrometastases in patients with non-small cell lung cancer.

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Abstract

Introduction: In early stage non-small cell lung cancer, presence of lymphatic micrometastases and isolated tumor cells, primarily detected by immunohistochemistry, is suggested to be a prognostic factor. However there is no consensus whether immunohistochemistry should be used routinely in lymph node assessment.

The goal of our study was to determine whether recurrent disease is associated with the presence of lymphatic micrometastases and/or isolated tumor cells, at the time of the lung resection.

Methods: We retrospectively analyzed the prevalence of lymphatic micrometastases and/or isolated tumor cells in 2 groups of patients, who underwent a curative resection for early stage non-small cell lung cancer. Group I had a follow up of 5 years without recurrent disease. Group II consisted of a matched group of patients with recurrent disease. Patients were originally classified as having negative mediastinal lymph nodes. All lymph nodes obtained by mediastinoscopy and thoracotomy were re-examined by serial sectioning and immunohistochemistry.

Results: Micrometastases and/or isolated tumor cells were found in 1 out of 16 patients in group I, which was significantly different from 6 out of 16 patients in group II. (Fischer's Exact test 4.6, p 0.04, risk ratio 2.4). Serial sectioning and immunohistochemistry did not change N-stage for the single patient in group I, in contrast to all 6 patients in group II.

Conclusion: Presence of lymphatic micrometastases and/or isolated tumor cells is associated with distant recurrence in patients with early stage non-small cell lung cancer. We recommend the routine use of serial sectioning and immunohistochemistry in lymph node assessment to improve the accuracy of staging.

Introduction

In patients with non-small cell lung cancer, regional lymph node involvement is a major prognostic factor and, in the absence of distant metastases, assessment is essential to determine the appropriate therapy. In clinical practice nodal assessment is based on CT scan and FDG-PET, to provide anatomic- and metabolic information respectively. Histologic proof of lymph node involvement is preoperatively obtained by endoscopic needle biopsy and/or mediastinoscopy. Moreover, in case of a lung resection, both intrapulmonary- and mediastinal lymph nodes are recommended to be resected, enabling classification in a pathologic stage of the disease [1].

However, despite an intended curative treatment, 25 to 50 % of patients with early stage lung cancer develop a recurrence during follow-up [2], thus suggesting occult disease and inaccurate staging. This occult disease may be represented by lymphatic spread of isolated tumor cells and micrometastases, defined as small clusters of tumor cells of 0.2 mm or less and clusters of 0.2 mm to 2 mm in diameter, respectively [3].

Several reports [4,5,6] have addressed the prognostic significance of lymphatic isolated tumor cells and micrometastases, but controversy remains about their clinical impact [7-11]. If clinically important, detection of isolated tumor cells and micrometastases not only affects staging and therapy, but may also act on the position of invasive diagnostics in the workup of patients with lung cancer, since there is a different yield of lymphatic tissue obtained by different diagnostic tools.

The goal of this study was to determine whether recurrent disease was associated with the presence of lymphatic isolated tumor cells and/or micrometastases at the time of the lung resection.

Patients and methods

Design

To determine the clinical value of lymphatic isolated tumor cells and micrometastases, we analyzed their prevalence in two groups of patients who had undergone a complete resection for early stage non-small cell lung cancer in a retrospective case-control study.

All patients were originally classified as having negative mediastinal lymph nodes, both after clinical work-up and based on the final pathology report after surgery.

Group I consisted of patients without any sign of recurrence during a follow-up of at least 5 years after the operation. This group was matched with a second group of patients, who did develop recurrent disease during follow-up, despite their complete resection (group II).

Patients were matched for age, sex, performance status, weight loss, histology, type of resection and pTNM stage [2]. Patient characteristics are presented in table 1.

Patients were included in this study retrospectively from a surgical data base. Follow-up information was collected from the patient's medical files of the referring pulmonologists.

Table 1. Clinical and pathologic characteristics of patients with and without recurrence after 5 years follow-up (n=32).

	No recurrence, group I (n=16)	**Recurrence**, group II (n=16)
Age		
Mean (range)	64 (54-77)	62 (38-70)
Sex:		
Male	15	13
Female	1	3
ECOG performance status:		
0	1	1
1	15	15
Weight loss*:		
yes	3	4
no	13	12
Histology:		
Squamous cell carcinoma	13	12
Adenocarcinoma	1	4
Large cell carcinoma	2	-
Type of resection:		
Lobectomy	7	6
Pneumonectomy	9	10
Stage (pTNM):		
T1N0	2	1
T2N0	9	9
T2N1	5	6

* >5% in 6 months prior to initial diagnosis.

Surgery

Surgical treatment consisted of (at least) a lobectomy with en bloc resection of the lobar lymph nodes. Dissection of interlobar and hilar lymph nodes was routinely performed, as well as a lobe specific mediastinal lymph node dissection [1]. On average 4.5 mediastinal lymph node stations (range 3-6) per patient were dissected. Surgery was supposed to be complete if the bronchial-, vascular- and pleural resection margins were free, and there was no involvement of the mediastinal lymph nodes.

None of the patients in this study received induction- nor adjuvant chemo- or radiotherapy.

Pathology

Of the patients included in this study first a re-examination of the original haematoxylin and eosin stained slides of both the primary tumor, bronchial resection margin and lymph nodes obtained by mediastinoscopy and thoracotomy was carried out to confirm histology and pathologic stage.

Next, all formalin-fixed and paraffin-embedded lymph nodes were once more sectioned at two levels of 50 and 85 µm deep. At each level a five µm tissue section was taken and hematoxylin-eosin stained for pathologic assessment. Secondly, two five µm tissue sections at levels of 60 and 65 µm deep were taken and immunohistochemically stained with the keratin monoclonal antibodies Cytokeratin pan AE1/AE3 (1:200; Neomarkers, Fremont, CA) and Cytokeratin 8/Cam5.2 (1:20; Becton & Dickinson, Franklin Lakes, NJ) using the standard avidin-biotin-complex (ABC) technique [12]. After the first incubation with the keratin antibodies, a second incubation was performed with horse-anti-mouse biotinylated antibody (Vector laboratories, Burlingame, CA). Subsequently, all attached antibodies were developed using the avidin-biotin-peroxidase method Vectastain, ABC-kit Elite standard (1:100, Vector Laboratories). Finally, all tissue sections were shortly counterstained with hematoxylin. Appropriate negative and positive controls were runned parallel with the staining procedures.

Assessment of these additional slides after immunohistochemistry and reclassification of nodal status was done by a pathologist unaware of a recurrence during follow-up.

Statistics

Based on previous reports [4-9,11] we hypothesized a prevalence of isolated tumor cells and/or micrometastases in our patients of 25 % and intended to demonstrate a different prevalence between the group with- and without recurrent disease of at least 35%. The α (error probability) was set to 0.05. A poweranalysis (with a z-test proportion method for differences between two proportions) revealed that the study population had to consist of two groups of 16 patients each. A Pearson

chi-square test (Fischer's Exact) was used to demonstrate the difference between both groups. A one-tailed significance level of 0.05 was considered significant. Statistical analyses were performed using SPSS software, version 17.0 (SPSS, Inc., Chicago,IL).

Results

Pathologic assesment

In addition to the lobar and interlobar lymph nodes of each patient, 145 mediastinal lymph node stations, with an average of 2.4 lymph nodes per station (range 1-7), in 32 patients were available for re-examination.

Re-assessment of the original haematoxylin and eosin stained slides, to confirm the histologic diagnosis and stage, revealed an overt hilar lymph node metastasis in one patient that was missed at first examination, but no mediastinal lymph node metastases were detected.

After subsequent immunohistochemical analysis additional lymph node metastases were identified in 7 out of 32 patiens (22%).

In group I, consisting of patients without recurrent disease, micrometastases were detected in hilar lymph nodes in only one patient (6%). This patient had already been staged pT2N1, based on direct tumor invasion of an adjacent lymph node.
In group II, patients with recurrent disease, isolated tumor cells and/or micrometastases were identified in 6 patients (38%), which was significantly different from the single patient in group I (Fischer's Exact test 4.6, p 0.04 , risk ratio 2.4).

Influence on stage

For the single patient in group I the pathologic stage remained unchanged.

In group II, initial staging was pT1N0 in 1 patient, pT2N0 in 9 patients and pT2N1 in 6 patients. In 3 out of these 9 patients staged pT2N0, isolated tumor cells and/or micrometastases were identified (33%), in 2 patients in both N1 and N2 lymph nodes, in 1 patient in hilar lymph nodes only.

In 3 out of the 6 patients initially staged pT2N1 positive mediastinal lymph nodes were identified (50%).

Due to serial sectioning and immunohistochemistry 5 out of 6 patients from group II were upstaged: from stage Ib to stage IIIa in 2 patients, from stage Ib to IIb in 1 patient and from stage IIb to IIIa in 2 patients. In the remaining patient from group II, initially staged IIb, the N-stage changed from N1 to N1(i+), since only isolated tumor cells were found in mediastinal lymph nodes, but no micrometastases.

The yield of pathologic re-examination and stage migration observed by serial sectioning and immunohistochemistry are shown in table 2.

Table 2. Stage migration of 7 patients with lymph node involvement detected by serial sectioning and immunohistochemistry.

Patient (study nr.)	Histology	Original p-stage	Yield of re-examination	p-stage after IHC
Group I: no recurrence				
26	Squamous cell	T2N1	micromet. N1	Unch.
Group II: with recurrence				
6	Squamous cell	T2N0	micromet. N1+ N2	T2N2
9	Adeno	T2N1	micromet.+ ITC's N2	T2N2
10	Adeno	T2N1	ITC's N2	T2N1(i+)
14	Squamous cell	T2N0	ITC's N1/ micromet. N2	T2N2
19	Squamous cell	T2N1	micromet. N2	T2N2
27	Adeno	T2N0	micromet. N1	T2N1

IHC = immunohistochemistry; micromet. = micrometastases; ITC's = isolated tumor cells; Unch. = unchanged.

Time to recurrence

For the patients in group II, the time interval from the operation until the first sign of a metastasis ranged from 3 to 48 months, with a mean interval of 12.8 months. The interval tended to be shorter for patients with micrometastases (mean 8.6 months, range 5-16) then for patients without micrometastases (mean 15.4 months, range 3-48), but there was no significant difference.

In all patients with micrometastases the first clinical recurrence was at a distant site.

Discussion

Our study shows that the prevalence of lymphatic micrometastases and isolated tumor cells is significantly increased in patients who underwent a complete resection for non-small cell lung cancer, and developed distant recurrent disease during follow-up, as compared to a matched group of patients without recurrent disease. This demonstrates that minimal lymph node involvement represents tumor dissemination with a significant clinical impact, that is, prediction of tumor recurrence.

Although micrometastases can be detected by using haematoxylin and eosin staining only, detection may be improved by serial sectioning, immunohistochemistry or molecular techniques as (reverse transcriptase-) polymerase chain reaction. Moreover, these methods are essential to detect isolated tumor cells, but thus far none of these methods is routinely used in lymph node assessment in non-small cell

lung cancer. We retrospectively demonstrated the presence of lymphatic micrometastases and isolated tumor cells by pathologic re-examination with serial sectioning and immunohistochemistry at two levels.

The overall prevalence of micrometastases and isolated tumor cells in our patients of 22 % is within the range of expected and comparable to other studies, with a prevalence ranging from 16% to 74% [4-9,11]. Obviously, the prevalence may be influenced by the study design. By definition half of our study population had a favorable outcome, with an expected limited prevalence of occult disease.

Due to serial sectioning and immunohistochemistry, 5 out of 16 patients with recurrent disease appeared to have mediastinal dissemination. Whether or not their prognosis is the same as for patients with overt N2 disease cannot be answered from this study. Minimal N2 disease may represent a favorable subgroup in patients with mediastinal lymph node involvement [13], on the other hand in a recent study by Riquet and colleagues [14] patients with micrometastatic N2 disease appeared to have the same poor outcome as patients with bulky N2 disease, although immunohistochemistry wasn't used to detect these micrometastases. The authors suggest micrometastases to be the consequence of a more aggressive biological behavior, resulting in a worse outcome. Moreover, a relationship of micrometastases with micropapillary adenocarcinoma has been suggested previously [15].

Rather than being a separate entity, micrometastases and isolated tumor cells may also just represent an early phase in the development of lymph node metastases and thus being the result of a more accurate pathologic assessment. This would be in line with a high prevalence of mediastinal micrometastases in patients with overt N1 disease, as found in our study.

The occurrence of any lymphatic dissemination may well be the result of specific biological features of a carcinoma, that can be different from one tumor to another. Detterbeck and colleagues [16] proposed four distinguished patterns of biological behavior of lung cancer, with a separate propensity for local invasion, lymphatic- and hematogenous dissemination and multifocal spread in lung parenchyma. Patients with micrometastastic lymph node involvement without metastases at a distant site, seem to have at least a propensity for lymphatic dissemination, detected in an early phase. Nevertheless, since all patients with lymphatic micrometastases in our study had a first recurrence at a distant site, the propensity for lymphatic dissemination seems to predict the propensity for haematogenous dissemination as well, as has been found by others [17].

In our study in 10 patients with recurrent disease no lymphatic micrometastases were detected. Although some lymphatic micrometastases may be missed, since we performed immunohistochemistry on 2 additional slides of each lymph node only, the propensity for hematogenous dissemination was probably independent from lymphatic dissemination in these patients. Moreover, the time interval until their first

recurrence for these patients was not significantly different from patients with lymphatic micrometastases, but both groups are small and our study was not designed to find a difference between these patient subsets.

If lymphatic micrometastases represent clinically important tumor dissemination, the question raises about the optimal staging and treatment algorithm. When immunohistochemistry is routinely applied in case of a cervical mediastinoscopy, the diagnostic yield is expected to increase [18], resulting in a new subset of patients with minimal mediastinal involvement. Results of surgery as a first line treatment in patients with preoperatively detected N2 involvement are poor [19], so probably induction- or even definitive chemo-radiotherapy will be offered to these patients.

On the other hand, mediastinal staging based on CT, FDG-PET and eventually EUS- or EBUS-FNA is gaining interest with an expected lower yield of lymphatic tissue [20], underestimating the incidence of micrometastases and isolated tumor cells. After a subsequent resection, including mediastinal lymph node dissection, the use of serial sectioning and immunohistochemistry will then increase the incidence of unexpected N2 involvement and hereby the indication for adjuvant therapy. Which of these treatment sequences is most optimal for this subset of patients with microscopic N2 disease is unclear and has to be determined.

Routine use of serial sectioning and immunohistochemistry in lymph node assessment will add extra cost and time to the pathology department, what may hamper general application. Yet, the price of serial sectioning and immunohistochemical staining at 2 levels in our study was only $ 22.50 per lymph node and assessment took about 5 minutes extra. Since we examined an average of 4.5 mediastinal lymph node stations per patient, containing 2.4 lymph nodes, the extra cost with regard to the mediastinal lymph nodes was $ 245.00 and about one hour of time. In comparison, the price of FDG-PET in our institution is about $ 1700.00 and assessment also takes half an hour.

Despite our results, confirmation in a large prospective trial is desirable. Preferably, only patients without any lymph node involvement at all after staining with haematoxylin and eosin are included, so that micrometastases are the only kind of dissemination.

In conclusion, the prevalence of lymphatic micrometastases detected by serial sectioning and immunohistochemistry is higher in non-small cell lung cancer patients with recurrent disease after a complete resection then in patients without recurrent disease, thus representing a kind of tumor dissemination with a clear impact on prognosis. We recommend the routine use of serial sectioning and immunohistochemistry in lymph node assessment of both lymphatic tissue obtained by mediastinoscopy and after thoracotomy, to improve the accuracy of staging. The optimal treatment for patients with minimal mediastinal lymph node involvement still has to be determined.

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Chapter 6

General discussion.

General discussion

When treating patients with lung cancer, staging is the cornerstone of treatment planning. Staging is a step by step approach to determine the extent of the disease. After each step the result has to be assessed and when considering the next step, the potential yield should be balanced against the therapeutic consequences and burden for the patient. Moreover, the staging algorithm changes over time, depending on proceeding knowledge about the biological behaviour of the disease and new techniques that become available. Therefore, a critical evaluation of the merits of each technique used in lung cancer staging is necessary.

An evolving system

Current staging appears to be not yet optimal. Despite improvements in clinical staging of patients with non-small cell lung cancer over the last decades, survival curves based on the pTNM stage exceed the survival curves of the corresponding cTNM stage in every stage, demonstrating potentiality for further amelioration (1). Moreover, 30% to 50% of patients develop recurrent disease within one to two years after an intended curative resection for early stage lung cancer, indicating current understaging, even after pathologic evaluation.

Improving the staging process may be reached by the implementation of new techniques, if they prove to have an additional value with regard to the determination of the disease extent, or in some instances predicting the biological behaviour. Otherwise, new techniques may be able to replace existing ones, when they outperform the current techniques, or reduce the harm to the patient. Furthermore, from a socio-economic point of view, new techniques have to be cost-effective, especially since the worldwide disease burden is large.

Historically, the implementation of cervical mediastinoscopy led to a major improvement in lung cancer staging, by identifying patients who did not benefit from surgical treatment (2). The use of CT scanning is proven to be essential too, because of the anatomic information provided and the detection of multifocal or distant disease, but it appears to have a low accuracy with regard to the mediastinal lymph nodes and thus cannot be a substitute for mediastinoscopy (3). The more recent addition of FDG-PET to the staging armamentarium appears to be valuable in reducing the number of exploratory thoracotomies, mainly by identifying previously undetected distant metastases (4). As a result, the use of FDG-PET appears to be cost-effective (5). Moreover, with regard to mediastinal lymph node staging, FDG-PET, in combination with CT scan, is able to reduce the need for tissue confirmation by mediastinoscopy, namely in patients with PET negative mediastinal lymph nodes without enlargement (6,7). However, as described in chapter 2, the accuracy of FDG-PET is insufficient in cases of centrally located tumours and, especially, positive

hilar lymph nodes, as was confirmed recently in a prediction model for pathologic N2 disease (8).

Improved staging may also be reached by assessing performance of current techniques in daily practice. Techniques, seemingly valuable in dedicated centres, cannot be taken for granted in hospitals with different circumstances. Although mediastinoscopy has proven to be a reliable staging tool (9), this is certainly not the case when the yield of the procedure does not contain lymphatic tissue in the majority of patients (10). Endosonography, as a first line staging tool to obtain tissue samples, is increasingly used. The additional value of cervical mediastinoscopy after a negative result of such a minimally invasive procedure, as studied in chapter 3, should in fact be determined in each hospital, based on the local experience and performance of both techniques. Only then a reliable and (cost-) effective local staging algorithm can be set up.

Evolvement of the staging system is demonstrated by the recent revision of the guidelines for preoperative mediastinal lymph node staging, by the European Society of Thoracic Surgeons (ESTS) (11). In contrast to the previous edition, invasive mediastinal staging should currently only be omitted in FDG-PET positive tumours under 3cm in diameter, peripherally located, with PET-negative hilar and mediastinal lymph nodes without enlargement. In cases of tumour over 3cm, especially in adeno-carcinomas with high FDG uptake, invasive mediastinal staging is recommended, despite a peripheral location and an otherwise negative mediastinum, because of an elevated probability of mediastinal metastases. Furthermore, endosonography has been added as the primary staging tool for tissue confirmation and, if performed completely, with representative samples taken from at least the lower paratracheal lymph nodes on both sides and the subcarinal lymph nodes, a negative result only has to be followed by mediastinoscopy (preferably video-mediastinoscopy) in cases of suspicious lymph nodes on FDG-PET and/or CT scan.

In determining the additional value of a procedure, the potential benefit should be balanced against the burden for the patient, but of course, also therapeutic considerations have to be taken into account. More extensive techniques to examine the mediastinal lymph nodes are available, such as video-assisted mediastinoscopic lymphadenectomy (VAMLA), transcervical extended mediastinal lymphadenectomy (TEMLA) and pre-operative video-assisted thoracoscopic lymphadenectomy, which have a higher accuracy than a classical cervical mediastinoscopy (12,13). On the other hand these procedures are only advantageous as a staging tool, when neo-adjuvant treatments are superior to adjuvant treatments in patients with minimal mediastinal lymph node involvement (14).

Nevertheless, these procedures may be worthwhile as part of an intended curative treatment, comprising both radiotherapy and surgery, and can be regarded as part of the pathologic staging. A major drawback of stereotactic body radiation therapy (SBRT) is the impossibility to assess lymph node involvement and thus the

desirability of adjuvant systemic therapy (15,16). Despite current clinical staging algorithms, the rate of upstaging following systematic lymph node dissection in surgically treated patients remains high (17). Pre-treatment mediastinal lymph-adenectomy by VAMLA or TEMLA in patients undergoing SBRT may then be beneficial.

In patients undergoing surgery, completeness of resection has been defined, also concerning the extent of lymph node dissection. At least three mediastinal- and three intrapulmonary lymph nodes have to be resected, but preferably a lobe specific- or complete systematic lymph node dissection has to be performed. Yet, there is a growing concern about the performance of lymph node dissection, especially in patients undergoing a lobectomy by video-assisted thoracic surgery (VATS). Nodal upstaging in these patients seems reduced, due to omitted or limited lymph node dissection, both intrapulmonary and mediastinally (18,19). Regarding the mediastinal lymph nodes, performing VAMLA or TEMLA as part of the therapeutic procedure may then contribute to improved pathologic staging. Of note, the recorded difference in upstaging may also reflect patient selection, since the observation is based on retrospective studies, because of a lack of randomized trials in this field.

However, not only in VATS, but also in conventional or open surgery, the criteria for a complete resection, with regard to lymph node dissection, are not routinely met, as discussed in chapter 4. First, assessment of current performance, followed by a critical evaluation of future procedures, may lead to improvement of per-operative lymph node staging, at the level of individual surgeons and hospitals (20). The importance of a complete resection has been demonstrated repeatedly, recently even the insufficiency of a lobe-specific lymph node dissection is suggested (21,22).

Pathologic evaluation is often the final step in the staging algorithm, either to prove distant metastatic disease in a tissue sample or loco-regional spread in lymphatic tissue obtained by endosonography or mediastinoscopy. In early-stage lung cancer treated surgically, final pathologic evaluation of the specimen determines completeness of resection and hereby the indication for adjuvant chemo- and/or radiotherapy. A method to improve the accuracy of pathologic lymph node assessment may be the addition of immuno-histochemistry and molecular techniques to conventional examination techniques, to detect micrometastases and isolated tumour cells, which are otherwise overlooked. However, additional use of these techniques is only valuable, if this so called “occult” lymphatic involvement proves to be clinically relevant, even more since these techniques are costly and time consuming. In chapter 5, we demonstrated the negative prognostic impact of “occult” lymphatic dissemination in our series. However, controversy about the relevance is continued, since a meta-analysis, based on reviewing literature from 1995 to 2008, suggested no upstaging as a result of micrometastases and isolated tumour cells (23). In contrast, a recently published report on a large patient cohort confirmed the worse prognosis of patients with occult lymph node involvement (24).

Future staging

The starting-point of staging is determining the anatomical disease extent, since the level of dissemination is corresponding to therapeutic options. This is a mechanical concept, by which a tumour is progressively disseminating, although it may be asymmetrical. A tumour with no- or a limited metastatic potential is treated by a local therapy, whereas proof of dissemination implies a systemic therapy. In addition to determine the therapeutic strategy, the disease extent, as described by T, N and M parameters, is a strong prognostic factor.

In future staging other factors probably also have to be taken into account. Patient related factors like performance status, age and sex, but especially tumour related factors, like cellular receptors and genetic mutations or histological aspects, like tumour vascularisation have an impact on prognosis too. Moreover, these tumour related factors may predict the biological behaviour of the process and offer a chance for therapeutic intervention, although detailed knowledge about the working mechanisms of, for example, mutation targeted therapy and already observed cellular resistance is still lacking (25). However, in fact also the disease extent represents the biological behaviour, as demonstrated for example by a patient with a large squamous cell carcinoma without any sign of metastases, versus a patient with a small undifferentiated carcinoma presenting with extensive bone metastases.

Instead of only anatomical extent, determining the biological behaviour of a tumour, based on a combination of disease extent plus histologic-, molecular-, genetic- and future additional biomarkers, and recorded in a kind of biological passport, will probably give best insight in prognosis and may guide future therapeutic strategies (26). The ultimate goal of staging is defining specific disease characteristics for each individual patient, leading to optimal personalized treatment.

Stage grouping, in the sense that different stages have a different prognosis, but comparable survival rates within one stage group, may come from this biological behaviour, thus representing both the anatomical stage, defined by the TNM system, and tumour biological factors.

Subsequently, future staging algorithms have to comprise methods determining both the anatomical extent of the process and classifying tumour biological behaviour related to specific biological factors. Every aspect in these staging algorithms should be critically evaluated with regard to their accuracy, prognostic value and therapeutic consequences to warrant best quality of care.

Conclusions

When treating patients with lung cancer accurate staging is of paramount importance. Until now, staging aims to determine the disease extent, leading to standardized treatment options for uniform patient groups. Results of treatment become comparable, as well as prognosis for cohorts of patients. Although the outcome of an

individual patient cannot be predicted, it reflects the chance of cure or life expectancy for a single patient.

These assumptions with regard to the benefit of staging can only be fulfilled when staging parameters are clinically relevant and staging methods are reliable, reproducible and uniformly performed, without disproportionate burden for the patient.

Since the staging algorithm is changing over time, depending on emerging techniques and understanding of the disease process, each aspect should be critically evaluated to assess the yield, clinical relevance and therapeutic consequences. Ideally, this evaluation is taking place not only at the level of involved physicians globally, to examine the potential benefit of a staging technique, but also at the level of individual physicians or hospitals, to assess performance and define minimal quality criteria, eventually resulting in local adaptations of the algorithm.

In this thesis we demonstrate that the additional use of FDG-PET improves the quality of staging and reduces the number of invasive staging procedures, although imaging modalities cannot replace the need for mediastinal tissue confirmation in every patient.

This tissue confirmation may be performed by endosonography with the advantage of being minimally invasive, but if negative, a subsequent mediastinoscopy, in patients with suspicious lymph nodes on FDG-PET, is needed to guarantee a high negative predictive value of pre-operative mediastinal lymph node staging.

The gold standard in mediastinal staging consists of a complete systematic lymph node dissection during surgery. Unfortunately only in a minority of patients performance appeared to be in accordance with established guidelines. Quality auditing may improve surgical performance on this aspect.

Finally, assessment of the surgical specimen and lymphatic dissemination is performed by pathologic examination. Use of immunohistochemistry in addition to conventional methods reveals otherwise occult lymph node involvement, which appears to be clinically relevant and has a negative impact on prognosis.

In addition to the above mentioned techniques, which improve the determination of the disease extent, future improvements of the staging system will probably reflect biological properties of a carcinoma, giving opportunity for targeted therapy based on individual disease characteristics.

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Chapter 7

Summary.

Samenvatting.

Summary

Chapter 1.
General introduction and outline of the thesis.

Introduction
Lung cancer is the most common cause of cancer in the global population. Treatment planning of patients with lung cancer depends on an accurate determination of the stage of the disease at the time of presentation. This stage is defined by the anatomical disease extent, determined by a T, N and M descriptor, representing respectively the primary tumour, lymphatic dissemination and the presence or absence of metastatic disease.

These descriptors were introduced by a French surgeon in the 1940's, as a universal method to classify malignant disease, and adopted by the international society involved in cancer research. With regard to lung cancer, a first staging system according to the TNM principles was proposed in the 1970's, but only in 1986 an internationally accepted staging system was published. Despite a revision in 1997, the system was not regarded as representative for all lung cancer patients worldwide.

As a result, the International Association for the Study of Lung Cancer (IASLC) initiated an international lung cancer database, finally containing parameters of over 80,000 patients. Based on these data the T, N and M descriptors were validated once more, as well as the grouping of TNM subsets into distinctive stage groups. Furthermore, the anatomic boundaries for different lymph node stations were clearly defined and made visible on a new lymph node map, accompanying the current, 7^{th} , edition of the staging system. Recently, data for the next edition have already been collected, which is intended to be published in 2016.

Accurate staging is important not only to determine optimal treatment, but also to give insight in prognosis and to compare results of different therapeutic strategies. In staging patients with lung cancer, without any sign of distant metastases, the mediastinal lymph nodes are essential. In this thesis four aspects of mediastinal lymph node staging, in patients with non-small cell lung cancer, are critically evaluated.

Staging methods
In patients with (suspicion of) lung cancer staging starts with clinical evaluation, but imaging by chest radiography and computed tomographic scanning are essential to locate a tumour and receive information about its dimensions and anatomic relationship. Lymph node enlargement, suspicious of metastases, may also be revealed. Additionally an FDG-PET scan is performed, providing metabolic information, to screen for distant metastases, but also lymph node involvement, both intrapulmonary, in the mediastinum and at distant sites.

Next, endoscopy is performed, assessing the central airways and potentially establishing the diagnosis by histology or cytology. Moreover, in the last decade, assessment of the mediastinal- and hilar lymph nodes by endoscopy guided fine needle aspiration has become available, making it possible to obtain tissue samples by a minimally invasive method.

Surgical staging comprises several techniques for mediastinal lymph node assessment during the work-up for an intended resection. Historically, a cervical mediastinoscopy is most commonly performed and is regarded the gold standard in pre-operative mediastinal staging. By this procedure, lymph nodes on both sides of the trachea can be biopsied, as well as the subcarinal lymph nodes, and if performed well a high negative predictive value with regard to metastatic involvement is ensured.

If an intended curative resection is performed, pre-operative staging has to be continued during the operation, since unexpected findings may be encountered and the resection should be complete, not only with regard to the tumour or lung parenchyma, but also with regard to intrapulmonary- and mediastinal lymph nodes. Guidelines regarding completeness of resection have been published.

Finally, pathological examination of tissue samples obtained during the staging process is necessary to screen for metastatic involvement. In case of an intended curative resection, examination of the surgical specimen determines the final pathologic stage.

Aim of the thesis

Determining the optimal treatment for each individual patient with non-small cell lung cancer, is the main goal of staging. When the staging process does not reveal distant metastases, treatment planning depends on mediastinal lymph node involvement. Techniques used in mediastinal staging change over time. The aim of this thesis is to examine the role and performance of four techniques currently used in mediastinal lymph node staging.

Chapter 2.

FDG-PET in staging lung cancer. How does it change the algorythm?

Since ^{18}FluoroDeoxyGlucose-Positron Emission Tomographic (FDG-PET) scanning is based on the increased glucose uptake by malignant cells, incorporation of FDG-PET into the work-up of patients with lung cancer provides metabolic information, complimentary to the anatomic information provided by CT scanning.

FDG-PET is therefore used to detect both extrathoracic metastases and lymph node metastases, potentially reducing the need for invasive mediastinal lymph node staging, because of a high negative predictive value with regard to lymph node involvement.

We performed a study to assess the additional value of FDG-PET in detecting extra- thoracic metastases and to compare the accuracy in mediastinal lymph node staging of FDG-PET to cervical mediastinoscopy, in patients with non-small cell lung cancer.

Analysis of 72 consecutive patients revealed unexpected distant metastases in 15 % of patients, detected by FDG-PET. In mediastinal lymph node staging, cervical mediastinoscopy proved to be more accurate than FDG-PET, especially in patients with positive intrapulmonary lymph nodes and a centrally located primary tumour. In these patients, the result of FDG-PET is hampered by the difficulty to distinguish involved mediastinal lymph nodes from activity in the adjacent primary tumour or positive intrapulmonary lymph nodes. Furthermore, a minimal tumour load is below the detection border of any imaging technique. However, in patients with a peripheral tumour without lymph node involvement FDG-PET proved to be accurate.

We concluded that addition of FDG-PET to the work-up of patients with lung cancer reduces the need for invasive mediastinal staging and prevents futile thoracotomies, but a cervical mediastinoscopy should not be omitted in patients with a centrally located tumour and/or positive hilar lymph nodes, despite a negative mediastinal result on FDG-PET.

Chapter 3.

Mediastinal staging in daily practice: endosonography, followed by cervical mediastinoscopy. Do we really need both?

In the last decade both esophageal ultrasound-guided fine needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) have emerged as minimal invasive techniques in mediastinal lymph node staging. After a negative result, an additional mediastinoscopy is currently recommended, but in daily practice a second procedure is often regarded as unnecessary.

We studied the additional value of a cervical mediastinoscopy, after a negative result of endosonography, in routine clinical practice.

A retrospective cohort of 147 patients was analyzed. When considering cervical mediastinoscopy as the gold standard, the negative predictive value of endosonography was 88.7%, resulting in almost nine patients who had to undergo an additional mediastinoscopy to find one false negative result of endosonography. For patients with FDG-PET positive mediastinal lymph nodes, this number needed to treat was reduced to just over six patients. Overall, by performing a subsequent mediastinoscopy, a futile thoracotomy was prevented in 50% of patients. Moreover, a representative lymph node aspirate by endosonography, containing adequate numbers of lymphocytes, did not exclude metastases.

In conclusion, in patients with a high probability of mediastinal metastases, based on imaging, and negative endosonography, cervical mediastinoscopy should not be omitted, not even when the aspirate seems representative.

Chapter 4.

Completeness of lung cancer surgery: is mediastinal dissection common practice?

Since no pre-operative staging method is able to guarantee the absence of mediastinal lymph node metastases in patients undergoing an intended curative resection, a systematic lymph node dissection should be performed. Guidelines for intra-operative lymph node staging have been published, but it is unclear whether these guidelines are followed in daily practice.

We performed a quality assessment by evaluating the extent of mediastinal lymph node dissection routinely performed during lung cancer surgery, and hereby the completeness of resection according to the guidelines of the European Society of Thoracic Surgeons (ESTS) for intra-operative lymph node staging.

Data of 216 patients who underwent surgery for lung cancer with a curative intent, in four different hospitals, three community hospitals and one university hospital, were evaluated.

According to the surgical report interlobar- and hilar lymph nodes were dissected in one third of patients. A mediastinal lymph node exploration was performed in 75% of patients, however subcarinal lymph nodes were dissected in less than 50% of patients and at least three mediastinal lymph node stations were investigated in 36% of patients. In 35% of the mediastinal stations explored, lymph nodes were sampled instead of performing a complete dissection of the entire station.

A complete lymph node dissection, according to the guidelines of the ESTS, was performed in only 4% of patients. Despite an incomplete dissection unexpected mediastinal lymph nodes were found in 5% of patients.

Thus, in daily practice, the intended curative resection for lung cancer cannot be considered complete in the majority of patients, because of an incomplete lymph node dissection according to the current guidelines of the ESTS.

Chapter 5.

The clinical value of lymphatic micrometastases in patients with non-small cell lung cancer.

In patients with non-small cell lung cancer, regional lymph node involvement is a major prognostic factor and accurate assessment is essential to determine the appropriate therapy. However, there is no consensus whether micrometastases and isolated tumour cells, primarily detected by immunohistochemistry in addition to conventional pathologic assessment, have a clinical impact.

To determine whether recurrent disease is associated with the presence of lymphatic micrometastases and/or isolated tumour cells at the time of the lung resection, we retrospectively analyzed their prevalence in two groups of patients, who had undergone a curative resection for early stage non-small cell lung cancer.

The first group had a follow-up of five years without recurrent disease. This group was matched on seven parameters with a second group of patients with recurrent disease during follow-up. All patients were originally classified as having negative mediastinal lymph nodes.

Lymphatic micrometastases and/or isolated tumour cells were found in one out of 16 patients in the first group, which was significantly different from six out of 16 patients in the second group.

We concluded that the presence of lymphatic micrometastases and/or isolated tumor cells was associated with distant recurrence in patients with early stage non-small cell lung cancer. Since this minimal lymph node involvement is easily overlooked during standard pathologic examination, we recommended the routine use of serial sectioning and immunohistochemistry in lymph node assessment to improve the accuracy of staging.

Chapter 6.

General discussion.

Accurate staging, crucial in treatment planning, is a step by step approach to determine the disease extent. The staging process has changed over time, but is not yet optimal. Further improvements may be reached by the additional use of new techniques, potentially replacing existing ones. Therefore, a critical evaluation of the merits of techniques used in lung cancer staging is necessary to develop an effective staging algorithm.

Historically, the implementation of cervical mediastinoscopy was a major improvement and is still regarded the gold standard in pre-operative mediastinal staging. The addition of CT scan provides essential anatomic information, but its accuracy with regard to lymph node staging is low. However, the combination of FDG-PET with CT scan reduces the need for invasive mediastinal staging, although not in patients with a central tumour or positive hilar lymph nodes, as described in chapter 2.

Invasive mediastinal staging may firstly be performed by endosonography. The additional value of a subsequent mediastinoscopy, as studied in chapter 3, should in fact be determined in each hospital, depending on local experience and performance of both techniques.

More extensive surgical techniques to examine mediastinal lymph nodes, such as VAMLA and TEMLA, may be beneficial as part of curative treatment, instead of a

staging tool. In SBRT no lymph node examination is performed; thoracoscopic resections are sometimes criticised for delivering an incomplete mediastinal dissection. Performing VAMLA or TEMLA as part of such therapeutic procedures may contribute to improved pathologic staging.

Also in conventional or open surgery criteria for completeness of resection, with regard to lymph node dissection, are not routinely met, as described in chapter 4. Quality auditing on the level of individual surgeons and hospitals may improve performance on this aspect.

Pathologic evaluation is often the final step in the staging algorithm. If micro-metastases and isolated tumour cells are clinically relevant, the accuracy of pathologic lymph node assessment may be improved by the addition of immuno-histochemistry and molecular techniques to conventional examination techniques. In chapter 5, we demonstrate the negative prognostic impact of “occult” lymphatic dissemination in our series. However, controversy about the relevance continues, since conflicting data are published.

Future staging will probably not only reflect the anatomical disease extent, but also tumour specific biomarkers, predicting the biological behaviour of a tumour, will have to be taken into account. Defining specific disease characteristics for each individual patient, will be the ultimate goal of staging, leading to optimal personalized treatment. Techniques used in future staging algorithms should be critically evaluated with regard to their accuracy, prognostic value and therapeutic consequences to warrant best quality of care.

Conclusions

In this thesis we demonstrate that the additional use of FDG-PET improves the quality of staging, although imaging modalities cannot replace the need for mediastinal tissue confirmation in every patient.

This tissue confirmation may be performed by endosonography, but if negative, a subsequent mediastinoscopy, in patients with suspicious lymph nodes on FDG-PET, remains indicated.

The gold standard in mediastinal staging consists of a complete systematic lymph node dissection during surgical treatment, unfortunately only in a minority of patients performance was in accordance with established guidelines.

Finally, use of immunohistochemistry in addition to conventional pathologic assessment, reveals otherwise occult lymph node involvement, which is clinically relevant and has a negative impact on prognosis.

Samenvatting

Hoofdstuk 1.
Algemene inleiding en opbouw van het proefschrift.

Inleiding
Longkanker is wereldwijd de meest voorkomende vorm van kanker. Voor de behandeling van patiënten met longkanker is een nauwkeurige bepaling van het ziekte stadium op het moment van presentatie noodzakelijk. Dit stadium is gedefinieerd als de anatomische uitbreiding van de ziekte en wordt bepaald door een T, N en M parameter, die respectievelijk de tumor, lymfeklier uitzaaiingen ofwel metastasen en de aan- of afwezigheid van metastasen op afstand vertegenwoordigen.

Deze parameters werden in de jaren ’40 van de vorige eeuw geïntroduceerd door een Franse chirurg, als een universele methode om kwaadaardige ziekten te classificeren en werden overgenomen door de internationale gemeenschap betrokken bij kanker onderzoek. Het eerste stadiërings-systeem voor longkanker, gebaseerd op het TNM principe, werd geïntroduceerd in de jaren ’70, maar pas in 1986 werd een internationaal geaccepteerd systeem gepubliceerd. Ondanks een revisie in 1997 werd dit systeem echter niet als representatief beschouwd voor all long kanker patiënten wereldwijd.

Als gevolg hiervan werd door de “International Association for the Study of Lung Cancer” (IASLC) een internationale longkanker database ontwikkeld, waarin de gegevens van meer dan 80.000 patiënten werden opgenomen. Op grond van deze data werden de T, N en M parameters opnieuw gevalideerd, evenals de groepering van TNM combinaties in verschillende, prognostische, stadium groepen. Bovendien werden de anatomische grenzen voor alle lymfeklier stations duidelijk vastgesteld en weergegeven op een nieuwe lymfeklier kaart, die de huidige, zevende, editie van het stadiërings-systeem begeleidt. Recent zijn de data voor de volgende editie al verzameld, die naar verwachting in 2016 wordt gepubliceerd.

Nauwkeurige stadiëring is niet alleen van belang om de juiste behandeling te bepalen, maar ook om inzicht in de prognose te geven en de resultaten van verschillende behandelingen te vergelijken. Bij het stadiëren van patiënten met longkanker, zonder aanwijzingen voor metastasen op afstand, zijn de lymfeklieren in het mediastinum cruciaal. In dit proefschrift worden vier aspecten van mediastinale lymfeklier stadiëring, bij patienten met niet-kleincellig longkanker, kritisch geëvalueerd.

Stadiërings methoden
De stadiëring van patiënten met (de verdenking op) longkanker begint bij de klinische beoordeling, maar een röntgen foto van de borst en een CT scan zijn essentieel om een tumor te lokaliseren en geïnformeerd te zijn over de afmetingen en anatomische

relaties. Bovendien kunnen vergrote lymfeklieren, verdacht voor metastasen, worden gevonden.

Aanvullend wordt een zogenaamde FDG-PET scan verricht, die metabole informatie levert, waarmee niet alleen metastasen op afstand, maar ook lymfeklier metastasen, zowel in de longen, in het mediastinum, als elders in het lichaam gelegen, kunnen worden opgespoord.

Vervolgens wordt endoscopisch onderzoek verricht, waarmee de centrale luchtwegen kunnen worden beoordeeld en mogelijk de diagnose kan worden vastgesteld. Bovendien is de laatste jaren beoordeling van de mediastinale- en hilaire lymfeklieren door middel van endoscopische naald aspiratie mogelijk geworden, waarbij op een minimaal invasieve wijze weefsel biopten verkregen kunnen worden.

Chirurgische stadiëring omvat verschillende technieken ter beoordeling van de mediastinale lymfeklieren die gebruikt kunnen worden tijdens de opwerking naar een operatie. Historisch wordt een cervicale mediastinoscopie het meest verricht en wordt beschouwd als de gouden standaard in de pre-operatieve beoordeling van het mediastinum. Door middel van deze ingreep kunnen lymfeklieren aan beide zijden van de trachea en tussen beide hoofdbronchi worden gebiopteerd en, mits goed uitgevoerd, heeft deze procedure een hoge negatief voorspellende waarde ten aanzien van mediastinale lymfeklier metastasen.

Wanneer een in opzet curatieve resectie wordt verricht, hoort de pre-operatieve stadiëring tijdens de operatie te worden voortgezet, enerzijds omdat onverwachte afwijkingen kunnen worden aangetroffen, anderzijds omdat een volledige resectie moet worden verricht, niet alleen met betrekking tot de tumor en het longweefsel, maar ook op het niveau van de lymfeklieren. Richtlijnen met betrekking tot de volledigheid van een resectie zijn gepubliceerd.

Tenslotte is pathologische beoordeling van weefsel biopten, verkregen tijdens het stadiëringsproces, noodzakelijk om de diagnose en eventuele metastasen aan te tonen. In geval van een operatie wordt het uiteindelijke (pathologische) stadium vastgesteld na beoordeling van het chirurgische preparaat.

Doel van het proefschrift

Het bepalen van de beste behandeling voor elke patiënt met niet-kleincellig longkanker, is het belangrijkste doel van stadiëren. Wanneer het stadiëringsproces geen metastasen op afstand aan het licht brengt, hangt het type behandeling af van de mediastinale lymfeklieren.

In de loop van de tijd zijn verschillende technieken gebruikt bij deze mediastinale stadiëring.

Dit proefschrift heeft als doel de rol en uitvoering van vier technieken, momenteel in gebruik bij mediastinale lymfeklier stadiëring, te onderzoeken.

Hoofdstuk 2.

FDG-PET ter stadiëring van longkanker. Wat verandert er aan het stadiërings-algoritme?

Omdat een ^{18}FluoroDeoxyGlucose-Positron Emissie Tomographie (FDG-PET) scan is gebaseerd op de verhoogde glucose opname door kwaadaardige cellen, levert het gebruik van FDG-PET tijdens de opwerking van patiënten met longkanker metabole informatie, in aanvulling op de anatomische informatie verkregen door een CT scan. FDG-PET wordt daarom gebruikt om zowel metastasen op afstand, als lymfeklier metastasen op te sporen, waarmee de noodzaak tot invasieve mediastinale lymfeklier stadiëring mogelijk wordt gereduceerd, vanwege een hoge negatief voorspellende waarde ten aanzien van lymfeklier metastasen.

We hebben een studie verricht om de toegevoegde waarde te bepalen van FDG-PET bij de detectie van metastasen op afstand, maar ook om de betrouwbaarheid ten aanzien van mediastinale lymfeklier metastasen te vergelijken van FDG-PET ten opzichte van cervicale mediastinoscopie bij patiënten met longkanker.

Het gebruik van FDG-PET bij 72 opeenvolgende patiënten, bracht bij 15% onverwachte metastasen op afstand aan het licht. Ten aanzien van mediastinale lymfeklier metastasen bleek cervicale mediastinoscopie betrouwbaarder dan FDG-PET, met name bij patiënten met positieve klieren gelegen in de long en/of een centraal gelegen tumor. Bij deze patiënten wordt het resultaat van FDG-PET beperkt door de moeilijkheid om mediastinale klier metastasen te onderscheiden ten opzichte van de tumor zelf, dan wel in de long gelegen positieve klieren. Bovendien kan de grootte van de klier metastase onder de detectie grens van deze techniek vallen. Echter bij patiënten met een perifeer gelegen tumor zonder verdenking op klier metastasen bleek FDG-PET zeer betrouwbaar.

We concludeerden dat het aanvullend gebruik van FDG-PET tijdens de opwerking van patiënten met longkanker de noodzaak van invasieve mediastinale stadiëring vermindert en nutteloze operaties voorkomt, maar een cervicale mediastinoscopie kan niet achterwege gelaten worden bij patiënten met een centraal gelegen tumor en/of positieve klieren aan de long basis, ondanks een negatieve mediastinale FDG-PET.

Hoofdstuk 3.

Mediastinale stadiëring in de dagelijkse praktijk: endosonographie gevolgd door cervicale mediastinoscopie. Zijn beiden nodig?

Tijdens het laatste decennium hebben zowel endoscopische naald aspiratie vanuit de slokdarm als vanuit de luchtwegen zich ontwikkeld als een minimaal invasieve methode voor mediastinale lymfeklier stadiëring. In geval van een negatief resultaat,

wordt momenteel een mediastinoscopie aanbevolen, maar in de dagelijkse praktijk wordt deze tweede procedure vaak als overbodig gezien.

We bestudeerden de aanvullende waarde van een cervicale mediastinoscopie, na een negatief resultaat van endosonographie, in de dagelijkse klinische praktijk.

De resultaten van 147 patiënten werden geanalyseerd. Wanneer cervicale mediastinoscopie wordt beschouwd als de gouden standaard, bleek de negatief voorspellende waarde van endosonographie 89%, wat betekent dat bijna 9 patiënten een aanvullende mediastinoscopie moesten ondergaan om 1 vals negatieve resultaat van endosonographie aan te tonen. Echter voor patiënten met FDG-PET positieve mediastinale lymfeklieren was dit aantal slechts 6 patiënten. In de gehele groep kon, door het verrichten van een aanvullende mediastinoscopie, een nutteloze thoracotomie worden voorkomen bij 50% van de patiënten. Bovendien bleek een representatieve endoscopische lymfeklier punctie, die voldoende aantallen lymfeklieren bevat, een metastase toch niet uit te sluiten.

Concluderend, kan bij patiënten met een grote kans op mediastinale metastasen, gebaseerd op beeldvorming, en een negatief resultaat van endosonographie, een aanvullende cervicale mediastinoscopie niet achterwege worden gelaten, zelfs niet wanneer de punctie representatief blijkt.

Hoofdstuk 4.

Volledigheid van long kanker chirurgie: is een mediastinale dissectie standaard zorg?

Omdat geen enkele preoperatieve stadiëringsmethode de afwezigheid garandeert van mediastinale lymfeklier metastasen bij patiënten die een in opzet curatieve operatie ondergaan, hoort een systematische lymfeklier dissectie te worden verricht. Richtlijnen aangaande intra-operatieve lymfeklier stadiëring zijn gepubliceerd, het is echter onduidelijk of deze richtlijnen in de praktijk ook worden gevolgd.

We verrichtten een kwaliteit beoordeling, door middel van evaluatie van de mate van mediastinale lymfeklier dissectie, zoals routinematig uitgevoerd tijdens longkanker chirurgie, en hiermee de volledigheid van de operatie volgens de richtlijnen voor intra-operatieve lymfeklier stadiëring van de European Society of Thoracic Surgeons (ESTS).

De gegevens van 216 patiënten, die een in opzet curatieve operatie hadden ondergaan in 4 verschillende ziekenhuizen, 3 algemene ziekenhuizen en 1 academisch ziekenhuis, werden geëvalueerd. Volgens het operatie verslag werden interlobaire en hilaire lymfeklieren uitgeprepareerd bij een derde van de patiënten. Onderzoek naar mediastinale lymfeklieren werd verricht bij 75% van de patiënten, echter subcarinale lymfeklieren werden uitgenomen bij minder dan 50% van de patiënten en tenminste 3 mediastinale lymfeklier stations werden onderzocht bij 36% van de patiënten.

Bij 35% van de onderzochte mediastinale stations werden willekeurige delen van lymfeklieren uitgenomen, in plaats van een volledige dissectie van het hele station.

Een volledige lymfeklier dissectie, volgens de richtlijnen van de ESTS, werd slechts verricht bij 4% van de patiënten. Ondanks een onvolledige dissectie werden bij 5% van de patiënten onverwacht mediastinale lymfeklieren gevonden.

Dus, in de dagelijkse praktijk kan de in opzet curatieve resectie voor longkanker bij de meerderheid van de patiënten niet als volledig worden beschouwd, vanwege een onvolledige lymfeklier dissectie volgens de huidige richtlijnen van de ESTS.

Hoofdstuk 5.

De klinische waarde van lymfeklier micrometastasen bij patiënten met niet-kleincellig longkanker.

Bij patiënten met niet-kleincellig longkanker is betrokkenheid van de regionale lymfeklieren een belangrijke prognostische factor en een nauwgezette beoordeling is essentieel om de meest geschikte therapie te bepalen. Echter, er bestaat geen consensus over het klinisch belang van micrometastasen en geïsoleerde tumor cellen, die met name worden gevonden door middel van immunohistochemie, in aanvulling op conventionele pathologische beoordeling.

Om te bepalen of terugkerende ziekte is geassocieerd met de aanwezigheid van micrometastasen en/of geïsoleerde tumor cellen in de lymfeklieren ten tijde van de long resectie, hebben we hun voorkomen geanalyseerd bij 2 groepen patiënten, die een in opzet curatieve operatie voor een vroeg stadium van long kanker hadden ondergaan.

De eerste groep had geen terugkerende ziekte gedurende 5 jaar na de operatie. De tweede groep patiënten was identiek aan de eerste groep op 7 parameters, maar ontwikkelde wel terugkerende ziekte tijdens de jaren na de operatie. Patiënten in beide groepen hadden aanvankelijk geen gediagnosticeerde lymfeklier metastasen. Micrometastasen en/of geïsoleerde tumor cellen in de lymfeklieren werden na herbeoordeling gevonden bij 1 van de 16 patiënten uit de eerste groep, wat significant afwijkend was van 6 van de 16 patiënten uit de tweede groep.

We concludeerden dat de aanwezigheid van micrometastasen en/of geïsoleerde tumor cellen in de lymfeklieren was geassocieerd met terugkerende ziekte bij patiënten met een vroeg stadium niet-kleincellig longkanker. Omdat deze minimale lymfeklier betrokkenheid tijdens standaard pathologische beoordeling makkelijk over het hoofd wordt gezien, bevelen wij het routinematig gebruik van meerdere coupes en immunohistochemie aan bij de beoordeling van lymfeklieren, om de nauwkeurigheid van stadiëring te verbeteren.

Hoofdstuk 6.

Algemene discussie.

Nauwkeurige stadiëring, cruciaal bij de behandel planning, is een stap voor stap benadering om de ziekte verspreiding vast te stellen. Het stadiëringsproces verandert in de tijd, maar is nog niet optimaal. Verdere verbetering kan worden bereikt door het aanvullend gebruik van nieuwe technieken, eventueel ter vervanging van bestaande technieken. Daarom is een kritische evaluatie van de waarde van de huidige technieken van belang om een doelmatig stadiërings algoritme te ontwikkelen.

Historisch was de implementatie van een cervicale mediastinoscopie een belangrijke verbetering en wordt nog steeds beschouwd als de gouden standaard wat betreft de pre-operatieve mediastinale stadiëring. De toevoeging van een CT scan levert essentiële anatomische informatie, maar de betrouwbaarheid ten aanzien van mediastinale lymfeklieren is laag. Echter de combinatie van FDG-PET en CT scan reduceert de noodzaak van invasieve mediastinale stadiëring, maar niet bij patiënten met een centrale tumor of positieve hilaire lymfeklieren, zoals beschreven in hoofdstuk 2.

Invasieve mediastinale stadiëring kan in eerste instantie worden verricht door middel van endosonographie. De toegevoegde waarde van een aanvullende mediastinoscopie, zoals bestudeerd in hoofdstuk 3, zou eigenlijk bepaald moeten worden in elk ziekenhuis, afhankelijk van de lokale ervaring en uitvoering van beide technieken.

Uitgebreidere chirurgische technieken om de mediastinale lymfeklieren te onderzoeken, zoals VAMLA en TEMLA, kunnen van voordeel zijn als onderdeel van een curatieve behandeling, in plaats van een stadiëring instrument. Bij stereotactische bestraling wordt geen lymfeklier onderzoek verricht; thoracoscopische resecties worden soms bekritiseerd vanwege een onvolledige mediastinale dissectie. Het verrichten van VAMLA of TEMLA als onderdeel van zulke therapeutische procedures kan bijdragen aan een verbeterde pathologische stadiëring.

Bij conventionele of open chirurgie wordt niet routinematig aan de criteria van een volledige resectie, wat betreft de lymfeklieren, voldaan, zoals beschreven in hoofdstuk 4. Kwaliteit beoordeling, zowel op het niveau van individuele chirurgen als op het niveau van ziekenhuizen, kan de uitvoering wat dit betreft verbeteren.

Pathologische beoordeling is vaak de laatste stap in het stadiërings algoritme. Wanneer micrometastasen en geïsoleerde tumor cellen klinisch relevant zijn, kan de nauwkeurigheid van pathologische lymfeklier beoordeling verbeterd worden door de toevoeging van immunohistochemie en moleculaire technieken aan conventionele onderzoek technieken. In hoofdstuk 5 hebben we de negatieve prognostische waarde van “verborgen” lymfeklier metastasen bij onze patiënten aangetoond. Echter er blijft een controverse over de betekenis bestaan, vanwege tegenstrijdige publicaties.

In de toekomst zal stadiëring waarschijnlijk niet alleen de anatomische weergave van ziekte verspreiding zijn, maar ook tumor specifieke biologische kenmerken omvatten, die het biologisch gedrag van een tumor voorspellen. Het definiëren van specifieke ziekte karakteristieken voor ieder individuele patiënt zal het ultieme doel van stadiëring zijn, leidend naar een optimale persoonlijke behandeling. De technieken in gebruik in toekomstige stadiëring algoritmen zullen kritisch geëvalueerd moeten worden met betrekking tot hun betrouwbaarheid, prognostische waarde en therapeutische consequenties om de beste kwaliteit van zorg te waarborgen.

Conclusie

In dit proefschrift tonen we aan dat het aanvullend gebruik van FDG-PET de stadiëring verbetert, hoewel beeldvormende technieken de noodzaak van weefsel diagnostiek niet in elke patiënt kunnen vervangen.

Deze weefsel diagnostiek kan worden verricht door middel van endosonographie, maar cervicale mediastinoscopie blijft geïndiceerd, in geval van een negatieve bevinding bij patiënten met verdachte lymfeklieren op FDG-PET.

De gouden standaard in mediastinale stadiëring bestaat uit een volledige systematische lymfeklier dissectie tijdens chirurgische behandeling, helaas is de uitvoering hiervan slechts in een minderheid van de patiënten in overeenstemming met vastgestelde richtlijnen.

Tenslotte toont het gebruik van immunohistochemie, in aanvulling op conventionele pathologische beoordeling, minimale verspreiding naar lymfeklieren aan, die klinisch relevant is en een negatieve invloed heeft op de prognose.

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Acknowledgement. *Dankwoord.*

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Een aantal mensen heeft hierbij een bijzondere plaats ingenomen, hen wil ik graag met name noemen.
Op de eerste plaats natuurlijk mijn promotoren en co-promotor.
Beste Henry, onze eerste kennismaking is inmiddels bijna 25 jaar geleden. Als harde werker en goede analyticus heb je in meerdere fasen, uiteenlopend van beginnend assistent tot op de dag van vandaag, aan mijn ontwikkeling en later concreet aan dit proefschrift bijgedragen. Sinds je komst naar het Radboudumc heb je de longchirurgie min of meer vanzelfsprekend aan mij toevertrouwd. Voor je blijk van vertrouwen en de samenwerking in verschillende hoedanigheden gedurende de afgelopen jaren wil ik je hartelijk danken.
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Dit proefschrift is voortgekomen uit dagelijkse, klinische overwegingen in de long oncologische keten, die een belangrijke plaats in neemt binnen de afdeling cardio-thoracale chirurgie. Mijn functioneren hierin zou niet mogelijk zijn geweest zonder het voorbeeld en de opleiding die ik van anderen heb genoten.

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List of publications.

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Curriculum Vitae.

Curriculum Vitae.

De auteur van dit proefschrift werd in 1961 geboren in Nijmegen. Na het behalen van zijn eindexamen VWO aan het Canisius College in 1980, studeerde hij geneeskunde aan de Radboud Universiteit in Nijmegen. Belangstelling voor de cardio-thoracale chirurgie, in het bijzonder de longchirurgie, ontstond tijdens de tweede helft van zijn studie. Na zijn artsexamen in juni 1989, werkte hij als assistent-niet-in-opleiding achtereenvolgens een jaar op de afdeling cardio-thoracale chirurgie van het St. Antonius ziekenhuis in Nieuwegein (hoofd: F.E.E. Vermeulen) en 14 maanden op deze afdeling van het Radboud universitair medisch centrum in Nijmegen (hoofd: Prof. dr. L.K. Lacquet).

Na aanvang van zijn opleiding tot medisch specialist in oktober 1991, werkte hij twee jaar als assistent algemene chirurgie in het St. Maartensgasthuis in Venlo (opleider: Dr. H. de Smet) en vervolgens drie jaar als assistent thorax-hart chirurgie in het Radboud universitair medisch centrum (opleider: Prof. dr. L.K. Lacquet). Het laatste jaar van zijn opleiding werkte hij opnieuw in het St. Antonius ziekenhuis in Nieuwegein (opleider: F.E.E. Vermeulen, opgevolgd door Dr. A. Brutel de la Rivière), waarna hij per 1 oktober 1997 als cardio-thoracaal chirurg werd geregistreerd.

Sindsdien werkt hij als staflid cardio-thoracale chirurgie in het Radboud universitair medisch centrum, met thorax/long chirurgie als bijzonder aandachtsgebied. Om specifieke expertise te ontwikkelen op dit gebied en met name de centrale luchtweg chirurgie, bezocht hij van december 1997 tot juni 1998 de afdeling thorax chirurgie van het Massachusetts General Hospital in Boston, USA, en nam deel aan het opleidings-programma (hoofd: Prof. Douglas J. Mathisen).

Onderkenning, tijdens het klinisch functioneren, van het grote belang van juiste stadiëring voor een succesvolle en doelmatige behandeling van patiënten met een long carcinoom, vormde de basis voor dit proefschrift.