EUS-FNA and EBUS-TBNA; the pulmonologist's and surgeon's perspective

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Introduction

Lung cancer is the leading cancer related cause of death in the western world [1]. The prognosis is directly related to the stage of the disease. Treatment strategies are largely based on the cell type of the tumor, i. e. either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC), and the presence of mediastinal involvement or distant spread of the tumor [1,2]. The treatment of SCLC is mainly chemotherapy whereas NSCLC treatment is fully stage dependent ranging from surgery only to down-staging chemotherapy with subsequent surgery or entirely experimental chemotherapy/radiotherapy.

Non-small cell lung cancer (NSCLC) usually metastasizes first to hilar and mediastinal lymph nodes. Subsequently, hematogenous metastasis to distant sites may occur. Because survival is inversely correlated with stage, a meticulous staging procedure is required to determine the treatment and prognosis [3,4]. For staging of NSCLC, the TNM classification has been developed, in which T stands for local tumor extension, N for lymph node metastasis, and M for distant metastasis. The lymph node map by Mountain et al, and its revisions are often used for the description of the N factor of the TNM classification [5] (Table **1** and **2**).

TNM Classification

The TNM classification is subdivided in cTNM and a pTNM where the cTNM is based on the clinical evaluation while the pTNM is based on the pathological results after operation.

The difference in the 5 years survival based on the cTNM classification compared to the pTNM stresses the importance of an exact classification (Fig. **1** and **2**).

Exact mediastinal staging of patients with non-small-cell lung cancer (NSCLC) is therefore important to improve selection of the treatment of patients with lung cancer. Up to 10% of lung cancer operations result in explorative thoracotomies without

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Table **1** TNM classification of lung Cancer

Primary tumor
· Tis – Carcinoma in situ
· TX – Positive malignant cytologic findings, no lesion observed
· T1 – diameter of 3 cm or smaller and surrounded by lung or visceral pleura (see Image 1) or endobronchial tumor distal to the lobar bronchus
· T2 – Diameter greater than 3 cm (see Images 2 – 3); extension to the visceral pleura, atelectasis, or obstructive pneumopathy involving less than 1 lung; lobar endobronchial tumor; or tumor of a main bronchus more than 2 cm from the carina
· T3 – Tumor at the apex (see Image 5); total atelectasis of 1 lung; endobronchial tumor of main bronchus within 2 cm of the carina but not invading it; or tumor of any size with direct extension to the adjacent structures such as the chest wall mediastinal pleura (see Image 8), diaphragm, pericardium parietal layer, or mediastinal fat of the phrenic nerve
· T4 – Invasion of the mediastinal organs, including the esophagus trachea, carina (see Image 11), great vessels (see Image 13), and/or heart; obstruction of the superior vena cava; involvement of a vertebral body; recurrent nerve involvement; malignant pleural or pericardial effusion; or satellite pulmonary nodules within the same lobe as the primary tumor
• Regional lymph node involvement
· N0 – No lymph nodes involved
· N1 – Ipsilateral bronchopulmonary or hilar nodes involved
· N2 – Ipsilateral mediastinal nodes or ligament involved
– Upper paratracheal lower paratracheal nodes
– Pretracheal (see Image 4, Image 7, Image 10) and retrotracheal nodes
– Aortic and aortic window nodes
– Para-aortic nodes
– Para-esophageal nodes
– Pulmonary ligament
– Subcarinal nodes (see Images 12 – 17)
· N3 – contralateral mediastinal or hilar nodes involved (see image 19) or any scalene or supraclavicular nodes involved
• Metastatic involvement
· M0 – No metastases
· M1 – Metastases present (see Images 20 – 27)

Table **2** Stage groupings

• IA – T1N0M0
• IB – T2N0M0
• IIA – T1N1M0
• IIB – T2N1M0 or T3N0M0
• IIIA – T1-3N2M0 or T3N1M0
• IIIB – Any T4 or any N3M0
• IV – Any M1

tumor resection, and an additional 25 – 35 % of the operations are unsuccessful because of postoperative recurrent disease [6, 7], apparently because the stage of the disease is more advanced than expected preoperatively.

Therefore the correct staging is critical because treatment is directly related to the stage of the. Thus, incorrect staging would lead to improper treatment, and material demunition of patient survivability (Fig. **3**).

Mediastinal lymph node staging can be divided into imaging and sampling. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) may be used to image mediastinal lymph nodes [8]. Pathologic sampling of suspicious lesions can be performed by mediastinoscopy, thoracoscopy, transthoracic fine-needle aspiration, transbronchial fine-needle aspiration, and endoscopic ultrasonography with fine-needle aspiration [8 – 11].

CT

The background of the differences in 5 years survival in cTNM and pTNM is based on the sensitivity and diagnostic values of the different modalities used in the cTNM classification compared to the operative findings.

Neither CT scan nor MRI are able to distinguish malignant from hyper plastic, anthracotic, granulomatous or fibrotic lesions, more so after induction treatment. With reported sensitivities and specificities of 69 %, respective 71 % for CT scan and 45 %, respective 65 % for MRI, both techniques prove too inaccurate for reliable loco regional staging.

Looking at the different objects in the TNM staging system, the accuracy in T staging is 60 % and N staging 65 %.

This result is depended of the N stage because the accuracy here is 65 % for N0, 42 % for N1, 32 % for N2 and 43 % for N3. Therefore N under staging is found in 23 % and an over staging in 30 %.

By CT scan which is one of the main methods in evaluating lung cancer the N-classification is only correct in 50 %, over staged in 25 % and under staged in 25 % [13, 14].

FDG PET

Many retrospective [15, 16] and prospective studies [17 – 19] have shown FDG PET to be an accurate imaging modality in the nodal

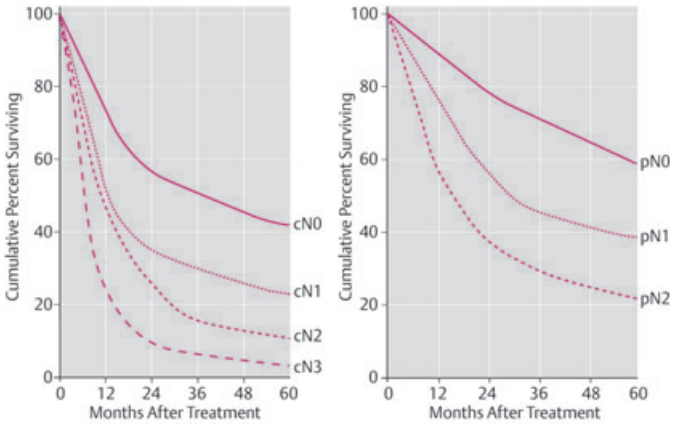

Fig. **1** 5 year survival cN versus pN.

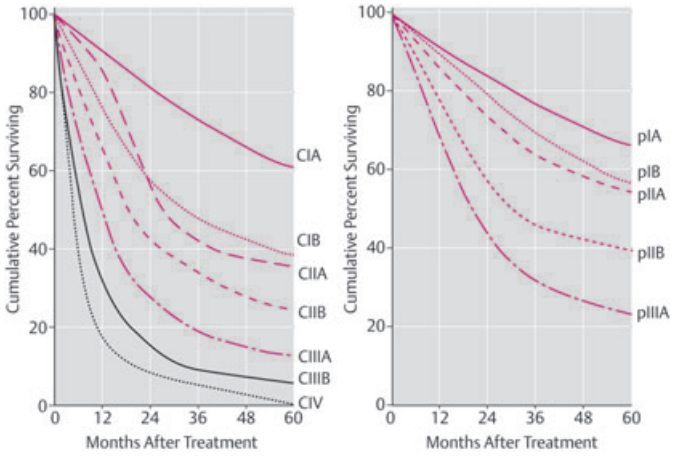

Fig. **2** Survival cTNM versus pTMN.

Operable		Inoperable	
☐ St. Ia	T1N0M0	☐ St. IIIa	T1N2M0 T2N2M0 T3N1N2M0
☐ St. Ib	T2N0M0	☐ St. IIIb	Any TN3M0 T4 any NM0
☐ St. IIa	T1N1M0	☐ St. VI	Any T any NM1
☐ St. IIb	T2N1M0 T3N0M0		

Fig. **3** Operability by stage.

staging of NSCLC. Meta-analytic comparisons of PET and CT [20–23] showed that PET was significantly more accurate than CT in demonstrating nodal metastases.

However, a metaanalysis (eller er det et review) has shown that PET/CT has a sensitivity of 0.84, a specificity of 0.89 and a PPV of 0.79 and a NPV of 0.93 [24].

The diagnostic capability of FDG PET is limited not only by cellular activity but also by tumor volume. FDG uptake by small tumor cell foci is often poorly depicted due to partial volume effect. Current PET scanner achieves transaxial resolution of 4–5 mm full-width-half-maximum. A tumor focus smaller than 5 mm may not be detected by the current scanners. The maximum dimensions of tumor focus in false-negative lymph nodes ranges from 1 to 7.5 mm (mean 3.4 mm) [25].

Yoshida et al. [25] showed that the spatial resolution limitations of FDG PET were responsible for 13 of 14 (93%) false-negative PET results demonstrating that FDG PET is not reliable in diagnosing small tumor foci in Lymph nodes.

Another disadvantage of FDG PET is its limited anatomical resolution due to the paucity of anatomic information in metabolic images [19]. Although PET-positive Lymph nodes were localized referring to contrast-enhanced CT findings, it is hard to distinguish hillar Lymph nodes from adjacent mediastinal Lymph nodes.

False-positive PET scans is mostly attributable to inflammatory conditions, including tumor necrosis, obstructive pneumonia, previous pulmonary tuberculosis, pulmonary fibrosis, and rheumatoid arthritis. FDG is not a specific marker of malignancy and FDG uptake can be seen at sites of active, acute inflammation, which is due to increased glucose uptake by activated macrophages and inflammatory cells [26]. Inflammatory conditions are well-known factors associated with false-positive PET scans in indeterminate pulmonary nodule evaluation [27]. Roberts et al. [28] reported that concurrent inflammatory lung disease and centrally located tumors were causative factors of false-positive PET scans in mediastinal nodal staging in NSCLC.

Fritscher-Ravens et al. showed that in using EUS FNA, PET and CT they found false positive inoperable diagnoses: PET = 9/36, CT = 3/20.

Sensitivity, specificity, accuracy in nodal staging for CT was 29, 83, and 65% and for PET 39, 79, and 66%, respectively. There were 10 (14%) false-positive PET scans and 14 (20%) false-negative PET scans.

Mediastinoscopy

Preoperative evaluation of the mediastinal lymph nodes is important in patients with lung cancer in order to determine operability and/or need for neoadjuvant treatment. 46 years after its introduction by Carlen's in 1959 [31], mediastinoscopy is still the golden standard in the evaluation of the mediastinal lymph node and in the preoperative staging of patients with lung cancer [32,33]. Mediastinal exploration is described as cervical mediastinoscopy, parasternal mediastinotomy, extended cervical mediastinoscopy and thoracoscopy depending on the surgical technique. Cervical mediastinoscopy (CM) is generally accepted as a safe and highly accurate procedure in the staging of lung cancer. Nodes accessible to CM are those of the superior (level 2R and 2L) and inferior (level 4R and 4L) Para tracheal and subcarinal (level 7) nodal stations. Additionally, extended CM and left parasternal mediastinotomy allow exploration of the aortopulmonary window (level 5) and anterior mediastinal nodes (level 6) (Fig. **4**).

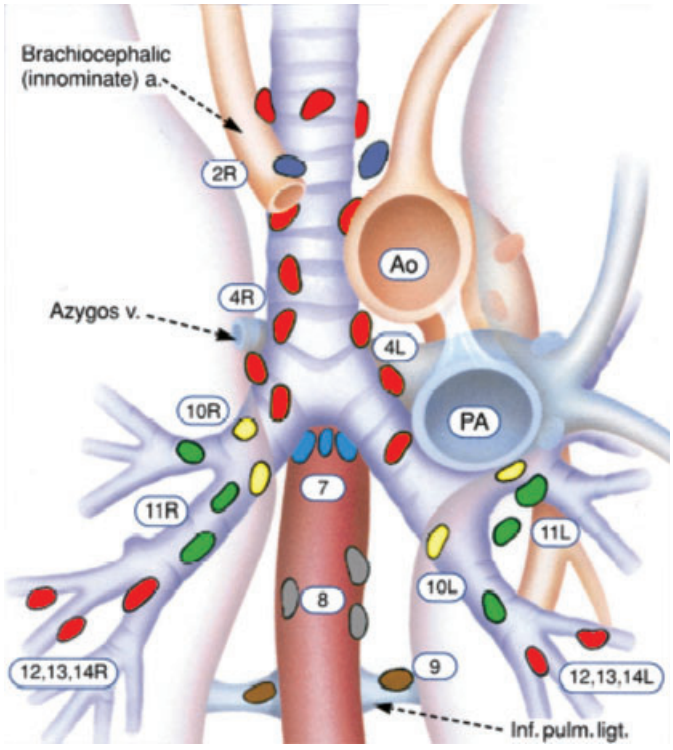

Fig. **4** Mediastinal and hillar lymph nodes stations.

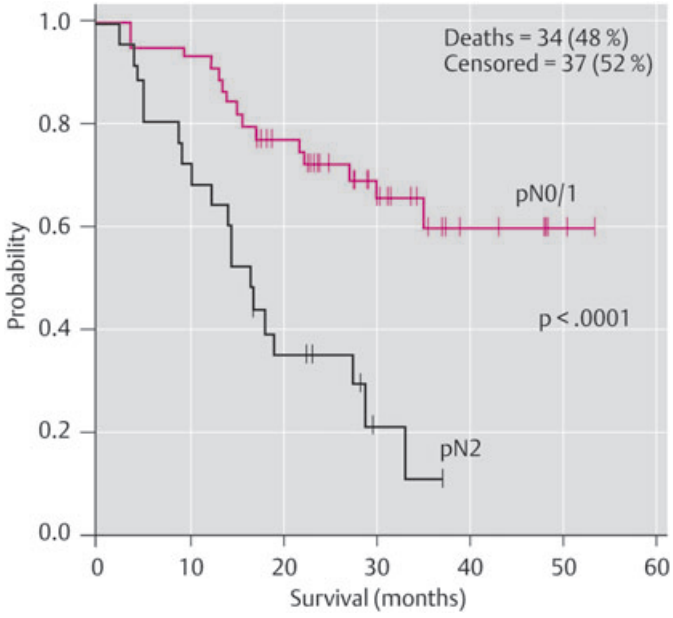

Fig. **5** Overall survival dependent on pN2 clearance in the univariate analysis (patients with tumor resection after downstaging treatment), n = 71; P = log-rank test P value Sugerbaker: ASCO Educational book, 1994.

A special problem is remediastinoscopy (RM) because of fibrosis due to the first procedure and the associated risk of injury to vital structures [34–36]. Neoadjuvant clinical trials with induction chemotherapy or chemo radiation should all involve a restaging procedure to confirm the differences in the results of different treatment modalities. In downstaged patients restaging is also important to select therapy-responsive patients with high probability of complete resectability, thereby reducing the number of futile thoracotomies in patients with locally advanced lung cancer [37–39].

EUS-FNA and EBUS-TBNA

To establish an easier and more accurate staging procedure EBUS TBNA and EUS FNA has been developed. They target lesions and lymph nodes adjacent to trachea, main bronchi and esophagus and the hillar regions. Both techniques are used to assess the entire mediastinum or to stage predominantly only one nodal station, and can be used for the systematical standardized exploration of individual nodes as performed by mediastinoscopy [41–45].

Comments

With the current status and the development of the multidisciplinary treatment modalities it is outmost important that we solve the basic problems with the imaging systems which do not enable us to establish an exact diagnosis and a precise stage because we need cells for an exact diagnose.

Mediastinoscopy is still the golden standard but has its limitations, i.e. incomplete mediastinoscopy, most frequently seen at station 7 and the posterior and inferior mediastinum, assessment of loco regional extent of recurrent cancer, a second primary cancer, re-staging after neoadjuvant chemotherapy and metastases from cancers in other organs to the mediastinum and hillar regions.

Remediastinoscopies is although possible often difficult to perform but it is very important to establish a correct stage also after downstaging so only patients who benefits from operation will be offered this treatment (Fig. **5**).

The often undiagnosed hillar lymph nodes metastases in N1 nodes, is a special problem. Traditionally hey can only be reached by thoracotomy (scopy). Because of the possibilities of neoadjuvant therapy in primary lung cancer it is nessecary also to diagnose the N1 lymphnodes. In the evaluation of patients after downstaging a correct restaging is important in evaluating the results from different treatment modalities, Metastasis from other organs is also often found in the N1 nodes.

In the staging process of cN1 disease, it is possible to perform mediastinoscopy and thoracoscopy to avoid unnecessary thoracotomy especially in adenocarcinoma, even though mediastinal nodes and pleural dissemination were negative on computed tomography investigation. These methods requires general anesthesia and open surgery.

Therefore we need a method which is easy and minimal invasive, based on an outpatient procedure and enables us to collect tissue on which basis a diagnose can be established and the stage of cancers can be determined so a proper and effective treatment can be established.

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