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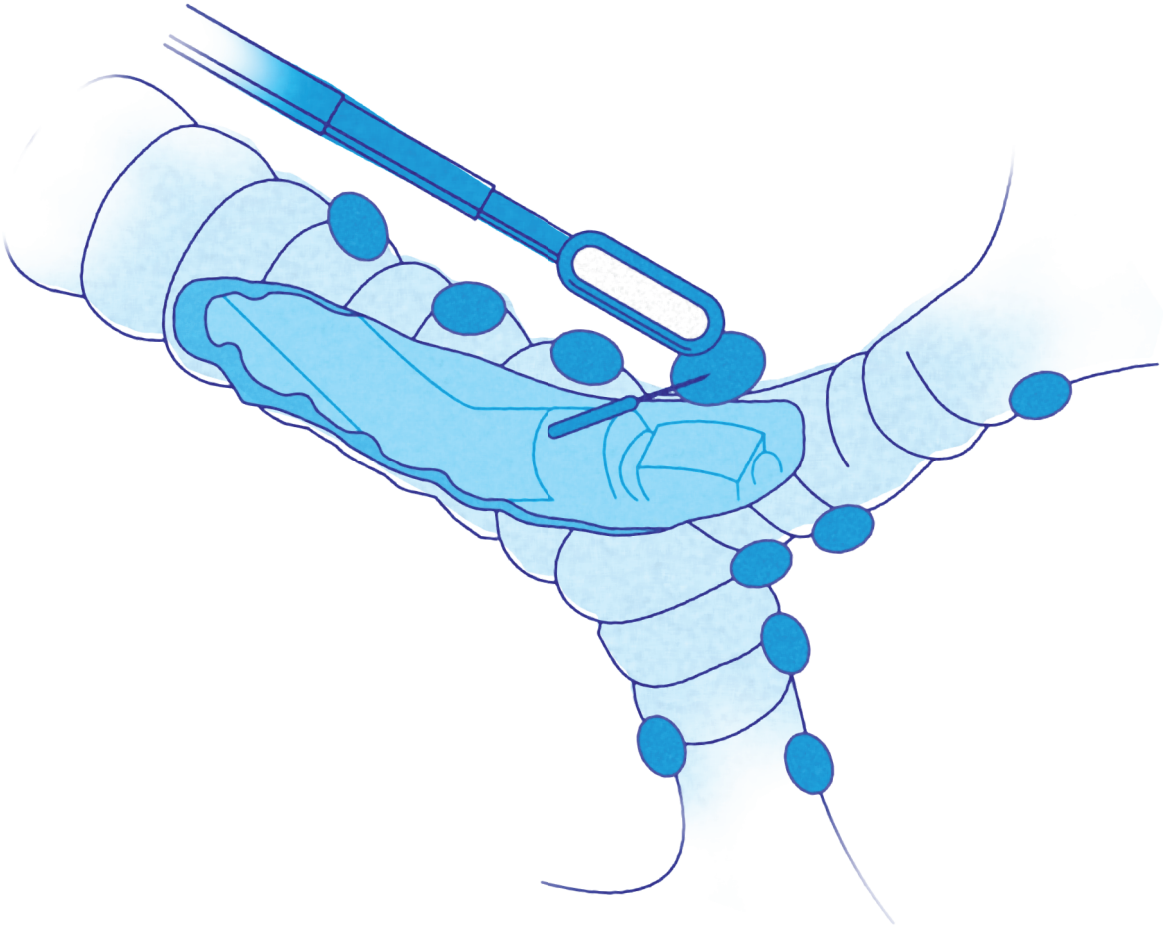

Jelle Egbert Bousema

Invasive Mediastinal Nodal Staging of Resectable Non-Small Cell Lung Cancer

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Colofon

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Invasive Mediastinal Nodal Staging of Resectable Non-Small Cell Lung Cancer

ACADEMISCH PROEFSCHRIFT

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The family tree will always grow

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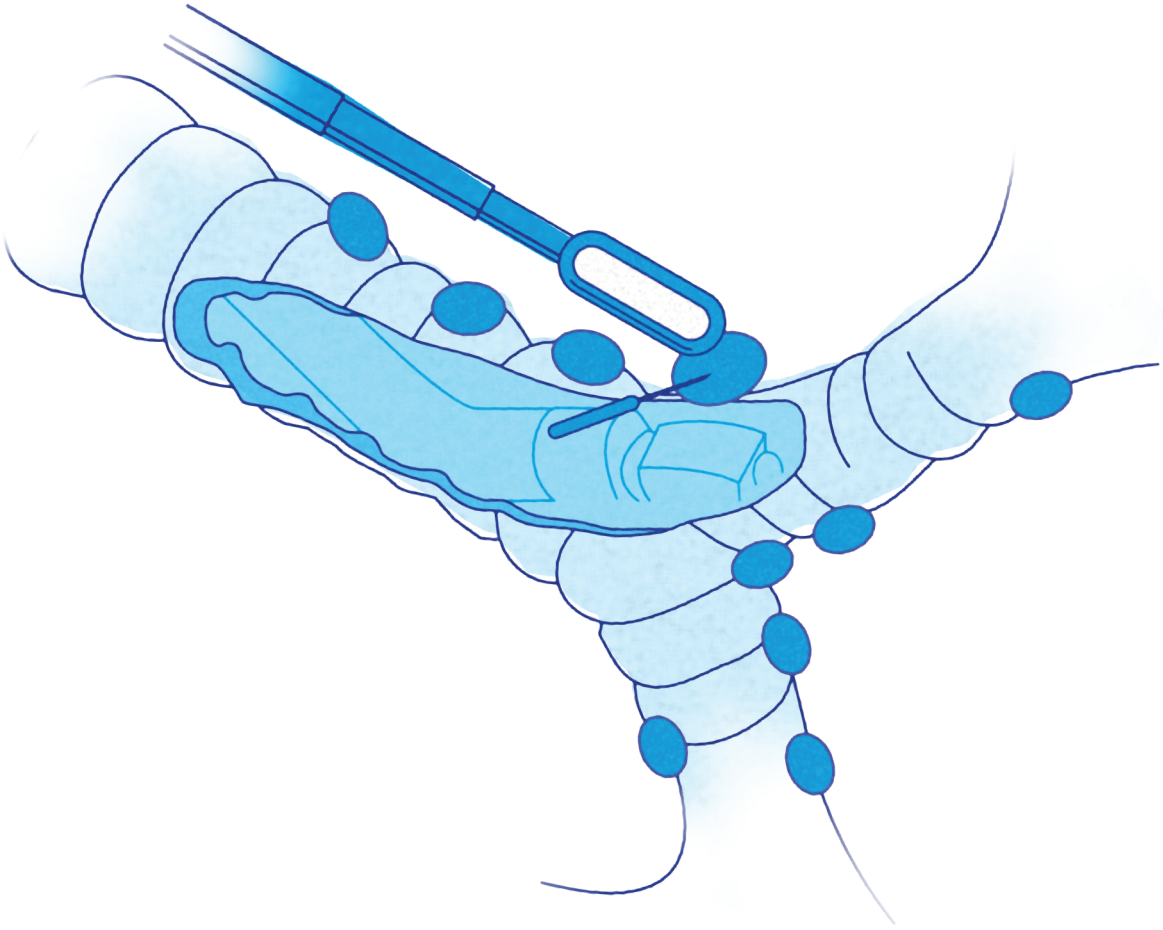


Chapter 1

General introduction

LUNG CANCER

Lung cancer is the third most prevalent and the deathliest cancer in Europe, with a five-year survival rate around 20%.[1-3] Tobacco use remains the main etiological factor in lung carcinogenesis, accounting for 80-90% of lung cancer cases in developed countries.[4, 5] Non-small cell lung cancer (NSCLC) is the most common lung cancer subtype. In the Netherlands NSCLC accounts for approximately 80% of all lung cancers, with over ten thousand new Dutch NSCLC cases annually.[2] At the time of diagnosis, 23% of NSCLC patients are eligible for intended curative surgical treatment.[6] These potential surgical candidates were the target population of this thesis.

CLASSIFICATION

Adequate diagnosis and staging of patients with lung cancer is important as it determines treatment choice, prognosis and it enables researchers to compare patients. The Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (IASLC) periodically updates the tumour, node and metastasis (TNM) lung cancer classification system. The eight edition is the most recent version and is effectual since 2017.[7]

The T stage is based on the tumour size, location and its relation to surrounding structures (such as airways, pleura, pericardium, mediastinum, chest wall or diaphragm). It is subdivided into four stages, ranging from T1a (tumor ≤1 cm in greatest dimension without invasion of surrounding structures) to T4 (tumor >7 cm in greatest dimension or associated with separate tumor nodule(s) in a different ipsilateral lobe or with invasion in surrounding structures).

The N stage is based on malignant involvement of locoregional lymph nodes. N0 indicates absence of lymph node metastases, N1 indicates metastasis in ipsilateral intrapulmonary, peribronchial and/or hilar lymph nodes, including involvement by direct invasion of the tumour. N2 indicates metastases in ipsilateral mediastinal and/or the subcarinal lymph node(s) and patients with metastases in contralateral mediastinal, hilar, peribronchial, intrapulmonary, scalene or supraclavicular lymph node(s) are classified having N3 disease.

The M stage is based on the presence of distant metastasis, ranging from M1a (intrathoracic metastasis) to M1c (multiple extrathoracic metastasis).[8]

After determining the TNM classification, patients can be placed into lung cancer stages (ranging from 1A to 4B) (Table 1). When classifying lung cancer an important distinction should be made through the clinical TNM-stage (cTNM) and the pathological TNM-stage (pTNM). The cTNM results from radiological and invasive staging procedures, while the pathologist provides the pTNM after combined lung tumour resection and lymph node dissection.

Table 1. Lung cancer stages based on the 8th edition of TNM in Lung Cancer

	N0	N1	N2	N3
T1	1A	2B	3A	3B
T2a	1B	2B	3A	3B
T2b	2A	2B	3A	3B
T3	2B	3A	3B	3C
T4	3A	3A	3B	3C
M1a	4A	4A	4A	4A
M1b	4A	4A	4A	4A
M1c	4B	4B	4B	4B

CLINICAL STAGING AND GENERAL TREATMENT PRINCIPLES

The work-up for diagnosing and staging lung cancer consists of a general examination, laboratory test, cardio-pulmonary function and bronchoscopy.[9] Chest Computed tomography (CT) and total body ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) are used for radiologically staging the primary tumour (cT stage), hilar and mediastinal lymph nodes (cN stage) and distant metastasis (cM stage). CT enlarged (>1 cm short axis) and/or FDG-avid lymph nodes as well as FDG-avid spots thorough the body are suspicious for the presence of metastases. If the primary tumour is judged resectable, FDG-PET-CT shows no signs of distant metastasis and the patient is deemed fit for surgery the tumour and mediastinal nodal status determines the further staging and/or treatment strategies:[10]

- Patients with small (<3 cm) peripherally located tumours with unsuspicious hilar and mediastinal lymph nodes on FDG-PET-CT (cN0) are deemed to undergo direct surgical lung tumour resection and lymph node dissection without further staging.
- Patients with suspicious hilar or mediastinal lymph nodes (cN1-3) or centrally located, FDG-non-avid or large (>3 cm) peripherally located tumours should undergo invasive mediastinal nodal staging first, as they are known to have increased risk of mediastinal lymph node involvement. For patients with cN1-3, the probability of me-

diastinal lymph node metastases is 24%–80%, for patients with central tumours this is 17%–24%, and for patients with FDG-non-avid tumours and peripherally located tumours>3 cm this is 6%–30%.[10]

Upfront detection of mediastinal nodal metastases is desirable, as it determines treatment options and prognosis. Patient with a resectable tumour without mediastinal and distant metastases (stage 1A-2B) are generally treated by surgical resection. The guidelines recommend to consider surgical multimodality treatment (including (neo) adjuvant chemoradiation and subsequent surgical resection) in patients with preoperatively proven single station N2 disease (stage 3A or 3B) (Table 1). In patients with preoperatively proven multi station N2 or N3 disease non-surgical multimodality treatment is advised.[9] To distinguish between these lung cancer stages and the most appropriate treatment strategy invasive mediastinal nodal staging is mandatory.[10]

LYMPH NODE ANATOMY

Universally accepted nomenclature of the anatomic position of mediastinal lymph node stations is important for staging purposes and to compare results among patients. The Japanese thoracic surgeon Tsuguo Naruke developed the first mediastinal lymph node map in 1967, which was widely used in North America, Europe and Asia.[11, 12] The American Thoracic Society (ATS) updated Naruke's lymph node map in 1983. The American thoracic surgeons Clinton Mountain and Carolyn Dresler added the classification of lymph node zones (i.e. supraclavicular, superior mediastinal, aortic, inferior mediastinal and N1 node zone) resulting in the MD-ATS lymph node map published in 1996.[13] The modifications of Naruke's widely used lymph node map however led to diversity over the world; it was fully accepted in North-America, criticised in Europe and Asian surgeons continued using the original Naruke map. The IASLC analysed Naruke's and the MD-ATS lymph node maps and found several differences in anatomic borders among mediastinal lymph nodes, even resulting in differences in the clinical nodal stage. Aiming for uniformity the IASLC lymph node map was published in 2009, which is currently still effective as internationally accepted nomenclature of mediastinal lymph node stations (Figure 1).[14]

The IASLC lymph node map was mainly based on the ability to distinguish the anatomical borders of nodal zones by either radiological staging, endosonography as well as during surgical lymph node dissection. A nodal zone is defined as an anatomical area that includes one or several neighbouring nodal stations. However, these nodal zones are designed as grouping classification for future survival analyses, not for standard

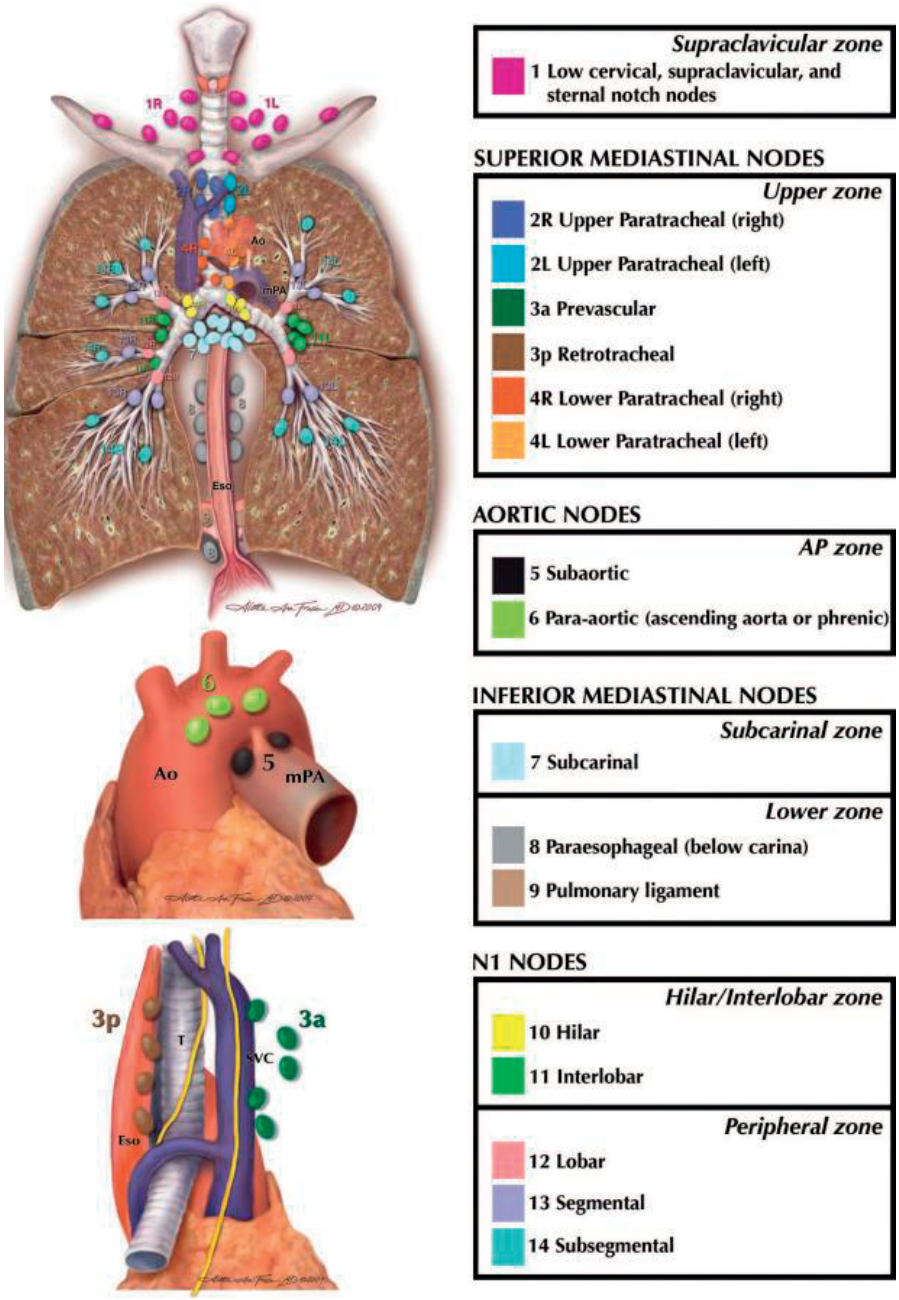


Figure 1. The International Association for the Study of Lung Cancer lymph node map.
Reprinted from the Journal of Thoracic Oncology, Volume 4 / May 2009, Valerie W. Rusch, Hisao Asamura, Hirokazu Watanabe, Dorothy J.Giroux, Ramon Rami-Porta and Peter Goldstraw, *The IASLC Lung Cancer Staging Project: A Proposal for a New International Lymph Node Map in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer*, pages 568-577, Copyright (2009) with permission from Elsevier.

nomenclature of lymph node stations.[14] The anatomical position and borders of lymph node station 1 through 14 are presented in Table 2. An important detail is that lymphatic drainage in the superior mediastinum predominantly occurs to the right paratracheal lymph nodes, which are known to pass the midline of the trachea. As result of this lymphatic anatomy the boundary between the right and left-sided station 2 and 4 lymph nodes was set to the left lateral wall of the trachea.[14, 15]

Table 2. Anatomical borders of lymph node stations based on the IASLC lymph node map

Lymph node station	Anatomical borders
Supraclavicular zone	
#1: low cervical, supraclavicular and sternal notch nodes	Upper border: lower margin of cricoid cartilage. Lower border: clavicles bilaterally and, in the midline, the upper border of the manubrium. 1R designates right-sided nodes, and 1L left-sided nodes in this region. For lymph node station 1, the midline of the trachea serves as the border between 1R and 1L.
Upper zone	
#2: upper paratracheal nodes*	2R: Upper border: apex of the right lung and pleural space and, in the midline, the upper border of the manubrium. Lower border: intersection of caudal margin of innominate vein with the trachea. 2L: Upper border: apex of the lung and pleural space and, in the midline, the upper border of the manubrium. Lower border: superior border of the aortic arch.
#3a: prevascular nodes	Right side: Upper border: apex of the chest. Lower border: level of carina. Anterior border: posterior aspect of the sternum. Posterior border: anterior border of the superior vena cava. Left side: Upper border: apex of the chest. Lower border: level of carina. Anterior border: posterior aspect of the sternum. Posterior border: left carotid artery.
#3p: retrotracheal nodes	Upper border: apex of the chest. Lower border: carina.
#4: lower paratracheal nodes*	4R: Upper border: intersection of caudal margin of innominate vein with the trachea. Lower border: lower border of the azygos vein. 4L: includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum. Upper border: upper margin of the aortic arch. Lower border: upper rim of the left main pulmonary artery.
Aorto-pulmonary zone	
#5: subaortic nodes (aorto-pulmonary window)	Subaortic lymph nodes lateral to the ligamentum arteriosum. Upper border: the lower border of the aortic arch. Lower border: upper rim of the left main pulmonary artery.

Table 2. Anatomical borders of lymph node stations based on the IASLC lymph node map (*continued*)

Lymph node station	Anatomical borders
#6: para-aortic nodes (ascending aorta or phrenic)	Lymph nodes anterior and lateral to the ascending aorta and aortic arch. Upper border: a line tangential to the upper border of the aortic arch. Lower border: the lower border of the aortic arch.
Subcarinal zone	
#7: subcarinal nodes	Upper border: the carina of the trachea. Lower border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right.
Lower zone	
#8: para-esophageal nodes (below carina)	Nodes lying adjacent to the wall of the oesophagus and to the right or the left of the midline, excluding subcarinal nodes. Upper border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right. Lower border: the diaphragm.
#9: pulmonary ligament nodes	Nodes lying within the pulmonary ligament. Upper border: the inferior pulmonary vein. Lower border: the diaphragm.
Hilar/interlobar zone	
#10: hilar nodes	Includes nodes immediately adjacent to the mainstem bronchus and hilar vessels including the proximal portions of the pulmonary veins and main pulmonary artery. Upper border: the lower rim of the azygos vein in the right; upper rim of the pulmonary artery on the left. Lower border: interlobar region bilaterally.
#11: interlobar nodes	Between the origin of the lobar bronchi. #11s: between the upper lobe bronchus and bronchus intermedius on the right. #11i: between the middle and lower bronchi on the right.
Peripheral zone	
#12: lobar nodes	Adjacent to the lobar bronchi.
#13: segmental nodes	Adjacent to the segmental bronchi.
#14: subsegmental nodes	Adjacent to the subsegmental bronchi.

The International Association for the Study of Lung Cancer lymph node map.
* Station 4R and 2R: includes pretracheal nodes extending to the left lateral border of the trachea.

INVASIVE MEDIASTINAL NODAL STAGING

Endosonography

Endobronchial ultrasonography (EBUS) and endoscopic ultrasonography (EUS(B)) provide ultrasonographic visualization of mediastinal lymph nodes and centrally

located lung tumours. Under real-time ultrasonography diagnostic sampling by using transbronchial needle aspiration (EBUS-TBNA) and fine needle aspiration (EUS(B)-FNA) can be performed. Depending on local preferences and availability the procedures are performed under local anaesthesia, conscious sedation or general anaesthesia. EBUS and EUS(B) are complementary to each other; EBUS provides access to station 2R-4R-10R/11R-7-10L/11L-4L-2L, while station 2L-4L-7-8-9 are accessible by EUS(B). (Figure 2) When indicated liver-, para-aortal or left adrenal gland metastasis can be visualized by EUS. Sampling should be performed from M1b -> N3 -> N2 -> N1 -> tumor to prevent patient from false positive upstaging. (Figure 2)

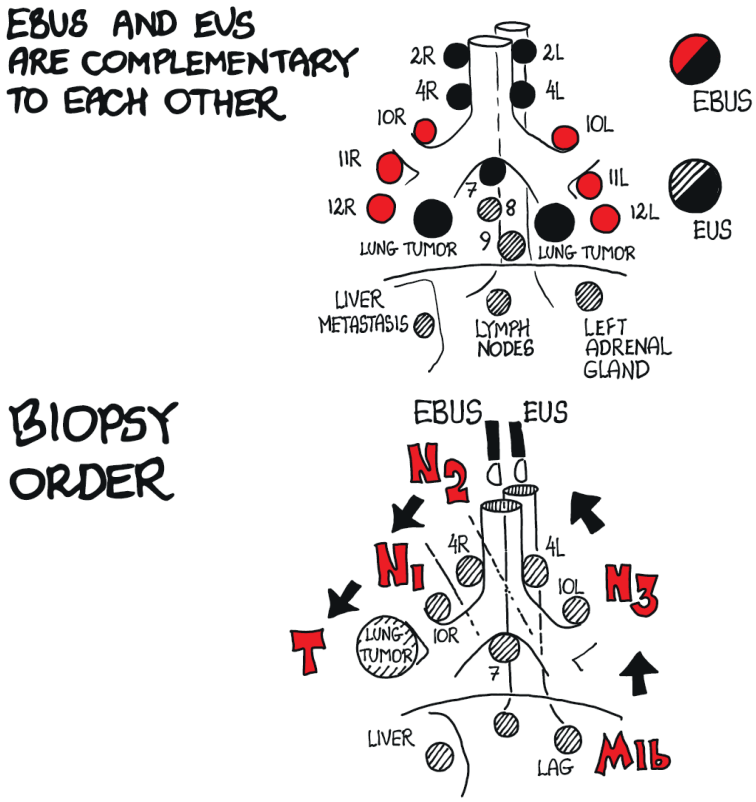


Figure 2. The overlapping reach and biopsy order of endobronchial ultrasonography (EBUS) and endoscopic ultrasonography (EUS(B)). Courtesy of Paul Frost Clementsen, reprinted with permission.

Cervical mediastinoscopy

Cervical mediastinoscopy is a surgical procedure performed under general anesthesia. A 3-4 cm incision 2 cm above the suprasternal notch is performed. Dissection straight to the trachea provides access to the superior mediastinum anterior to the trachea and posterior to the large vessels. Surgical samples of lymph node stations 2R-4R-7-4L-2L can be obtained by cervical mediastinoscopy.

Mediastinal lymph node dissection

The gold standard for mediastinal nodal staging is a surgical mediastinal lymph node dissection, which is generally performed during resection of the lung tumour. This procedure can be performed by either thoracotomy, video-assisted thoracoscopic surgery (VATS) or robotic-assisted thoracoscopic surgery (RATS). Current international guidelines prescribe dissection of at least three mediastinal lymph node stations, always including station 7.[16-18] In current practice this usually results in a lobe-specific distribution of dissected stations including station 2R-4R-7 in right upper or middle lobe tumors, station 4R-7-8-9 in right lower lobe tumors, station 5-6-7 in left upper lobe tumors and station 7-8-9 in left lower lobe tumors.[19]

MEDIASTINAL NODAL STAGING STRATEGY

Patients with a resectable lung tumor without distant metastases with suspicious hilar or mediastinal lymph nodes (cN1-3) or centrally located, FDG-non-avid or large (>3 cm) peripherally located tumours should undergo invasive mediastinal nodal staging to potentially prevent them from oncological unnecessary surgical resections. The current international guidelines recommend endosonography (preferably EBUS combined with EUS(B)) as initial staging procedure. Confirmatory mediastinoscopy after N2-3 negative endosonography is recommended in patients with cN1-3, while it should be considered in patients with centrally located, FDG-non-avid or large peripheral tumours (>3 cm).[10] These recommendations were based on the randomized ASTER trial comparing endosonography (EBUS and EUS(B)) versus surgical staging (mediastinoscopy), demonstrating a sensitivity for mediastinal nodal spread of 85% for endosonography and 79% for mediastinoscopy. Subsequent mediastinoscopy after negative endosonography diagnosed mediastinal lymph node metastases in another 9.2% of patients, resulting in a combined sensitivity of 94%.[20]

The role of confirmatory mediastinoscopy is however under debate due to a number needed to test of eleven, and its associated morbidity, hospital admission, general anaesthesia and delay in definite lung cancer treatment.[21-25] In addition, the tumor load

of mediastinal lymph node metastases that were detected by mediastinoscopy was low, predominantly demonstrating minimal N2 (e.g. microscopic metastases within one lymph node station or single tumor cells only). The debate about the efficacy of confirmatory mediastinoscopy already resulted in wide practice variation and deviance of guideline advises in clinical practice in the United States and Canada.[26, 27]

MEDIASTrial

The long-term outcomes of the ASTER trial showed that despite the significant differences in sensitivity and unforeseen N2 (pathologically proven N2 disease at final lung tumour resection and lymph node dissection when previous mediastinal staging showed N0 or N1 disease (uN2)), the 5-year overall survival was 35% in both groups.[20, 28] These numbers potentially leave room for de-escalation of the mediastinal nodal staging pattern, however it was unclear what would be the clinical effect of omitting confirmatory mediastinoscopy after negative endosonography. Despite an inevitable reduction in sensitivity (with an opposite increase of uN2) by omitting mediastinoscopy, the elimination of mediastinoscopy may be associated with lower morbidity and mortality and improved patient satisfaction, and hence may be more efficient concerning lung cancer treatment as a whole. Since the sensitivity of endosonography and mediastinoscopy alone were already known, as well as the combined use of endosonography plus mediastinoscopy from the ASTER trial, we decided uN2 after final lung tumor resection to be the most clinically relevant primary outcome measure in the MEDIASTrial. uN2 represents the undesirable outcome of mediastinal staging and includes both benefits (nodal spread detection among patients with N2 disease) and potential harms (demonstrating absence of nodal spread among patients without N2 at the cost of morbidity) of confirmatory mediastinoscopy. Importantly, for the MEDIASTrial we were able to determine an acceptable upper non-inferiority limit for uN2 rate based on the survival data of the ASTER trial.[20, 28]

OUTLINE OF THIS THESIS

This thesis originated from variability in mediastinal nodal staging of non-small cell lung cancer in the Netherlands and the debate on the role of confirmatory mediastinoscopy. The main research question was: can confirmatory mediastinoscopy after negative endosonography be safely omitted in invasive mediastinal staging of resectable non-small cell lung cancer?

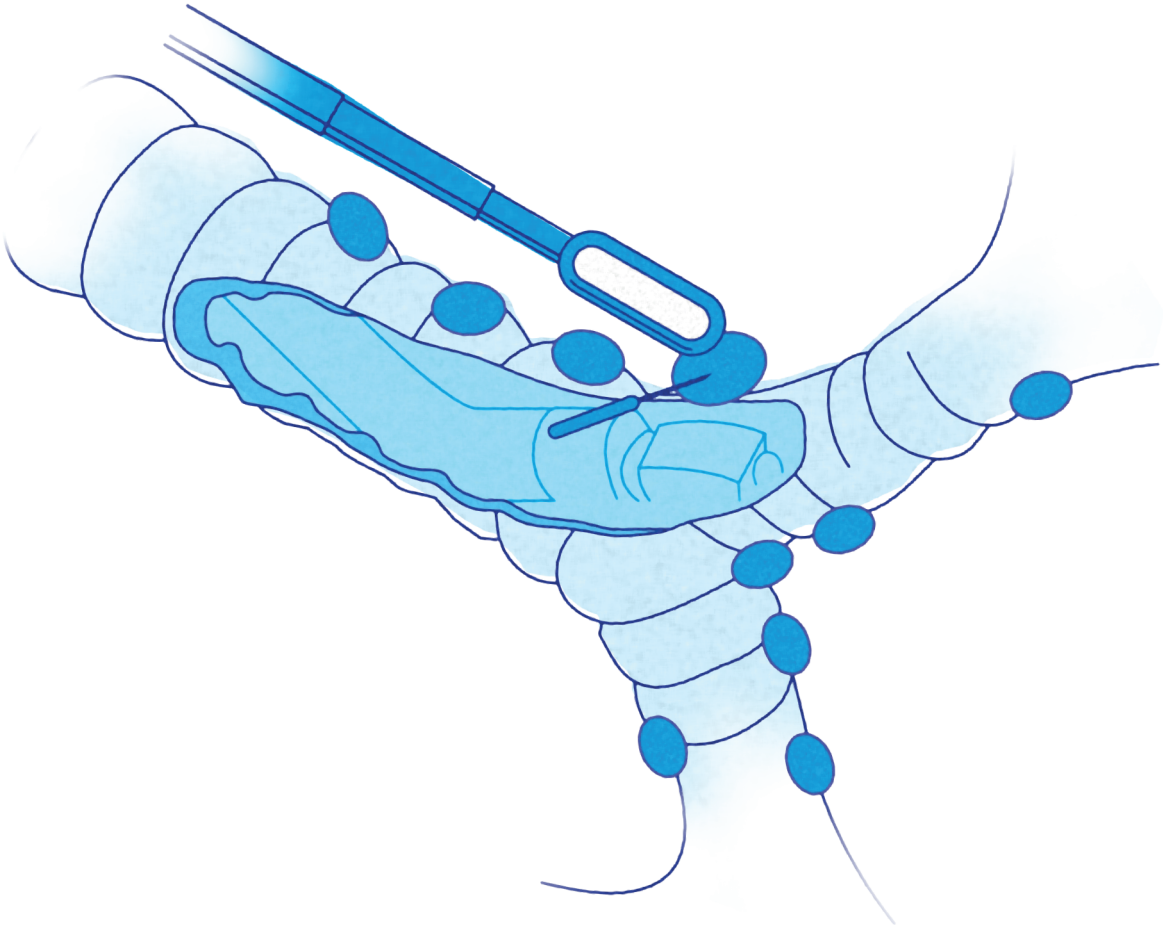
The first part of the thesis focusses on the daily practice of invasive mediastinal nodal staging and adherence to the (inter)national guidelines. In **Chapter 2** a multicenter retrospective analyses of invasive mediastinal nodal staging procedures and completeness of these procedures in six Dutch hospitals is described. In **Chapter 3** a Dutch nationwide database is analysed regarding the use of initial endosonography and confirmatory mediastinoscopy as well as uN2 rates after different staging strategies were analysed. In **Chapter 4** we describe trends in invasive staging and unforeseen N2 from data of the Netherlands Cancer Registry and assessed the effect of different staging strategies on overall survival.

In the second part of this thesis we focussed on the value of confirmatory mediastinoscopy after tumor negative endosonography in mediastinal nodal staging of resectable non-small cell lung cancer. In **Chapter 5** patients' preferences regarding invasive mediastinal nodal staging of resectable lung cancer were investigated by an adaptive-conjoint-analysis and Hierarchical Bayes estimation and a treatment-trade-off experiment. **Chapter 6** is a systematic review and meta-analysis assessing unforeseen N2 rates after staging with endosonography with or without confirmatory mediastinoscopy and the complications of mediastinoscopy. Aiming to answer the main research question on the effect of omitting confirmatory mediastinoscopy, we designed the randomized controlled multicenter non-inferiority MEDIASTrial. **Chapter 7** describes the MEDIASTrial study protocol and **Chapter 8** the MEDIASTrial statistical analysis plan. Finally, in **Chapter 9** we describe the primary outcomes of the MEDIASTrial assessing whether confirmatory mediastinoscopy after endosonography can safely be omitted based on non-inferiority in unforeseen N2 disease.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al: Cancer incidence and mortality patterns in europe: Estimates for 40 countries and 25 major cancers in 2018. European journal of cancer (1990) 103:356-387, 2018
2. IKNL: Nederlandse kanker registratie cijfers. https://iknl.nl/nkr-cijfers, 2023
3. American Cancer Society: Lung cancer guide. https://www.cancer.org/cancer/types/lung-cancer.html, 2023
4. Alberg AJ, Brock MV, Ford JG, et al: Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143:e1S-e29S, 2013
5. Malhotra J, Malvezzi M, Negri E, et al: Risk factors for lung cancer worldwide. The European respiratory journal 48:889-902, 2016
6. Heineman DJ, Hoeijmakers F, Beck N, et al: Impact of health care organization on surgical lung cancer care. Lung Cancer 135:181-187, 2019
7. Detterbeck FC, Bolejack V, Crowley J, et al: The IASLC lung cancer staging project: Methodology and validation used in the development of proposals for revision of the stage classification of NSCLC in the forthcoming (eighth) edition of the TNM classification of lung cancer. Journal of thoracic oncology 11:1433-1446, 2016
8. Goldstraw P, Chansky K, Crowley J, et al: The IASLC lung cancer staging project: Proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. Journal of thoracic oncology 11:39-51, 2016
9. Postmus PE, Kerr KM, Oudkerk M, et al: Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Annals of Oncology 28:iv1-iv21, 2017
10. Vilmann P, Clementsen PF, Colella S, et al: Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European society of gastrointestinal endoscopy (ESGE) guideline, in cooperation with the european respiratory society (ERS) and the european society of thoracic surgeons (ESTS). Endoscopy 47:546-560, 2015
11. Naruke T: The spread of lung cancer and its relevance to surgery. Nippon Kyobu Geka Gakkai Zasshi 68:1607-1621, 1967
12. Naruke T, Suemasu K, Ishikawa S: Lymph node mapping and curability at various levels of metastasis in resected lung cancer. The Journal of thoracic and cardiovascular surgery 76:832-839, 1978
13. Mountain CF, Dresler CM: Regional lymph node classification for lung cancer staging. Chest 111:1718-1723, 1997
14. Rusch V, Asamura H, Watanabe H, et al: The IASLC lung cancer staging project A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. Journal of Thoracic Oncology 4:568-577, 2009
15. De Leyn P, Dooms C, Kuzdzal J, et al: Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 45:787-798, 2014
16. Ettinger D, Johnson B: Update: NCCN small cell and non-small cell lung cancer clinical practice guidelines. Journal of the National Comprehensive Cancer Network 3 Suppl 1:S17-S21, 2005
17. Goldstraw P: Report on the international workshop on intrathoracic staging. london, october 1996. Lung cancer (Amsterdam, Netherlands) 18:107-111, 1997

18. Lardinois D, De Leyn P, Van Schil P, et al: ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 30:787-792, 2006
19. Adachi H, Sakamaki K, Nishii T, et al: Lobe-specific lymph node dissection as a standard procedure in surgery for Non–Small cell lung cancer: A propensity score matching study. Journal of thoracic oncology 12:85-93, 2017
20. Annema JT, van Meerbeeck JP, Rintoul RC, et al: Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: A randomized trial. JAMA 304:2245-2252, 2010
21. Rusch VW: Mediastinoscopy: An obsolete procedure? The Journal of Thoracic and Cardiovascular Surgery 142:1400-1402, 2011
22. Annema JT, de Leyn P, Clementsen P, et al: Mediastinoscopy after negative endoscopic mediastinal nodal staging: Can it be omitted? European respiratory journal 46:1848-1849, 2015
23. Kim H: Reply to “Are we at the dusk of mediastinoscopy in modern clinical practice?”. Journal of Thoracic Oncology 10:e91-e92, 2015
24. Verhagen, A F T M, Schuurbiers OCJ, Looijen-Salamon MG, et al: Mediastinal staging in daily practice: Endosonography, followed by cervical mediastinoscopy. do we really need both? Interactive Cardiovascular and Thoracic Surgery 17:823-828, 2013
25. Li WWL, Heijden, H F M van der, Verhagen AF: Mediastinoscopy after negative endoscopic mediastinal nodal staging: Can it be omitted? European Respiratory Journal 46:1846-1848, 2015
26. Krantz SB, Howington JA, Wood DE, et al: Invasive mediastinal staging for lung cancer by the society of thoracic surgeons database participants. The Annals of Thoracic Surgery 106:1055-1062, 2018
27. Turner SR, Seyednejad N, Nasir BS: Patterns of practice in mediastinal lymph node staging for non-small cell lung cancer in canada. The Annals of Thoracic Surgery 106:428-434, 2018
28. Kuijvenhoven JC, Korevaar DA, Tournoy KG, et al: Five-year survival after endosonography vs mediastinoscopy for mediastinal nodal staging of lung cancer. JAMA 316:1110-1112, 2016



Chapter 2

Guideline adherence of mediastinal staging of non-small cell lung cancer: a multicentre retrospective analysis

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ABSTRACT

Objectives Mediastinal lymph node staging of NSCLC by initial endosonography and confirmatory mediastinoscopy is recommended by the European guideline. We assessed guideline adherence on mediastinal staging, whether staging procedures were performed systematically and unforeseen N2 rates following staging by endosonography with or without confirmatory mediastinoscopy.

Material and Methods We performed a multicentre (n=6) retrospective analysis of NSCLC patients without distant metastases, who were surgical candidates and had an indication for mediastinal staging in the year 2015. All patients who underwent EBUS, EUS and/or mediastinoscopy were included. Surgical lymph node dissection was the reference standard. Guideline adherence was based on the 2014 ESTS guideline.

Results 330 consecutive patients (mean age 69 years; 61% male) were included. The overall prevalence of N2/N3 disease was 42%. Initial mediastinal staging by endosonography was done in 84% (277/330; range among centres 71-100%; p<.01). Confirmatory mediastinoscopy was performed in 40% of patients with tumour negative endosonography (61/154; range among centres 10%-73%; p<.01). Endosonography procedures were performed 'systematically' in 21% of patients (57/277) with significant variability among centres (range 0-56%; p<.01). Unforeseen N2 rates after lobe-specific lymph node dissection were 8.6% (3/35; 95%-CI 3.0-22.4) after negative endosonography versus 7.5% (3/40; 95% CI 2.6-19.9) after negative endosonography and confirmatory mediastinoscopy.

Conclusion Although adherence to the European NSCLC mediastinal staging guideline on initial use of endosonography was good, 30% of endosonography procedures were performed insufficiently. Confirmatory mediastinoscopy following negative endosonography was frequently omitted. Significant variability was found among participating centres regarding staging strategy and systematic performance of procedures. However, unforeseen N2 rates after mediastinal staging by endosonography with and without confirmatory mediastinoscopy were comparable.

LIST OF DEFINITIONS

Mediastinal staging Mediastinal lymph node staging to determine the nodal status of lung cancer.

EBUS(-TBNA) Endobronchial Ultrasound guided-Transbronchial Needle Aspiration. Investigation of mediastinal and hilar lymph nodes with a linear ultrasound probe from the airways with the possibility of nodal sampling under real-time ultrasound control.

EUS(-FNA) Endoscopic Ultrasound guided-Fine Needle Aspiration. Investigation of mediastinal lymph nodes with a linear ultrasound probe from the oesophagus with the possibility of nodal sampling under real-time ultrasound control.

EUS-B(-FNA) Endoscopic Ultrasound guided-Fine Needle Aspiration using the EBUS scope.

Mediastinoscopy Surgical procedure to examine mediastinal lymph nodes with the possibility to take surgical biopsies.

Rapid On Site Evaluation (ROSE) Immediate cytological assessment of tissue specimen obtained by during EBUS or EUS procedures respectively. It could reduce inadequate sample results and could avoid repeat samples in case of tumour positive results.

Unforeseen N2 Pathologically proven N2 disease at final lung tumour resection and lymph node dissection when previous mediastinal staging showed N0 or N1 disease.

Surgical treatment Anatomical lung parenchyma resection of the primary tumour combined with a lobe-specific mediastinal lymph node dissection.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is a common disease with 410,000 new cases in Europe annually.[1] In the absence of distant metastases on computed tomography (CT) and positron emission tomography fluorodeoxyglucose (FDG-PET), selected surgical candidates are recommended to undergo invasive mediastinal staging depending on certain risk factors for regional metastatic nodal spread. Cervical mediastinoscopy has been the gold standard for mediastinal nodal staging. However, in the current European guideline endosonography (i.e. endobronchial ultrasound (EBUS) preferably followed by transoesophageal endoscopic ultrasound (EUS) with transluminal fine needle aspiration) is recommended over cervical mediastinoscopy as initial staging procedure for mediastinal nodal tissue staging. In case of tumour negative endosonography findings, cervical mediastinoscopy is recommended to rule out false-negative endosonography results.[2, 3] The routine use of confirmatory cervical mediastinoscopy is under debate since it only detects metastases in approximately 9% of patients. Additionally it is associated with significant morbidity, hospital admission, general anaesthesia and delay in definite treatment.[4-10] Adequate staging of NSCLC is however important to determine treatment and prognosis. Strict adherence to the guideline will probably ensure high quality of staging of NSCLC. Therefore, we assessed adherence to the guideline and the amount of systematically performed procedures of mediastinal staging of NSCLC in the Netherlands. Furthermore, we assessed the unforeseen N2 rates of staging strategies by endosonography with or without confirmatory mediastinoscopy after anatomical lung parenchyma resection with lobe-specific mediastinal lymph node dissection.

METHODS

We performed a multicentre (n=6) retrospective analysis of all patients who underwent EBUS, EUS and/or cervical mediastinoscopy for mediastinal staging of NSCLC in the year 2015. Guideline adherence was estimated using the 2014 European guideline by De Leyn, et al., since this was the latest published guideline on January 1, 2015.[2] This study was performed in the preparation of the multicentre randomised MEDIASTrial (NTR6528). We selected 6 centres to participate in this analysis based on geography (north, west, east, south Netherlands) and the national distribution of academic and non-academic lung surgical centres. The Institutional Review Board of Máxima Medical Centre approved the study and waived the need for individual informed consent.

Research questions

(1) What is the variability among centres in using endosonography as initial mediastinal staging procedure?
(2) What is the variability among centres in performing confirmatory mediastinoscopy after tumour-negative endosonography?
(3) What is the variability among centres in systematic performance of endosonography and cervical mediastinoscopy?
(4) What is the unforeseen N2 rate of endosonography alone versus endosonography followed by cervical mediastinoscopy?

Patient selection

Lists of all patients who underwent EBUS, EUS and/or mediastinoscopy in 2015 in the participating centres were collected. Subsequently we selected those patients who underwent mediastinal staging for proven or suspected NSCLC. Patients who underwent EBUS, EUS or mediastinoscopy for other purposes (diagnosing lung cancer or mediastinal metastases of other primary tumours, tuberculosis, sarcoidosis, lymphomas or restaging the mediastinum after induction therapy) were excluded, as well as patients with proven distant metastasis at time of mediastinal staging and patients who objected for retrospective chart research in advance.

Data collection

Data collection was done using a structured case report form which included the indication for diagnostic test(s), gender, age at time of the test(s) and clinical tumour, node and metastases (cTNM) classification. Data of mediastinal staging procedures were obtained from written endosonography reports, written surgical reports and macroscopic description of tissue (amount of tissue samples) in pathology reports. For endosonography the following data were collected: presence of Rapid On Site Evaluation (ROSE), visualized lymph nodes stations, sampled lymph nodes stations, number of samples per lymph node station and pathologic result whether lymphoid tissue and/or metastases were present. For cervical mediastinoscopy and definite surgical lymph node dissection the following data were collected: level of sampled lymph node stations, extent of resection per lymph node station (number of biopsies or complete lymph node or station removal) and pathological result whether lymphoid tissue and/or metastases were present.

For this study we used the 7th edition of the TNM staging method, since this version was the latest version in 2015. All data were stored and analysed pseudonymously. Key codes to identify the patients were safeguarded in the participating centres.

Assessment of endosonography procedures

According to the 2014 European guideline a systematic EBUS is defined as endosonographic examination of at least lymph node stations 4L, 7 and 4R.[2] Lymph nodes in stations 4L, 7 and 4R larger than 5 mm as well as all CT-enlarged (>1 cm) and/or FDG-avid (SUV>2.5) lymph nodes in reach of EBUS should be sampled. Systematic EUS is defined as endosonographic examination of at least lymph node station 4L, 7 and 8. Lymph nodes in stations 4L, 7 and 8 larger than 5 mm as well as all CT-enlarged and/or FDG-avid lymph nodes in reach of EUS should be sampled. For both procedures FDG-avid nodes that are smaller than 5 mm without suspicious appearance on endosonography (malignant criteria: round shape, sharp borders or hypo-echoic texture) biopsies are not obligatory.[2, 3] Endosonographic procedures were judged to be 'systematic' if the criteria mentioned above were fulfilled. When only the suspicious lymph nodes on CT and/or FDG-PET were sampled the procedure was defined as 'targeted'. If only a selection of suspicious lymph nodes was sampled the procedure was defined as 'insufficient'. Endosonographic procedures with available ROSE and proven N3 metastases were defined as 'systematic', since after diagnosing N3 metastases sampling of other suspect lymph nodes in N1 or N2 stations is not necessary. Procedures with ROSE and proven N2 metastases results were defined as 'systematic' when N3 metastases were excluded adequately. Since lymph node stations 5 and 6 are not accessible with conventional EBUS and EUS these stations were not included in the assessment of endosonography procedures.

All endosonography procedures were performed under conscious, moderate or deep sedation. None of the centres used general anaesthesia for endosonography procedures within the time frame of this study. In nearly all patients undergoing EUS, an esophageal endoscope was used instead of an endobronchial endoscope.

Assessment of cervical mediastinoscopy

Complete systematic cervical mediastinoscopy consists of assessment of mediastinal lymph node stations 2R, 4R, 7, 4L and 2L. One entire lymph node or 4 surgical biopsies should be taken from each lymph node station. Cervical mediastinoscopy was defined as 'complete' when performed according to criteria mentioned above. The 2014 European guideline recommends four surgical biopsies or one entire lymph node from lymph node station 4R, 7 and 4L.[2] If these criteria were met the procedure was defined as 'sufficient'. Mediastinoscopies that did not at least contain samples of station 4R, 7 and 4L were defined as 'insufficient'. One centre performed video-assisted mediastinoscopic lymphadenectomy (VAMLA), all other centres used cervical videomediastinoscopy with sampling.

Reference standard

Tumour positive pathology results of endosonography or cervical mediastinoscopy samples were interpreted as definite positive lymph node metastasis, since no surgical confirmation will be done in these cases and false positive results are extremely rare. In case of tumour negative pathology or proven N1 metastases, patients will generally be referred for surgical treatment including mediastinal lymph node dissection which is the surgical reference standard. According to the guideline an anatomical lung parenchyma resection with lobe-specific mediastinal lymph node dissection should be done. If the right upper or middle lobe is resected, lymph node stations 2R, 4R and 7 need to be dissected. In case of a resection of the right lower lobe lymph node stations 4R, 7, 8 and 9 need to be dissected. In left-sided resections lymph node stations 5, 6 and 7 need to be dissected with the left upper lobe and stations 7, 8 and 9 with the left lower lobe.[2, 3, 11] In order to value the surgical reference standard, mediastinal lymph node dissection performed according to the abovementioned criteria will be defined as 'complete' whereas other procedures were defined as 'insufficient'.

Data analysis

Results were reported according to the STrengthening Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational studies.[12] Descriptive data were presented as means (with standard deviation (SD) and/or range) or medians (with interquartile range (IQR) and/or range) depending on (normally or skewed) distribution of data. Categorical data were presented as counts and percentages (with 95% confidence intervals (CI) and/or range) and were compared among centres and staging strategy group by the Chi-squared test. In case of zero cell frequencies, the Fisher's exact test was performed. Numerical baseline characteristics were compared among centres by one-way ANOVA or Kruskal Wallis test depending on (normal or skewed) distribution of data.

Adherence to the guideline regarding the preferred staging strategy was calculated as the proportion of patients who underwent endosonography (either EBUS and/or EUS) as initial staging procedure. Next, the proportion of patients who underwent confirmatory mediastinoscopy of all patients with tumour negative endosonography was calculated. Since some patients will not undergo definite surgical treatment after negative staging we additionally calculated the proportion of patients who underwent confirmatory mediastinoscopy before definite surgical treatment. Guideline adherence was compared among centres and between patients divided on the indication for mediastinal staging using the Chi-squared test.

After construction of 2x2 tables for individual staging techniques the proportion of unforeseen N2 disease was calculated. We calculated 95% confidence intervals (CI)

around the unforeseen N2 rates using the Wilson interval.[13] Significance was set at a p-value of less than 0.05. All calculations and statistical analysis were performed using the statistical package for the social sciences (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY).

RESULTS

Patients

A total of 1,115 unique patients who underwent 1,211 diagnostic procedures (677 EBUS, 380 EUS, 154 mediastinoscopy) in six Dutch thoracic surgery centres (one academic and five non-academic) in the year 2015 were identified. Most patients (n=785) underwent the procedures for other purposes; diagnosing lung cancer or tissue diagnosis of metastasized NSCLC (n=163), mediastinal metastases of other primary tumours (n=217), diagnosis of tuberculosis, sarcoidosis, lymphoma or other (n=363) or mediastinal restaging after induction therapy for NSCLC (n=42). The remaining 330 patients with proven or suspected, probably resectable, NSCLC were included for analysis (Figure 1). The mean age was 69 years (SD 9; range 41-92) and 61% of patients were male. All patients underwent preoperative CT and 97% of patients underwent additional preoperative FDG-PET. We found a pathologically proven N2/N3 prevalence of 42% (140/330; range among centres 29-60%; p=.02) (Table 1).

Table 1. Clinical characteristics of included patients

Centre	1 (n=40)	2 (n=67)	3 (n=79)	4 (n=22)	5 (n=47)	6 (n=75)	P value
Age, mean (SD), y	69 (10)	69 (9)	66 (9)	73 (7)	68 (9)	69 (9)	.05
Sex, No. (%)							
Male	26 (65)	42 (63)	43 (54)	13 (59)	29 (62)	48 (64)	.83
Female	14 (35)	25 (37)	36 (46)	9 (41)	18 (38)	27 (36)	
Indication for staging, No (%)							
cN1	2 (5)	7 (10)	15 (19)	0	4 (9)	4 (5)	<.01
cN2	6 (15)	37 (55)	39 (49)	9 (41)	23 (49)	27 (36)	
cN3	17 (42)	13 (19)	18 (23)	9 (41)	11 (23)	15 (20)	
cN0 and central tumour	8 (20)	6 (9)	7 (9)	1 (4)	2 (4)	17 (23)	
cN1 and central tumour	0	2 (3)	0	0	0	0	
cN2 and central tumour	4 (10)	1 (2)	0	2 (10)	4 (9)	10 (13)	
cN3 and central tumour	3 (8)	1 (2)	0	1 (4)	3 (6)	2 (3)	

Table 1. Clinical characteristics of included patients (*continued*)

Centre	1 (n=40)	2 (n=67)	3 (n=79)	4 (n=22)	5 (n=47)	6 (n=75)	P value
Tumour localization, No. (%)							
Right lower lobe	5 (13)	14 (21)	16 (20)	4 (18)	6 (13)	13 (17)	
Right middle lobe	3 (8)	6 (9)	5 (6)	0	3 (6)	5 (7)	
Right upper lobe	13 (33)	22 (33)	29 (37)	11 (50)	23 (49)	23 (31)	.69
Left upper lobe	12 (30)	21 (31)	24 (30)	6 (27)	9 (19)	24 (32)	
Left lower lobe	7 (18)	4 (6)	5 (6)	1 (5)	6 (13)	10 (13)	
Tumour stage PET/CT, No. (%)							
Tx	1 (3)	0	4 (5)	0	0	0	
T1	14 (35)	14 (21)	23 (29)	6 (27)	8 (17)	19 (25)	
T2	7 (18)	25(37)	27 (34)	10 (45)	16 (34)	30 (40)	.22
T3	10 (25)	13 (19)	13 (16)	3 (14)	13 (28)	17 (23)	
T4	8 (20)	15 (22)	12 (15)	3 (14)	10 (21)	9 (12)	
Clinical nodal stage, No. (%)							
N0	8 (20)	6 (9)	7 (9)	1 (5)	2 (4)	17 (23)	
N1	2 (5)	9 (13)	15 (19)	0	4 (9)	4 (5)	<.01
N2	10 (25)	38 (57)	39 (49)	11 (50)	27 (57)	37 (49)	
N3	20 (50)	14 (21)	18 (23)	10 (46)	14 (30)	17 (23)	
Staging strategy, No. (%)							
EBUS	36 (89)	35 (52)	21 (27)	15 (68)	37 (79)	17 (23)	
EUS	0	11 (16)	6 (8)	0	6 (13)	25 (33)	
EBUS + EUS	1 (3)	3 (5)	0	1 (5)	2 (4)	1 (1)	
EBUS + mediastinoscopy	3 (8)	7 (10)	21 (26)	5 (22)	1 (2)	2 (3)	<.01
EUS + mediastinoscopy	0	0	7 (9)	0	1 (2)	9 (12)	
EBUS + EUS + mediastinoscopy	0	2 (3)	1 (1)	0	0	1 (1)	
Mediastinoscopy	0	9 (14)	23 (29)	1 (5)	0	20 (27)	
Pathologically proven N2/3 prevalence	40%	43%	29%	50%	60%	47%	.02

SD=standard deviation; No.=number; cN1-3=clinical nodal stage N1, N2 or N3; EBUS= endobronchial ultrasonography; EUS= endoscopic ultrasonography.

Guideline adherence

Initial mediastinal staging by endosonography was performed in 84% of patients (277/330; range among centres 71-100%; p<.01). EBUS was performed in 61% (200/330; range among centres 25-93%; p<.01), EUS was performed in in 20% (65/330; range among centres 0-45%; p<.01) and combined EBUS and EUS was performed in 3% (12/330; range among centres 1-8%; p=.48). Immediate mediastinoscopy without prior endosonography was performed in the remaining 16% of patients (53/330; range among centres 0-29%; p<.01). Confirmatory mediastinoscopy was performed in 40% of patients with tumour negative endosonography (61/154; range among centres 10%-73%; p<.01) (Figure 1).

Eighty-two out of 197 patients (42%) with tumour-negative mediastinal staging (either endosonography or mediastinoscopy) did not undergo surgical treatment due to primary treatment with chemoradiotherapy, clinical deterioration or refusal of surgery as main reasons. Of the 75 patients undergoing surgical resection after negative endosonography, 53% underwent prior confirmatory mediastinoscopy (40/75; range among centres 14-100%; p<.01) (Figure 1).

Mediastinoscopy as only staging procedure was performed in 59% (19/32), 49% (20/41) and 100% (2/2) of patients with cN1, cN0 with central tumour and cN1 with central tumour respectively, while in patients with cN2-cN3 with or without central tumour location endosonography is the modality of first choice in 94-100% of patients (p<.01) (Table 2).

Table 2. Initial staging technique subdivided by indication for mediastinal staging

		Initial staging technique		
Indication for staging	**Total, No. (%)**	**Endosonography, No. (%)**	**Mediastinoscopy, No. (%)**	**P value**
cN1	32 (10)	13 (41)	19 (59)	<.01
cN2	141 (43)	133 (94)	8 (6)	
cN3	83 (25)	79 (95)	4 (5)	
cN0 and central tumour	41 (12)	21 (51)	20 (49)	
cN1 and central tumour	2 (1)	0	2 (100)	
cN2 and central tumour	21 (6)	21 (100)	0	
cN3 and central tumour	10 (3)	10 (100)	0	

No.=number; cN1-3=clinical nodal status N1, N2 or N3.

Mediastinoscopy results

Mediastinoscopy following tumour negative endosonography diagnosed N2/N3 metastases in 8.2% of patients (5/61). Three patients underwent prior EBUS: one patient had representative tumour negative samples of the affected lymph node station (4R, FDG-avid, 3 punctures), in one patient the affected lymph node station (4R, not FDG-non-avid) was visualized but not sampled and in one patient the affected lymph node station (7, FDG-non-avid) had inconclusive samples (3 punctures, without ROSE) by EBUS. The other two patients initially underwent EUS; one with inconclusive results (station 4L, FDG-non-avid, 4 punctures, without ROSE) and one with representative but tumour negative samples (station 7 and 4L, CT-enlarged, FDG-non-avid, 3 and 1 punctures respectively). Of the 53 patients who underwent mediastinoscopy without prior endosonography 9.4% (5/53) had tumour positive N2/N3 nodes (all located in lymph node stations 4R, 7 and/or 4L) at mediastinoscopy.

Systematic performance of staging procedures

EBUS (n=200) was performed 'systematically' in 28%, 'targeted' in 38% and 'insufficient' in 34% of patients with a significant difference in performance among centres (range 'systematic': 0-56%; p<.01). EUS (n=65) was performed 'systematically' in 2% of patients, 'targeted' in 71% of patients and 'insufficient' in 27% of patients. The combined endosonographic strategy (i.e. EBUS + EUS, n=12) was performed 'targeted' in 50% of patients and 'insufficient' in the remaining 50%. We found no significant difference among centres on the amount of systematic performed EUS or combined EBUS and EUS procedures. Mediastinoscopy (n=114) was performed 'complete' in 34%, 'sufficient' in 55% and 'insufficient' in 11% of patients, without differences among centres.

Unforeseen N2 disease

Mediastinal lymph node dissection (n=115) was performed 'complete' in 54% and 'insufficient' in 46% of patients, with no significant difference among centres (p=.11). Unforeseen N2 disease was found in 8.6% (3/36; 95%-CI 3.0-22.4) after tumour negative endosonography versus 7.5% (3/40; 95% CI 2.6-19.9) after tumour negative endosonography and confirmatory mediastinoscopy. The EBUS procedures of two (67%) patients who underwent EBUS as only staging technique were performed insufficient, whereas all other EBUS and mediastinoscopy at least were performed 'targeted' or 'sufficient'. Unforeseen N2 disease after mediastinoscopy (without prior endosonography) was found in 5.0% (2/40; 95% CI 0.8%-18.2%) (Figure 1).

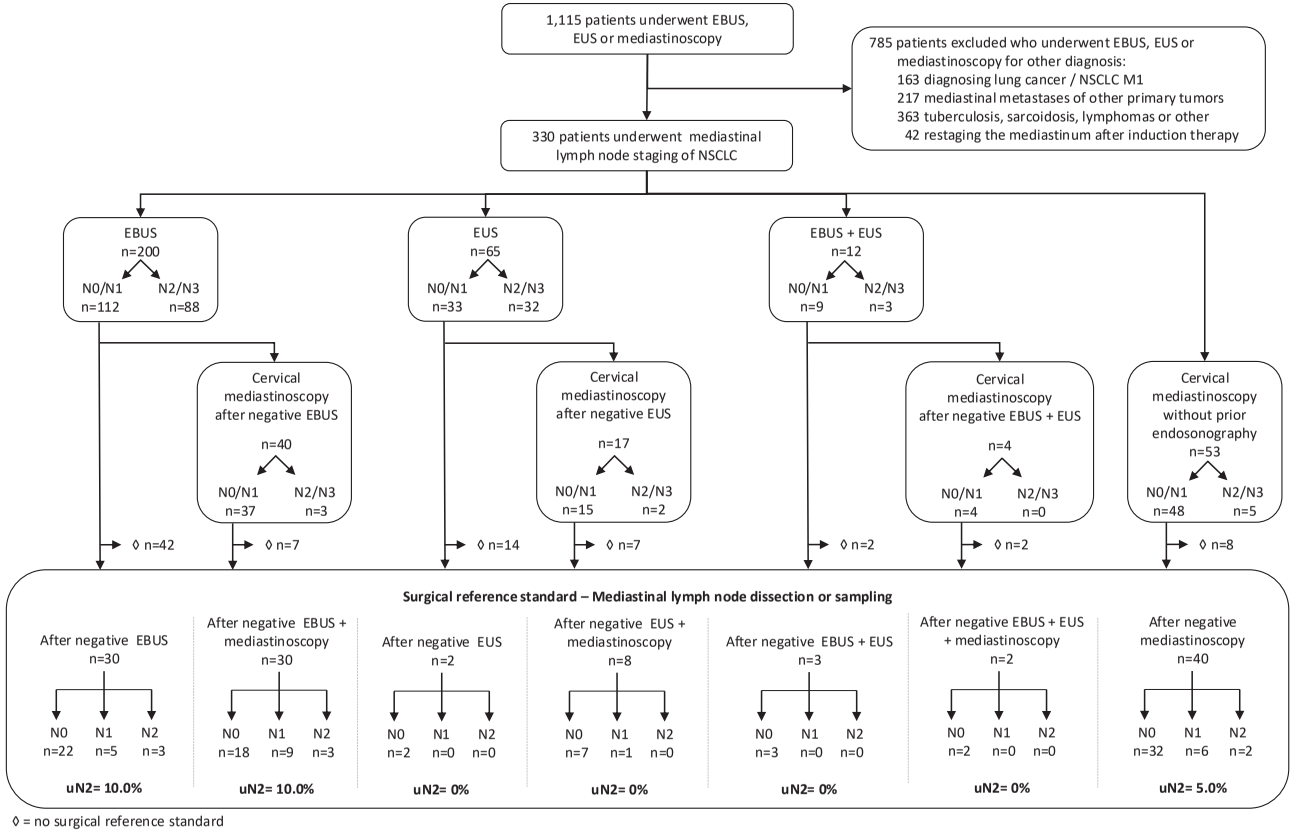

Figure 1. Flowchart of included patients in different mediastinal lymph node staging strategies.

◊ = no surgical reference standard; EBUS= endobronchial ultrasonography; EUS= endoscopic ultrasonography; NSCLC=non-small cell lung cancer; n=number; uN2=unforeseen N2.

DISCUSSION

Adherence to the 2014 European guideline regarding the initial usage of endosonography in mediastinal staging of NSCLC is good (84%), although 30% of endosonographic procedures were performed insufficiently. Confirmatory mediastinoscopy after negative endosonography is frequently omitted (60%), whereas only 11% of mediastinoscopies were performed insufficiently. Additionally, significant variability among centres was found regarding staging strategy and systematic performance of procedures. However, unforeseen N2 rates after mediastinal staging by endosonography with and without confirmatory mediastinoscopy were comparable and within the acceptable limit of 10% that was mentioned in the 2014 European guideline.[2]

Possible sources for the significant variability among centres in mediastinal staging strategy and performance are differences in patient population, availability of endosonography equipment and preferences of local physicians. EUS was used as primary staging technique in 45% of patients in one participating centre (compromising 52% of all patients who underwent EUS as primary staging procedure in this analysis). The pulmonologists in this centre had only one EBUS-scope at their disposal whereas multiple EUS-scopes were available. Possibly patients with left-sided suspect lymph nodes more likely underwent EUS, whereas patients with right-sided suspect lymph nodes may have undergone more often immediate mediastinoscopy or EBUS. Next to the availability of equipment, differences in patient population and selection might have influenced results of mediastinal staging among centres. The current ERS-ESTS-ESGE guideline describes four indications (suspect lymph nodes, central tumours, large peripheral tumours or FDG-non-avid tumours) for invasive mediastinal staging.[3]

Direct use of mediastinoscopy without initial endosonography in our analysis was done in the majority of patients with central tumours (cN0) and cN1 patients. Skipping endosonography in these patients has the advantage of decreasing the total time for staging and earlier starting lung cancer treatment. Besides, primary use of mediastinoscopy in cN0-1 patients is also recommended by the Leuven Lung Cancer Group since sensitivity may be better.[14, 15] However, these results are not implemented in the guidelines so far and further research on this topic is needed. Variability in adherence to the guideline also exists in other countries. A questionnaire among Canadian thoracic surgeons (n=47) showed significant variability in indications for invasive staging and choice of initial staging procedure (47.9% EBUS, 43.5% mediastinoscopy).[16] A retrospective analysis in the US (n=406, 5 centres) showed variability in frequency of mediastinal staging among the centres (range 17-94%).[17]

In addition to patient selection and type of staging strategy, systematic performance of individual staging procedures is important regarding quality of staging. After publication of the ESTS guideline in 2014 the combined ERS-ESTS-ESGE published in 2015 already changed the recommendation on initial endosonography by EBUS or EUS to always perform EBUS, preferably added by EUS.[2, 3] Since publication of this guideline additional evidence on this topic has been published. A meta-analysis showed a significant increase in sensitivity (12%) and detection rate for the combined use of EBUS and EUS(-B) compared with either procedure alone.[18] Beside the additional value on the combined use of both procedures a prospective multicentre international randomised controlled trial showed the value of a systematically performed combined endosonography (EBUS and EUS) versus targeted EBUS alone. The sensitivity for detection of mediastinal lymph node metastases was 9% higher in the systematic combined approach compared to targeted EBUS strategy alone. Additional clinically relevant staging information was found in 10% of patients.[19] In the present analysis most endosonographic procedures were performed using a 'targeted' strategy (EBUS 38%, EUS 71%, EBUS+EUS 50%) or even 'insufficient' (EBUS 34%, EUS 27%, EBUS+EUS 50%) with significant variability on the amount of systematically performed procedures among centres. Sedation and patient comfort could be compromising factors on the length and extensiveness of the endosonography procedure. Routine use of conscious sedation could possibly improve systematic performance of endosonographic procedures as well as patient comfort. However, first we need to invest in changing the pulmonologists' mind-set from a 'hit-and-run' strategy towards the 'systematic' approach to adequately stage the mediastinum. Structured training in performance and implementation of EBUS and EUS(-B) is strongly advised. Within the ERS, a structured three step (theory online modules; clinical observation and simulator training; self-practice and video analysis) training and certification programme has been developed.[20] The detected significant variability in the use of confirmatory mediastinoscopy in our analysis confirms the current debate in international literature regarding this topic.[5-8, 10] The amount of 'complete' (34%) or 'sufficient' (55%) performed mediastinoscopies in our analysis was high. This corresponds with results from a nationwide analysis of data from the Dutch Lung Cancer Audit for Surgery. Performance according to the European guideline was done in 75% of 1,729 mediastinoscopies.[21] However, the additional diagnostic value of confirmatory mediastinoscopy should be weighed against the burden for the patient (6.0% complications [9] and delay in definite treatment). Although with 46% insufficiently performed lymph node dissections in mind, we found comparable unforeseen N2 rates for staging strategies with or without confirmatory mediastinoscopy. This possibly implies limited additional value of confirmatory mediastinoscopy after negative endosonography. A meta-analysis on this topic showed comparable unforeseen N2 disease rates in the range of 9.6% to 9.9% in patients who underwent mediastinal lymph node

staging by EBUS alone or combined endosonography strategy with or without confirmatory mediastinoscopy.[9] The unforeseen N2 rate of 5.0% in patients undergoing direct mediastinoscopy without prior endosonography is probably caused by the selected population of which 77% only had cN0-1 (with or without centrally located tumour). The additional value of confirmatory mediastinoscopy after negative endosonography in NSCLC is currently under investigation in a large multicentre randomised controlled trial (MEDIASTrial, NTR6528).[22]

Despite the clear value of 'systematic' performance of staging techniques on sensitivity and unforeseen N2 rates, no studies have reported favourable effect on patient reported outcome measures and only few on survival. In the ASTER-trial unforeseen N2 was found in 14.3% of patients after mediastinoscopy only versus 6.9% after endosonography and mediastinoscopy.[23] Despite this difference in unforeseen N2 disease, 5-year survival was exactly the same in both groups.[24] Therefore future research should not only focus on training and concentration of technically demanding diagnostics in qualified centres in order to improve diagnostic accuracy, but also on the clinically relevant effects of improved (systematic) staging on treatment and outcome.

A limitation of the current study was the unclear representativeness for the entire Dutch situation of the included centres in our sample. In the year 2015 lung surgery was performed in 46 centres in the Netherlands (8 academic, 38 non-academic). Since our analysis only included a sample of 1 academic and 5 non-academic centres, the staging strategy and quality may be different in the remaining centres in the Netherlands. Nationwide analysis with data from the Dutch Lung Surgical Audit may provide additional evidence on generalizability of results on this topic. Another limitation was the retrospective design since incomplete documentation of endosonographic and surgical procedures could have influenced results in a negative way. Patients with an indication for mediastinal staging who underwent direct anatomical resection for NSCLC are missing in this analysis. Although this group will probably be a minority, it could possibly have led to guideline adherence overestimation and unreliable unforeseen N2 rates. A substantial part of included patients with negative mediastinal staging results did not undergo the surgical reference standard because of clinical deterioration or refusal of surgery, which implies that the unforeseen N2 rates should be interpreted with care. In our opinion future research should focus on guideline adherence and possible oncologic and therapeutic consequences of non-adherence on a nationwide or European level.

Based on our results we suggest to comply with the guidelines to optimize preoperative mediastinal lymph node staging and to prevent practice variation based solely on availability of equipment and local preferences. Endosonographic training and use of con-

scious or deep sedation may play a role in reducing non-systematic performed staging procedures and subsequently prevent patients from unnecessary mediastinoscopies or major lung surgery. When strict adherence to the guideline remains problematic due to unavailability of well-trained physicians or equipment, concentration of mediastinal staging of lung cancer in qualified centres should be considered to guarantee high quality.

CONCLUSION

Although adherence to the European NSCLC mediastinal staging guideline on initial use of endosonography was good, however 30% of endosonography procedures were performed insufficiently. Confirmatory mediastinoscopy following negative endosonography was frequently omitted. Significant variability was found among participating centres in staging strategy and systematic performance of procedures. However, unforeseen N2 rates after mediastinal staging by endosonography with and without confirmatory mediastinoscopy were comparable and within the acceptable limit mentioned in the ESTS guideline.

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Role of the funding source

The funding sources had no involvement in the study design, data analysis and interpretation and the decision to submit the article for publication.

Author contributions

JB, MvD, MD, JA and FvdB have been involved in the design on the study. NB, GB, WB, NC, AMD, WH, RK, JWL, JM, WS, YV, MYES provided the lists of patients who underwent mediastinal staging. JB, MvD, FH and EH have been involved in acquisition of data. JB and FvdB analysed and interpreted the data and JB and MvD drafted the manuscript. All authors critically revised the manuscript and gave approval for publication of the final version.

Conflict of interest

Dr. Bousema and Dr. van den Broek report grants from ZonMw and the Dutch Cancer Society, during the conduct of this study. Prof. Dr. Annema reports non-financial support from Hitachi Medical systems and Pentax and a grant from Cook medical, outside the submitted work. Dr. van Dorp, Dr. Hoeijmakers, E. Huijbregts, Dr. Barlo, Dr. Bootsma, Dr. Van Boven, Dr. Claessens, Prof. Dr. Dingemans, Dr. Hanselaar, Dr. Kortekaas, Dr. Lardenoije, Prof. Dr. Maessen, Dr. Schreurs, Dr. Vissers, Dr. Youssef-El Soud and Prof. Dr. Dijkgraaf have nothing to disclose.

REFERENCES

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians 2015;65:87-108.

[2] De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2014;45:787-98.

[3] Vilmann P, Clementsen PF, Colella S, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015;47:546-60.

[4] Steunenberg B, Aerts B, Aerts J, et al. Quality Assessment of Video Mediastinoscopy Performed for Staging in Non-Small Cell Lung Cancer. Thorac cardiovasc Surg 2016;64:520-5.

[5] Rusch VW. Mediastinoscopy: An obsolete procedure? The Journal of Thoracic and Cardiovascular Surgery 2011;142:1400-2.

[6] Annema JT, de Leyn P, Clementsen P, Siemsen M, Vilmann P. Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European respiratory journal 2015;46:1848-9.

[7] Kim H. Reply to “Are We at the Dusk of Mediastinoscopy in Modern Clinical Practice?”: An Irresistible Trend. Journal of Thoracic Oncology 2015;10:e92.

[8] Li WWL, Heijden, H F M van der, Verhagen AF. Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European Respiratory Journal 2015;46:1846-8.

[9] Bousema JE, van Dorp M, Noyez VJJM, Dijkgraaf MGW, Annema JT, van den Broek, Frank J.C. Unforeseen N2 disease following negative endosonography with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. Journal of Thoracic Oncology 2019.

[10] Verhagen, A F T M, Schuurbiers OCJ, Looijen-Salamon MG, Heide, S M van der, Swieten HAv, Heijden, E H M van der. Mediastinal staging in daily practice: endosonography, followed by cervical mediastinoscopy. Do we really need both? Interactive Cardiovascular and Thoracic Surgery 2013;17:823-8.

[11] Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.

[12] von Elm, Erik|Altman, Douglas G.|Egger, Matthias|Pocock, Stuart J.|Gøtzsche, Peter C.|Vandenbroucke, Jan P. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies. International Journal of Surgery 2014;12:1495-9.

[13] Lawrence D. Brown, T. Tony Cai, Anirban DasGupta. Interval Estimation for a Binomial Proportion. Statistical Science 2001;16:101-17.

[14] Decaluwé Herbert, Dooms Christophe, D’Journo Xavier Benoit, et al. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study. The European Respiratory Journal 2017;50:1701493.

[15] Dooms C, Tournoy KG, Schuurbiers O, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest 2015;147:209-15.

[16] Turner SR, Seyednejad N, Nasir BS. Patterns of Practice in Mediastinal Lymph Node Staging for Non-Small Cell Lung Cancer in Canada. The Annals of Thoracic Surgery 2018;106:428-34.

[17] Thornblade LW, Wood DE, Mulligan MS, et al. Variability in invasive mediastinal staging for lung cancer: A multicenter regional study. The Journal of Thoracic and Cardiovascular Surgery 2018;155:2671.e1.

[18] Korevaar DA, Crombag LM, Cohen JF, Spijker R, Bossuyt PM, Annema JT. Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. The Lancet Respiratory Medicine 2016;4:960-8.

[19] Crombag LMM, Dooms C, Stigt JA, et al. Systematic and combined endosonographic staging of lung cancer (SCORE Study). The European respiratory journal 2018:1800800.

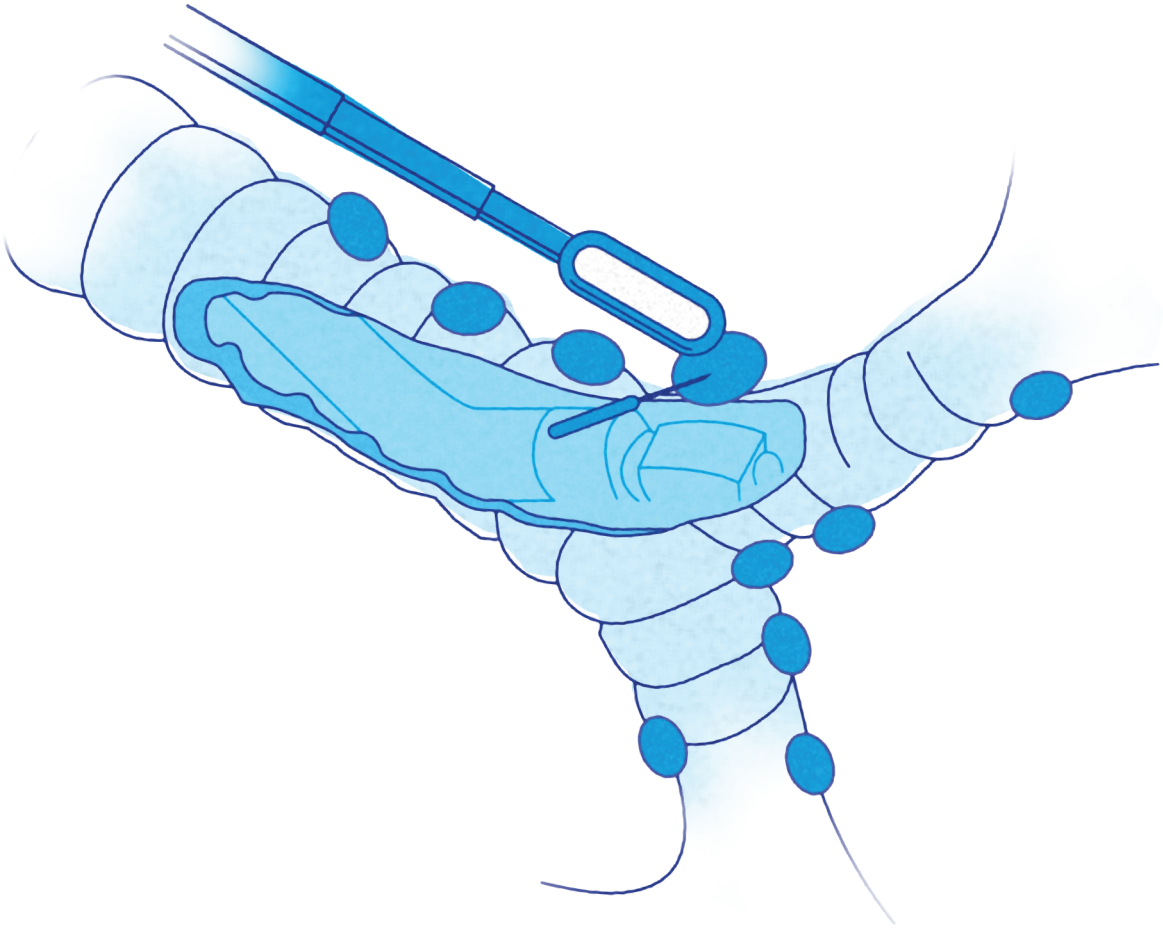
[20] Farr A, Clementsen P, Herth F, et al. Endobronchial ultrasound: launch of an ERS structured training programme. Breathe (Sheffield, England) 2016;12:217-20.

[21] Hoeijmakers F, Heineman DJ, Beck N, et al. Mediastinoscopy for staging of Non-Small Cell Lung Cancer: surgical performance in the Netherlands. The Annals of Thoracic Surgery 2018.

[22] Bousema JE, Dijkgraaf MGW, Papen-Botterhuis NE, et al. MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a multicenter randomised controlled trial. BMC surgery 2018;18:27.

[23] Annema JT, Van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. JAMA 2010;304:2245-52.

[24] Kuijvenhoven JC, Korevaar DA, Tournoy KG, et al. Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer. JAMA 2016;316:1110-2.



Chapter 3

Adherence to the mediastinal staging guideline and unforeseen N2 disease in patients with resectable non-small cell lung cancer: Nationwide results from the Dutch Lung Cancer Audit - Surgery

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ABSTRACT

Objectives Invasive mediastinal staging is advised by guidelines in patients with resectable non-small cell lung cancer (NSCLC) and suspicious lymph nodes (cN1-3) or for central, FDG-non-avid or peripheral tumours >3 cm. Our objective was to assess current guideline adherence and consequent unforeseen N2 disease (uN2) in NSCLC patients having various indications for mediastinal staging.

Materials and methods We analysed the Dutch Lung Cancer Audit – Surgery data of all patients who underwent a primary lung resection with lymph node dissection for NSCLC in 2017-2018. Based on the 2015 ESTS-ERS-ESGE guideline we assessed the use of initial endosonography and confirmatory mediastinoscopy as well as uN2 rates.

Results A total of 2,238 patients were analysed. 43% (95%-CI: 41-45) underwent initial endosonography followed by a confirmatory mediastinoscopy in 44% (95%-CI:40-47) of them, resulting in a 19% (95%-CI: 17-20) rate of properly staged patients according to the guidelines. uN2 was demonstrated in 12.5% (95%-CI: 9.7-16.0) of correctly staged patients compared to 10.9% (95%-CI: 9.6-12.4) who were not (p=.36). The highest uN2 rate was found in cN1-3 patients who were not staged (23.0%, 95%-CI: 16.4-31.2) compared to 13.0% (95%-CI: 9.7-17.1) who were (p=.01).

Conclusion Guideline adherence in Dutch NSCLC patients with an indication for invasive mediastinal staging is poor. The highest uN2 rate was found in unstaged cN1-3 patients, suggesting that this subgroup may benefit from an appropriate staging conform guidelines.

LIST OF DEFINITIONS

Central tumour Centrally located primary lung tumour defined as visibility of the tumor on video bronchoscopy in the main stem, lobair or segment bronchi or tumor adherent to or in between segment bronchi or blood vessels on computed tomography. (DLCA-S definition)

DLCA-S An acronym for Dutch Lung Cancer Audit - Surgery. This national registry contains all patients who underwent mediastinal or lung surgery in the Netherlands.

EBUS(-TBNA) An acronym for endobronchial ultrasound guided transbronchial needle aspiration. Investigation of mediastinal and hilar lymph nodes with a linear ultrasound probe from the airways with the possibility of nodal sampling under real-time ultrasound control.

EUS(-FNA) An acronym for endoscopic ultrasound guided fine needle aspiration. Investigation of mediastinal lymph nodes with a linear ultrasound probe from the oesophagus with the possibility of nodal sampling under real-time ultrasound control.

Mediastinal lymph node dissection Surgical lymph node dissection at time of lung tumour resection to ensure the pathological nodal stage. The DLCA-S provides no information to distinguish lymph node dissection from sampling. Despite of this uncertainty we describe lymph node assessment at time of resection of the lung tumour as mediastinal lymph node dissection in this paper.

Mediastinal staging Invasive mediastinal lymph node staging to determine the nodal status of lung cancer by using EBUS, EUS and/or mediastinoscopy.

Mediastinoscopy Surgical procedure under general anaesthesia to examine mediastinal lymph nodes with the possibility to take extensive surgical biopsies.

Peripheral tumour Primary tumour located in the outer two third of the lung.

Unforeseen N2 disease (uN2) Pathologically proven N2 disease at final lymph node dissection at time of tumour resection when previous mediastinal staging showed N0 or N1 disease.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer with over 9,000 new cases in the Netherlands annually. At the time of diagnosis, 23% of patients are eligible for intended curative surgical treatment.[1, 2] Computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) are used for primary tumour and hilar and mediastinal lymph node assessment. CT enlarged (>1 cm short axis) and/or FDG-avid lymph nodes are suspicious for the presence of metastases.[3] Patients with suspicious hilar or mediastinal lymph nodes (cN1-3) or centrally located, FDG-non-avid or large (>3 cm) peripherally located tumours are advised to undergo invasive mediastinal staging prior to surgical treatment according to European guidelines.[3, 4]

Invasive mediastinal staging consists of initial endosonographic assessment of hilar and mediastinal lymph nodes by using endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA), preferably combined with endoscopic ultrasound guided fine needle aspiration (EUS-FNA). Confirmatory mediastinoscopy is recommended in patients with cN1-3 but negative N2-3 cytology after endosonography. In patients with centrally located, FDG-non-avid or large peripheral tumours (>3 cm), the guideline suggests that confirmatory mediastinoscopy should be considered after negative endosonography.[3]

An adequate staging is crucial since unnecessary pulmonary resection and associated morbidity and mortality may be prevented. NSCLC with mediastinal lymph node metastases is treated with definitive chemoradiotherapy or a multimodality strategy with induction therapy followed by surgery.[5] Therefore, unforeseen N2 (uN2) after pulmonary resection and lymph node dissection is to be avoided by strict compliance to the guideline. However, retrospective series from the United States, the Netherlands and Canada indicated that invasive mediastinal staging varied widely.[6-8] It is unknown if rates of uN2 are affected by non-adherence to the guidelines in populations with different indications for invasive mediastinal staging.

The main objective of this study was to assess the effect of adherence to the invasive mediastinal staging guideline on uN2 rates in a national database of patients who underwent lung resection and mediastinal lymph node dissection for NSCLC from 2017-2018 in the Netherlands.

MATERIALS AND METHODS

Data source

We used data from the Dutch Lung Cancer Audit – Surgery (DLCA-S), which is part of the Dutch Lung Cancer Audit (DLCA). The DLCA prospectively records the pathway of all Dutch lung cancer patients from diagnosis until definite treatment and subsequent follow-up. The DLCA-S focusses on the surgical part of lung cancer treatment and includes all patients who underwent mediastinal or lung surgery in the Netherlands. The quality of data in this database is regularly checked on completeness and reliability at a patient level. If in doubt, queries are sent out to these hospitals. Additionally, data verification is randomly performed by an external organization.[9]

Patients

This study includes all patients who underwent a surgical lung tumour resection (i.e. wedge resection, segmentectomy, (bi-)lobectomy, pneumonectomy) combined with mediastinal lymph node dissection or sampling between January 1, 2017 and December 31, 2018, and were registered in the DLCA-S (n=5,135). Patients were excluded if histopathology other than NSCLC was found (n=504), if no mediastinal lymph node dissection was performed (only hilar (N1) lymph nodes dissected n=193, no lymph nodes dissected n=162), if induction treatment before surgery was given (n=321), if data on indication for invasive mediastinal staging were missing (n=234), if stage IV NSCLC was preoperatively detected (n=115), if no preoperative FDG-PET was provided (n=79), if surgery was performed for recurrent lung cancer (n=53), if N2 or N3 metastases were already demonstrated at invasive mediastinal staging (n=47), if no lymph node stations were sampled at mediastinoscopy (n=5) or if endosonography (n=67), mediastinoscopy (n=28) or mediastinal lymph node dissection (n=64) data were missing. Applying these criteria, a total of 3,263 patients were eligible for analysis. (Figure 1).

DLCA-S data collection

The DLCA-S database includes age, gender, tumour localization (lobe) and clinical tumour stage as baseline characteristics. Radiological staging contains information on CT derived anatomy (>1 cm short axis) of lymph node stations at the mediastinum (station 2-9), hilar (station 10-11) and interlobar levels (station 12-14) and on FDG-avidness of these lymph nodes. Additionally, primary tumour localization (central or peripheral) and FDG-avidness of the primary tumour are registered. The lymph node stations were reported according to the International Association for the Study of Lung Cancer mediastinal lymph node map. Lymph nodes that were obtained by EBUS (stations 2, 4, 7 and 10-12) and/or by EUS (station 4, 7-9) and corresponding pathological results were tabulated. However, details on extent and number of samples per lymph node station

were not available. Data that were registered at cervical mediastinoscopy and surgical lymph node dissection at the time of tumour resection were sampling of lymph node stations (yes/no) and whether metastases were found (yes/no). The DLCA-S provides no additional information to distinguish lymph node dissection from sampling and no information on the number of biopsies during mediastinoscopic or surgical lymph node dissection. Despite these uncertainties we consider the lymph node assessment at time of tumour resection as mediastinal lymph node dissection in this paper. Data on pathology include the definitive diagnosis, tumour diameter (mm) and pathologic TNM-stage (8^{th} edition). All data were stored and analysed pseudonymously. Key codes to identify individual patients were safeguarded by the DLCA-S.

Primary outcome

The primary outcome measure was the uN2 rate, defined as the percentage of patients with a pathological proof of N2-3 disease after surgical lymph node dissection at the time of tumour resection, whereas the cytological and/or pathological results of invasive mediastinal staging by endosonography and/or mediastinoscopy of N2-3 lymph nodes were benign, or if no invasive staging was performed. These uN2 rates were reported for different staging strategies (whether or not adhering to the European guideline) and for different indications for invasive mediastinal staging (i.e. cN1-3, central tumour, FDG-non-avid tumour, peripheral tumour >3 cm or no indication for invasive staging).

Data analysis

Whether the staging strategy was in concert with the European guideline was determined by comparison with the recommendations of the conjoint European Society of Gastrointestinal Endoscopy (ESGE), European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) guideline.[3] To assess adherence to a guideline we first determined whether individual patients had a strict indication for invasive mediastinal lymph node staging. Allocation of included patients was done based on tumour and nodal characteristics determining an indication for invasive staging. In case patients had two or more indications for invasive mediastinal staging, they were allocated to the indication group with the highest risk of lymph node metastases. For patients with cN1-3, the probability is 24% to 80%, for patients with central tumours this is 17% to 24%, and for patients with FDG-non-avid tumours and peripherally located tumours >3cm this is 6% to 30%.[3] Patients with a cN0, FDG-avid peripheral tumour <3 cm were classified as patients without indication for invasive mediastinal staging.

Guideline adherence for mediastinal staging was analysed in patients with an indication for mediastinal staging only. We calculated the proportion of patients who underwent endosonography as initial staging procedure and the proportion of patients who received

a confirmatory mediastinoscopy after N2-3 negative cytology after endosonography. Finally, we calculated the proportion of patients who underwent initial endosonography and confirmatory mediastinoscopy as prescribed by the guideline.

Unforeseen N2 disease was calculated for patients with or without adherence to the European guideline and for different indications for invasive mediastinal staging (i.e. cN1-3, central tumour, FDG-non-avid tumour, peripheral tumour >3 cm and patients without indication for invasive staging). In addition, uN2 was subdivided in single-level (only one mediastinal lymph node station with metastasis) and multi-level uN2 (>1 mediastinal lymph node stations with metastases). In order to interpret the value of the uN2 rates we estimated the quality of lymph node dissections by determining the mean number of assessed mediastinal lymph node stations per patient. Lymph node stations 5 and 6 are not accessible by EBUS and mediastinoscopy, and are sometimes considered N1 nodes in left upper lobe tumours, which makes pre-operative tissue confirmation less necessary in these cases. Since only limited data are reported by expert centres on transaortic EUS-guided fine needle aspiration of station 5 and 6, routine use of this procedure is not recommended.[4, 10] Therefore, separate analysis was done of single-level uN2 excluding metastases in stations 5 and 6 in patients with and without indication for invasive mediastinal staging. We calculated 95%-confidence intervals (95%-CI) of the uN2 rates by using the Wilson interval for proportions.[11] Comparisons were done by using the Chi-squared test. In case of zero cell frequencies the Fisher's exact test was performed.

Descriptive data were presented as means (with standard deviation (SD)) or medians (with interquartile range (IQR)) depending on (normal or skewed) distribution of data. Categorical data were presented as counts and percentages (with 95%-CI). Numerical baseline characteristics were compared among groups by using the unpaired T-test or Mann-Whitney U-test depending on distribution of data. Significance was set at a p-value of less than 0.05. All calculations and statistical analyses were performed by using the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients

A total of 5,135 lung resection procedures were registered in the DLCA-S during the two years of interest. After applying the exclusion criteria a total of 3,263 NSCLC patients who were primarily treated with a lung resection and mediastinal lymph node dissection were eligible for analysis (Figure 1). The mean age of the included patients was 68 years (SD 9) and 53% was male. Final histopathology showed adenocarcinoma in 61% and squa-

mous cell carcinoma in 29% (Table 1). A total of 2,238 (69%) patients had an indication for invasive mediastinal staging. Of these 878 had cN1-3 disease (27%), 396 had central tumours (12%), 187 had FDG-non-avid tumours (6%) and 777 had peripheral tumours >3 cm (24%). The remaining 1,025 (31%) patients having no indication for invasive staging were candidates for immediate lung resection with mediastinal lymph node dissection.

Table 1. Clinical characteristics of patients with and without an indication for invasive mediastinal lymph node staging.

	With indication for invasive staging			Without an indication for invasive staging (n=1,025)
	Staging conform guideline (n=416)	Staging not conform guideline (n=1,822)	P value	
Age, mean (SD), y	68 (9)	69 (9)	.05	66 (8)
Sex, No. (%) *				
Male	286 (69)	997 (55)	<.01	436 (42)
Female	130 (31)	824 (45)		589 (58)
Tumour stage PET/CT, No. (%)				
cTx	7 (1)	76 (4)	<.01	23 (2)
cTis	0	14 (1)		16 (2)
cT1	81 (20)	539 (30)		808 (78)
cT2	126 (30)	656 (35)		121(12)
cT3	128 (31)	378 (21)		49 (5)
cT4	74 (18)	159 (9)		8 (1)
Nodal stage PET/CT, No. (%)				
cN0	92 (22)	1,268 (70)	<.01	0
cN1	83 (20)	259 (14)		0
cN2	178 (43)	236 (13)		0
cN3	63 (15)	59 (3)		0
Indication for staging, No (%)				
cN1-3	324 (78)	554 (30)	<.01	0
Central tumour	42 (10)	354 (20)		0
FDG-non-avid tumour	6 (1)	181 (10)		0
Peripheral tumour >3 cm	44 (11)	733 (40)		0

Table 1. Clinical characteristics of patients with and without an indication for invasive mediastinal lymph node staging. (*continued*)

	With indication for invasive staging			Without an indication for invasive staging (n=1,025)
	Staging conform guideline (n=416)	Staging not conform guideline (n=1,822)	P value	
Tumour localization1, No. (%)				
Right upper lobe	125 (30)	529 (29)	.59	370 (36)
Right middle lobe	15 (4)	99 (5)		71 (7)
Right lower lobe	94 (23)	391 (21)		164 (16)
Left upper lobe	114 (27)	476 (26)		272 (27)
Left lower lobe	66 (16)	323 (18)		145 (14)
Staging technique, No. (%)				
No invasive staging	0	1,063 (58)	<.01	892 (88)
EBUS	0	444 (24)		72 (7)
EUS	0	45 (3)		13 (1)
EBUS + EUS	0	50 (3)		4
EBUS + mediastinoscopy	333 (80)	0		9 (1)
EUS + mediastinoscopy	44 (11)	0		0
EBUS + EUS + mediastinoscopy	39 (9)	0		1
Mediastinoscopy	0	220 (12)		23 (2)
Final histopathology data, No. (%)				
Adenocarcinoma	173 (41)	1,095 (59)	<.01	735 (71)
Squamous cell carcinoma	220 (53)	552 (30)		171 (17)
Adenosquamous carcinoma	5 (1)	21 (1)		17 (2)
Large cell carcinoma	4 (1)	29 (2)		12 (1)
Large cell NEC	11 (3)	37 (2)		22 (2)
Carcinoid	3 (1)	59 (5)		68 (7)

*gender unknown in 1 patient with in indication for staging. 1 tumour location unknown in 2 patients in the conform the guideline group and 4 patients in the not conform the guideline group; SD=standard deviation; No=number; cN1-3=clinical nodal stage N1, N2 or N3; Tis=carcinoma in situ; EBUS= endobronchial ultrasonography; EUS= endoscopic ultrasonography; N/A=not applicable; NEC=neuro endocrine carcinoma.

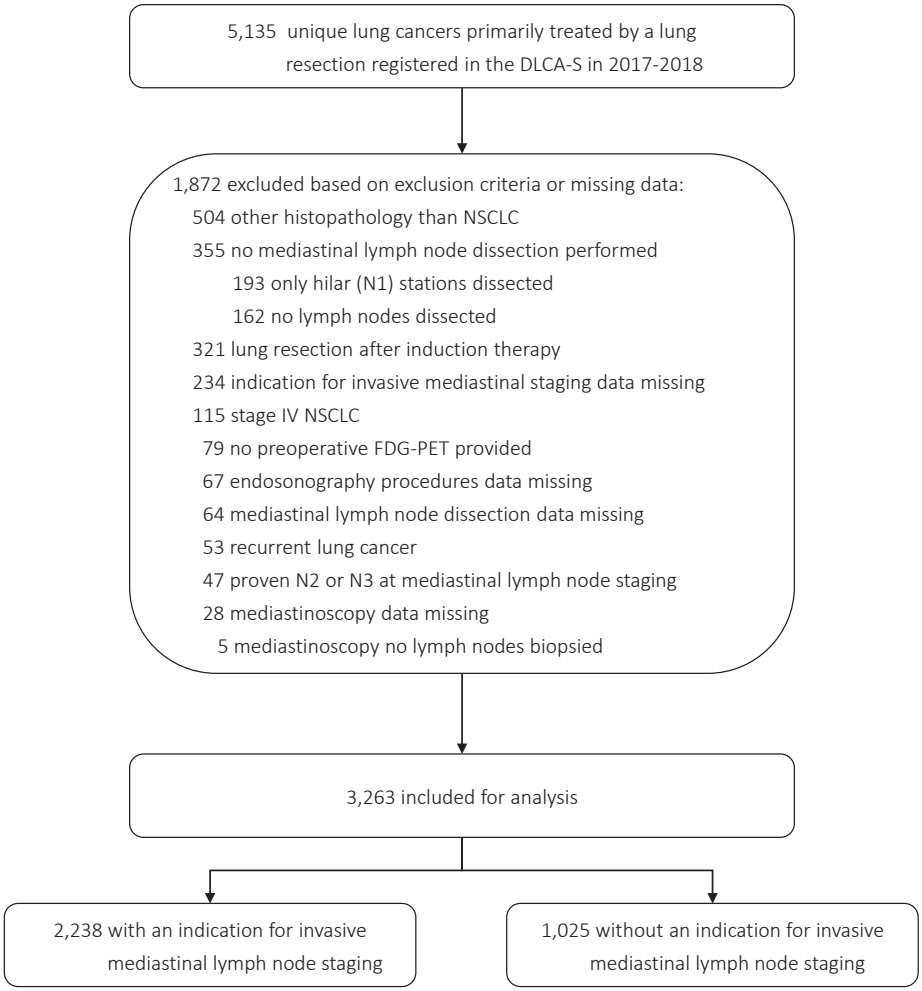

Figure 1. Flowchart of patient selection.
DLCA-S=Dutch Lung Cancer Audit - Surgery; NSCLC=non-small cell lung cancer; FDG-PET=^{18}F-fluorodeoxyglucose positron emission tomography.

Guideline adherence

In patients qualifying for mediastinal staging, endosonography was used as initial staging technique in 43% (955/2,238; 95% CI: 41-45, EBUS 82%, EUS 9%, EBUS and EUS 9%). A mean of 0.3 (SD 0.8) mediastinal lymph node stations were sampled during endosonography.

Confirmatory mediastinoscopy was performed in 416 of 955 (44%; 95%-CI: 40-47) patients with negative N2-3 cytology after endosonography. Immediate mediastinoscopy without prior endosonography was performed in 10% (220/2,238; 95%-CI: 9-11)

of patients. A mean number of 3.9 (SD 1.0) mediastinal lymph node stations were sampled during both primary and confirmatory mediastinoscopy. The remaining 47% (1,063/2,238; 95%-CI: 45-50) of patients with an indication for mediastinal staging underwent direct anatomical lung resection without prior staging (Figure 2).

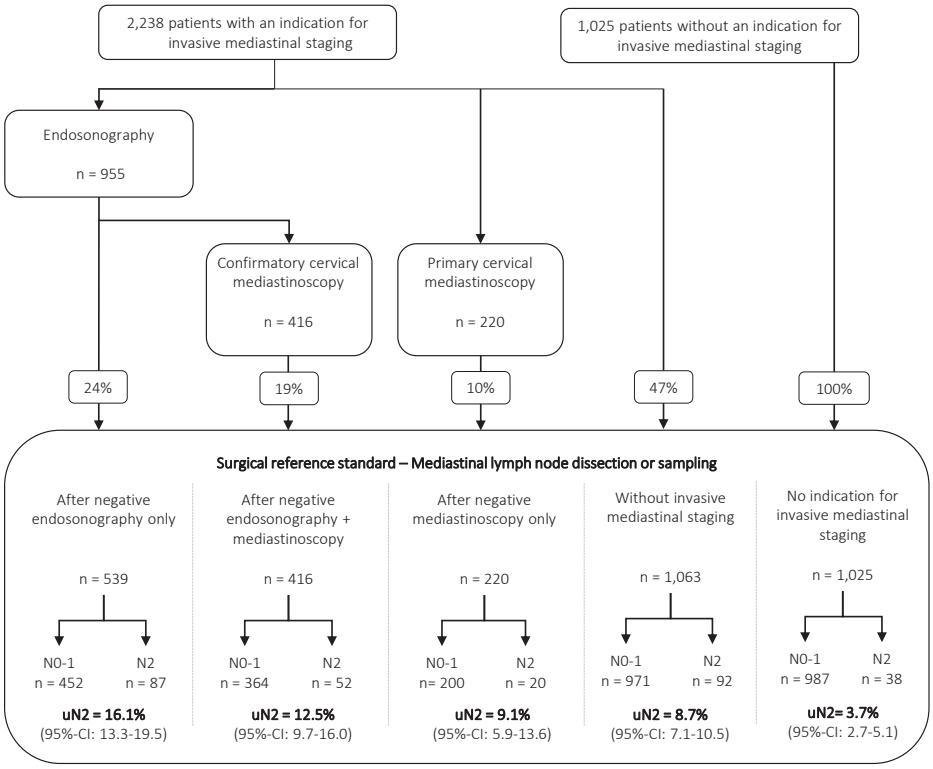

Figure 2. Flowchart of invasive mediastinal staging strategies and uN2 rates.
uN2=unforeseen N2; 95%-CI= 95% confidence interval.

Overall, 19% of patients (416/2,238; 95%-CI: 17-20) with an indication for mediastinal staging underwent staging as suggested by recommendations of the European guideline on mediastinal staging in NSCLC with an EBUS and/or EUS, followed by a confirmatory mediastinoscopy. Patients with an indication for staging but who were not had significantly lower clinical tumour and nodal stages compared to patients who did (p<.01). Additionally, guideline adherence was significantly better in males and patients with squamous cell carcinomas (Table 1). Most patients who underwent invasive staging according to the guideline had cN1-3 disease as indication, while the group of patients who were not staged as suggested by the guideline most patients had a peripheral tumour (>3 cm) as indication for invasive staging (Table 1).

Unforeseen N2 disease

A mean 2.7 (SD 1.1) mediastinal and 1.7 (SD 0.9) hilar lymph node stations per patient were harvested during the mediastinal lymph node dissection. Among patients with an indication for invasive mediastinal staging the uN2 rate was 11.2% (251/2,238; 95%-CI: 10.0-12.6). The uN2 rate in patients in whom the staging strategy was in concert with the guideline was 12.5% (52/416; 95%-CI: 9.7-16.0) compared to 10.9% (199/1822; 95%-CI: 9.6-12.4) who were not (p=.36). When confirmatory mediastinoscopy after negative endosonography was omitted, the uN2 rate was 16.1% (87/539; 95%-CI: 13.3-19.5) compared to 12.5% uN2 after endosonography combined with mediastinoscopy (p=.11) (Figure 2).

Unforeseen N2 in patients with an indication for staging were single-level metastases in 9.2% (205/2,238; 95%-CI: 8.0-10.4) while the remaining 2.0% (46/2,238; 95%-CI: 1.6-2.7) had multi-level uN2 metastases (Table 2). The single-level uN2 metastases were located in station 5 or 6 in 40% (82/206; 95% CI: 33-47) (Table 3). When excluding single-level station 5 and 6 metastases, uN2 was found in 7.6 % of patients (169/2,238; 95%-CI: 6.5-8.7) with an indication for staging.

In patients without an indication for invasive mediastinal staging, the uN2 rate was 3.7% (38/1,025; 95% CI: 2.7-5.1), of which 3.1% (32/1,025; 95% CI: 2.2-4.4) was single-level uN2 and 0.6% (6/1,025; 95% CI: 0.3-1.3) multi-level uN2 (Table 2). The single-level uN2 metastases were located in station 5 or 6 in 26% (10/38; 95% CI: 15-42) (Table 3). When excluding single-level station 5 and 6 metastases, uN2 was found in 2.9% of patients (30/1,025; 95% CI: 2.1-4.2) without an indication for staging.

'Indication for invasive staging' subgroups

In patients with cN1-3, invasive mediastinal staging was performed according to the European guideline in 37% (324/878; 95%-CI: 34-40). In patients with central tumours, FDG-non-avid tumours and peripheral tumour >3 cm respectively, corresponding figures were 11% (42/396; 95%-CI: 8-14), 3% (6/187; 95%-CI: 1-7) and 6%, respectively (44/777; 95%-CI: 4-8) (p<.01) (Table 2). Moreover, invasive mediastinal staging was completely omitted in 63% (231/369; 95%-CI: 58-67), 77% (144/187; 95%-CI: 70-82) and 73% (566/777; 95%-CI: 70-76) of patients with central tumours, FDG-non-avid tumours and peripheral tumours >3 cm, respectively. Just 14% (122/878; 95% CI: 12-16) of patients with cN1-3 underwent surgery without prior invasive staging (p<.01) (Table 2).

A higher uN2 rate was found in cN1-3 patients (16.2%; 142/878; 95%-CI: 13.9-18.8) compared to patients with central tumours (8.8%; 35/396; 95%-CI: 6.4-12.1; p<.01),

Table 2. Staging strategy and uN2 rate per indication for invasive staging

Indication for staging Staging technique	n (%)	uN2 all % (95%-CI)	uN2 single-level % (95%-CI)	uN2 multi-level % (95%-CI)
Without indication for invasive staging	1,025 (100)	3.7 (2.7-5.1)	3.1 (2.2-4.4)	0.6 (0.3-1.3)
With indication for invasive staging	2,238 (100)	11.3 (10.0-12.6)	9.2 (8.1-10.5)	2.1 (1.6-2.7)
Endosonography	539 (24)	16.1 (13.3-19.5)	13.1 (10.6-16.3)	3.0 (1.8-4.8)
Endosonography + mediastinoscopy	416 (19)	12.5 (9.7-16.0)	10.6 (8.0-13.9)	1.9 (1.0-3.7)
Mediastinoscopy	220 (10)	9.1 (5.9-13.6)	6.4 (3.8-10.4)	2.7 (1.3-5.8)
No invasive staging	1,063 (47)	8.7 (7.1-10.5)	7.2 (5.8-8.9)	1.5 (0.9-2.4)
cN1-3	878 (100)	16.2 (14.0-18.9)	13.2 (11.2-15.7)	3.0 (2.0-4.3)
Endosonography	305 (35)	19.3 (15.3-24.1)	15.7 (12.1-20.3)	3.6 (2.0-6.4)
Endosonography + mediastinoscopy	324 (37)	13.0 (9.7-17.1)	10.8 (7.9-14.7)	2.2 (1.1-4.4)
Mediastinoscopy	127 (14)	10.2 (6.1-16.7)	7.1 (3.8-12.9)	3.2 (1.2-7.8)
No invasive staging	122 (14)	23.0 (16.4-31.2)	19.7 (13.6-27.6)	3.3 (1.3-8.1)
Central tumour	396 (100)	8.8 (6.4-12.1)	6.8 (4.7-9.7)	2.0 (1.0-3.9)
Endosonography	75 (19)	10.7 (5.5-19.7)	8.0 (3.7-16.4)	2.7 (0.7-9.2)
Endosonography + mediastinoscopy	42 (11)	16.7 (8.3-30.6)	14.3 (6.7-27.9)	2.4 (0.4-12.3)
Mediastinoscopy	48 (12)	8.3 (3.3-19.6)	6.2 (2.2-16.9)	2.1 (0.4-10.9)
No invasive staging	231 (58)	6.9 (4.3-11.0)	5.2 (3.0-8.9)	1.7 (0.7-4.4)
FDG-non-avid-tumour	187 (100)	6.4 (3.7-10.9)	5.9 (3.3-10.2)	0.5 (0.1-3.0)
Endosonography	23 (13)	8.7 (2.4-26.8)	8.7 (2.4-26.8)	0
Endosonography + mediastinoscopy	6 (3)	16.7 (3.0-56.4)	16.7 (3.0-56.4)	0
Mediastinoscopy	14 (7)	14.3 (4.0-40.0)	14.3 (4.0-40.0)	0
No invasive staging	144 (77)	4.9 (2.4-9.7)	4.2 (1.9-8.8)	0.7 (0.1-3.8)
Peripheral tumour >3 cm	777 (100)	8.0 (6.3-10.1)	6.6 (5.0-8.5)	1.4 (0.8-2.5)
Endosonography	136 (17)	13.2 (8.5-20.0)	11.0 (6.8-17.4)	2.2 (0.8-6.3)
Endosonography + mediastinoscopy	44 (6)	4.6 (1.3-15.1)	4.6 (1.3-15.1)	0
Mediastinoscopy	31 (4)	3.2 (0.6-16.2)	0	3.2 (0.6-16.2)
No invasive staging	566 (73)	7.2 (5.4-9.7)	6.0 (4.3-8.3)	1.2 (0.6-2.5)

n=number of patients; uN2=unforeseen N2; 95% CI=95% confidence interval; cN1-3=clinical nodal stage N1-N3 on FDG-PET-CT; FDG=fluorodeoxyglucose.

Table 3. Distribution of single-level unforeseen N2 disease

	With indication for invasive staging (n=205)					Without indication for invasive staging (n=32)				
	Primary tumour localization					Primary tumour localization				
uN2, No. (%)	**RUL**	**RML**	**RLL**	**LUL**	**LLL**	**RUL**	**RML**	**RLL**	**LUL**	**LLL**
Station 2R	5 (2)		1							
Station 4R	19 (9)	1	4 (2)			7 (22)	1 (3)			
Station 5-6				73 (36)	9 (4)				10 (31)	
Station 7*	3 (2)	4 (2)	27 (13)	6 (3)	23 (11)		2 (6)	6 (19)		4 (13)
Station 8		1	7 (3)	2 (1)	3 (2)					
Station 9			4 (2)	1	4 (2)			1 (3)		1 (3)
Station 4L*				5 (2)	1					

uN2=unforeseen N2; No.=number; RUL=right upper lobe; RML=right middle lobe; RLL=right lower lobe; LUL=left upper lobe; LLL=left lower lobe. *= the affected lobes of a left sided primary tumours with single-level metastasis in station 4L and in station 7 in two patients with indication for invasive staging were unknown.

FDG-non-avid tumours (6.4%; 12/187; 95%-CI: 3.7-10.9; p<.01) and peripheral tumours >3 cm (8.0%; 62/777; 95%-CI: 6.3-10.1; p<.01) (Table 2). Within the subgroup of patients with cN1-3, the highest uN2 rate was found in patients in whom invasive mediastinal staging was omitted (23.0%; 28/122; 95%-CI: 16.4-31.2). When only endosonography was performed, uN2 was found in 19.3% (59/305; 95%-CI: 15.3-24.1), while after adding confirmatory mediastinoscopy after negative endosonography. uN2 was found in 13.0% (43/324; 95%-CI: 9.7-17.1). When only mediastinoscopy was performed in the cN1-3 subgroup, uN2 was found in 10.2% (13/127; 95%-CI: 6.1-16.7) (Table 2).

Within the subgroups of patients with central tumours, FDG-non-avid tumours and peripheral tumours >3 cm varying uN2 rates were found among patients in whom endosonography and/or mediastinoscopy were performed. Remarkably, within the subgroups of patients with central tumours or FDG-non-avid tumours the lowest uN2 rates were found in patients in whom invasive mediastinal staging was completely omitted (6.9%; 16/231; 95%-CI: 4.3-11.0 and 4.9%; 7/144; 95%-CI: 2.4-9.7 respectively) (Table 2).

DISCUSSION

The present study showed comparable uN2 rates in patients with primary resectable NSCLC with an indication for invasive mediastinal staging who are either staged according to the European guidelines or not (12.5% vs 10.9% respectively, p=.36). In addition,

only 19% of patients with an indication for invasive mediastinal staging underwent such a procedure as suggested by the 2015 ESTS-ERS-ESGE guideline.

Mediastinal lymph node staging is crucial, since this adjunctive procedure determines treatment choice and prognosis. Adherence to an initial endosonography as indicated by the guideline appeared poor in our analysis, while the ASTER-trial showed the clear value of the use of endosonography prior to surgical staging.[12] After publication of the European guideline in 2015, additional evidence on the benefits of endosonography for mediastinal lung cancer staging has been published. A meta-analysis showed a significant increase in sensitivity (+12%) and detection rate for diagnosing lymph node metastases by using combined EBUS and EUS compared with either procedure alone. [13] Furthermore, a multicentre international randomized controlled trial (SCORE-study) compared systematically performed combined EBUS and EUS (endosonographic investigation of FDG-PET-CT suspect lymph nodes and routinely sampling of station 4R, 4L and 7 if short axis ≥ 8 mm) with targeted EBUS (endosonographic investigation of FDG-PET-CT suspect lymph nodes only). Such a systematic approach was found to have 9% higher sensitivity for the detection of mediastinal lymph node metastases, while additional clinically relevant staging information was found in 10% of patients. [14] In our analysis only 0.3 mediastinal lymph node stations per patient were sampled by endosonography and only 9% of endosonography procedures were a combination of EBUS and EUS. Based on the recommendations in the latest guidelines it therefore appears that rates of endosonography in our analysis were too low. However, it must be appreciated that the currently used DLCA-S database provides no information whether lymph node stations were visualized. Therefore, endosonography observing lymph nodes without malignant characteristics (i.e. lymph nodes >10mm, round shape, sharp borders and/or hypoechoic texture) could in fact have been a very systematic procedure although samples were just not taken. As DLCA-S only records whether lymph nodes were sampled or not, the extensiveness of endosonography procedures is potentially underestimated. Nevertheless, based on the promising results of routinely sampling mediastinal lymph nodes in the SCORE-study the accuracy of endosonography in the Netherlands could probably be improved.[13]

Among patients with an indication for invasive mediastinal staging in whom the guideline was not followed, 42% of patients at least underwent any form of invasive staging. The use of mediastinoscopy as the single staging procedure in patients with cN1-3 could be based on studies from the Leuven Lung Cancer Group reporting on a mere 38% sensitivity of endosonography in cN1 patients, while a direct mediastinoscopy resulted in a 73% sensitivity.[15, 16] However, endosonography in the Leuven Lung Cancer Group study consisted only of lobe-specific EBUS examination of mediastinal

lymph nodes in the majority of patients, while most of the uN2 metastases detected at surgical lymph node dissection were within reach of EBUS and/or EUS.[17] A systematic use of EBUS added by EUS may therefore lead to higher endosonographic sensitivity rates, warranting further investigation. The remaining 58% of patients with an aborted staging contrary to guidelines underwent no invasive mediastinal staging at all. A reason for European guideline non-adherence is likely related to the fact that a peripheral >3 cm tumour is not considered as recommendation for invasive staging in the Dutch guideline.[18] Of all patients with a large peripheral tumour, invasive staging was omitted in 73%, accounting for approximately half of patients with an indication for staging in whom staging was omitted in our analysis. Overall, significant lower clinical tumour and nodal stages were found in patients in whom staging was not performed conform the guideline, which implies preferences other than the guideline whether to perform invasive mediastinal staging or not. Clinical features such as fast grow, cavitation with necrosis possibly inducing reactivity in lymph nodes and compromised prognosis of squamous cell carcinomas may on other hand have incited better guideline adherence in these patients compared to patients with other tumour histology.[19, 20] Additionally, the general worse overall survival of male lung cancer patients may have implied better adherence to the guideline in males compared to females.[21] Detailed information on medical decision is however lacking in DLCA-S, making it impossible to retrieve possible arguments for non-adherence to the guideline.

Regarding invasive mediastinal staging as part of optimal lung cancer treatment, a pivotal question is to what extent uN2 disease is acceptable before long-term survival is compromised. In the ASTER-trial, uN2 disease was found in 6.9% after tumour negative endosonography and mediastinoscopy versus 14.3% after mediastinoscopy only.[12] Despite these differences, 5-year survival was 35% in both groups.[22] Several other studies showed 5-year survival rates of 34-48% in surgical patients with uN2 disease undergoing adjuvant therapy with similar survival rates compared to primary surgically treated patients with N1 disease.[23-26] However, N2 metastasis extend is important as overall survival rates were different between patients with single and multiple station N2 disease and between patients with microscopic (0.2 to 2 mm) and macroscopic N2 disease.[27, 28] DLCA-S provides no information on metastases size, but the majority (81%) of uN2 in our analysis were single-level metastases. More importantly, 39% of uN2 metastases were located in lymph node station 5 and 6, locations that cannot be reached by either EBUS, EUS or mediastinoscopy. In patients with left upper lobe tumours, a significantly better 3-year survival was found in patients with station 5 or 6 metastases compared to patients with N2 disease in station 7.[29] Based on this superior survival, the challenging anatomical position and a generally limited effect on treatment choice, the value of staging these lymph nodes is likely lower in patients with left upper lobe

tumours. Therefore it remains doubtful whether these metastases should be included in uN2 calculations.

When discussing the role of uN2 rates, the quality of mediastinal lymph node dissection is of utmost importance. Being the gold standard for N1-2 status in surgical NSCLC patients, the N status determines adjuvant treatment choice, prognosis as well as reflects the accuracy of mediastinal lymph node staging. Additionally, there is increasing evidence indicating that a radical lymph node dissection, as proposed by the International Association for the Study of Lung Cancer, also has a positive influence on survival.[30, 31] The ESTS guideline recommends lobe-specific lymph node dissection with dissection of at least 3 mediastinal lymph node stations per lobe.[4, 32] In our analysis a mean of 2.7 mediastinal lymph node stations were sampled. Unfortunately, no details on the extent of sampling or dissection of the lymph node stations were registered in the DLSA. Additionally, uN2 metastases can be missed during histopathological investigation since only slices of the dissected tissue are generally investigated. Based on these uncertainties uN2 rates may be underestimated.

This study has some limitations including a limited number of patients due to our strict exclusion criteria and missing information on primary tumour and mediastinal lymph nodes. Since this information in the DLCA-S registry was only obtained after 2016, earlier patients were not eligible. Additionally, the DLCA-S is designed to assess and improve the quality of medical care. Since data in the DLCA-S are self-reported by data managers, specialized nurses and doctors the registration burden has to be restricted to maintain quality and completeness of data registry. This approach may have resulted in missing variables and less detailed information than is desired for research purposes. Nevertheless, regular random checks are performed to optimize data quality in this nationwide database.

CONCLUSION

Adherence to the 2015 ESTS-ERS-ESGE guideline on mediastinal lymph node staging in NSCLC was poor, although comparable uN2 rates were found among patients who were staged according to the guideline or not. Highest uN2 rate was found in patients with cN1-3 as indication for staging, whereas this also was the only subgroup in whom strict adherence to the guideline appeared effective regarding uN2 rate. Most uN2 metastases however were single level and/or located in station 5 or 6, suggesting minimal N2 disease of which the oncological relevance remains doubtful. Direct surgical lung tumour resection in patients without an indication for staging according to the guideline seems

appropriate based on a low uN2 rate in these patients. Based on our results we suggest strict adherence to the guideline on mediastinal staging of NSCLC at least in patients with cN1-3. Further research is needed whether adaptation of guidelines concerning patients with other indications for invasive mediastinal staging should be considered.

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ABBREVIATIONS

NSCLC=non-small cell lung cancer; CT=computed tomography; FDG-PET=18F-fluorodeoxyglucose positron emission tomography; cN=clinical nodal stage; EBUS-TBNA= endobronchial ultrasound guided transbronchial needle aspiration; EUS-FNA= endoscopic ultrasound guided fine needle aspiration; uN2=unforeseen N2 disease; DLCA-S=Dutch Lung Cancer Audit-Surgery; ESGE=European Society of Gastrointestinal Endoscopy; ERS=European Respiratory Society; ESTS=European Society of Thoracic Surgeons; CI=confidence interval; SD=standard deviation; IQR=interquartile range;

AUTHOR'S CONTRIBUTIONS

Jelle Bousema: Conceptualization, methodology, formal analysis, writing – original draft, visualisation, project administration. David Heineman: Conceptualization, methodology, writing – review & editing. Marcel Dijkgraaf: Conceptualization, methodology, writing – review & editing, supervision. Jouke Annema: Conceptualization, methodology, writing – review & editing, supervision. Frank van den Broek: Conceptualization, methodology, writing – review & editing, supervision.

CONFLICT OF INTEREST

Dr. Bousema, Dr. Heineman, Prof. Dr. Dijkgraaf and Dr. Van Den Broek have nothing to disclose. Prof. Dr. Annema reports non-financial support from Hitachi Medical systems, non-financial support from Pentax, grants from Cook medical, outside the submitted work.

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REFERENCES

[1] Integraal Kanker Centrum Nederland, (IKNL). Cijfers over Kanker (Dutch Cancer Registry) . 2019;2019.

[2] Heineman DJ, Hoeijmakers F, Beck N, et al. Impact of health care organization on surgical lung cancer care. Lung Cancer 2019;135:181-7.

[3] Vilmann P, Clementsen PF, Colella S, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015;47:546-60.

[4] De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2014;45:787-98.

[5] Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017;28:iv1-iv21.

[6] Krantz SB, Howington JA, Wood DE, et al. Invasive Mediastinal Staging for Lung Cancer by The Society of Thoracic Surgeons Database Participants. The Annals of Thoracic Surgery 2018;106:1055-62.

[7] Turner SR, Seyednejad N, Nasir BS. Patterns of Practice in Mediastinal Lymph Node Staging for Non-Small Cell Lung Cancer in Canada. The Annals of Thoracic Surgery 2018;106:428-34.

[8] Bousema JE, van Dorp M, Hoeijmakers F, et al. Guideline adherence of mediastinal staging of non-small cell lung cancer: A multicentre retrospective analysis. Lung Cancer 2019;134:52-8.

[9] ten Berge M, Beck N, Heineman DJ, et al. Dutch Lung Surgery Audit: A National Audit Comprising Lung and Thoracic Surgery Patients. The Annals of Thoracic Surgery 2018;106:390-7.

[10] von Bartheld, Martin B., BSc, Rabe, Klaus F., MD, PhD, Annema, Jouke T., MD, PhD. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. Gastrointestinal Endoscopy 2009;69:345-9.

[11] Lawrence D. Brown, T. Tony Cai, Anirban DasGupta. Interval Estimation for a Binomial Proportion. Statistical Science 2001;16:101-17.

[12] Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. JAMA 2010;304:2245-52.

[13] Korevaar DA, Crombag LM, Cohen JF, Spijker R, Bossuyt PM, Annema JT. Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. The Lancet Respiratory Medicine 2016;4:960-8.

[14] Crombag LMM, Dooms C, Stigt JA, et al. Systematic and combined endosonographic staging of lung cancer (SCORE Study). The European respiratory journal 2018:1800800.

[15] Dooms C, Tournoy KG, Schuurbiers O, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest 2015;147:209-15.

[16] Decaluwé Herbert, Dooms Christophe, D'Journo Xavier Benoit, et al. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study. The European Respiratory Journal 2017;50:1701493.

[17] Annema, Jouke T., MD, PhD. Endosonographic Staging for N1 Disease. Chest 2015;147:e122.

[18] Federatie Medisch Specialisten. Richtlijn NSCLC (niet-kleincellig longcarcinoom). 2015.

[19] Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic Features of Advanced Squamous NSCLC. Journal of Thoracic Oncology 2016;11:1411-22.

[20] Wang B, Huang J, Chen H, et al. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. Journal of Cancer Research and Clinical Oncology 2019.

[21] Yoshida Y, Murayama T, Sato Y, Suzuki Y, Saito H, Nomura Y. Gender Differences in Long-Term Survival after Surgery for Non-Small Cell Lung Cancer. The Thoracic and Cardiovascular Surgeon 2016;64:507-14.

[22] Kuijvenhoven JC, Korevaar DA, Tournoy KG, et al. Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer. JAMA 2016;316:1110-2.

[23] Cerfolio RJ, Bryant AS. Survival of Patients With Unsuspected N2 (Stage IIIA) Nonsmall-Cell Lung Cancer. The Annals of Thoracic Surgery 2008;86:362-7.

[24] Obiols C, Call S, Rami-Porta R, et al. Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. The Annals of thoracic surgery 2014;97:957-64.

[25] Deok Heon Lee, Jae Bum Kim, Dong Yoon Keum, Ilseon Hwang, Chang Kwon Park. Long Term Survival of Patients with Unsuspected N2 Disease in Non-Small Cell Lung Cancer. Korean J Thorac Cardiovasc Surg 2013;46:49-55.

[26] Kim MP, Correa AM, Hofstetter WL, et al. Occult stage IIIA-N2 patients have excellent overall survival with initial surgery. Journal of thoracic disease 2018;10:6670-6.

[27] Yoo, Changhoon|Yoon, Shinkyo|Lee, Dae Ho|Park, Seung-Il|Kim, Dong Kwan|Kim, Yong-Hee|Kim, Hyeong Ryul|Choi, Se Hoon|Kim, Woo Sung|Choi, Chang-Min|Jang, Se Jin|Song, Si Yeol|Kim, Su Ssan|Choi, Eun Kyung|Lee, Jae Cheol|Suh, Cheolwon|Lee, Jung-Shin|Kim, Sang-We. Prognostic Significance of the Number of Metastatic pN2 Lymph Nodes in Stage IIIA-N2 Non–Small-Cell Lung Cancer After Curative Resection. Clinical Lung Cancer 2015;16:e203-12.

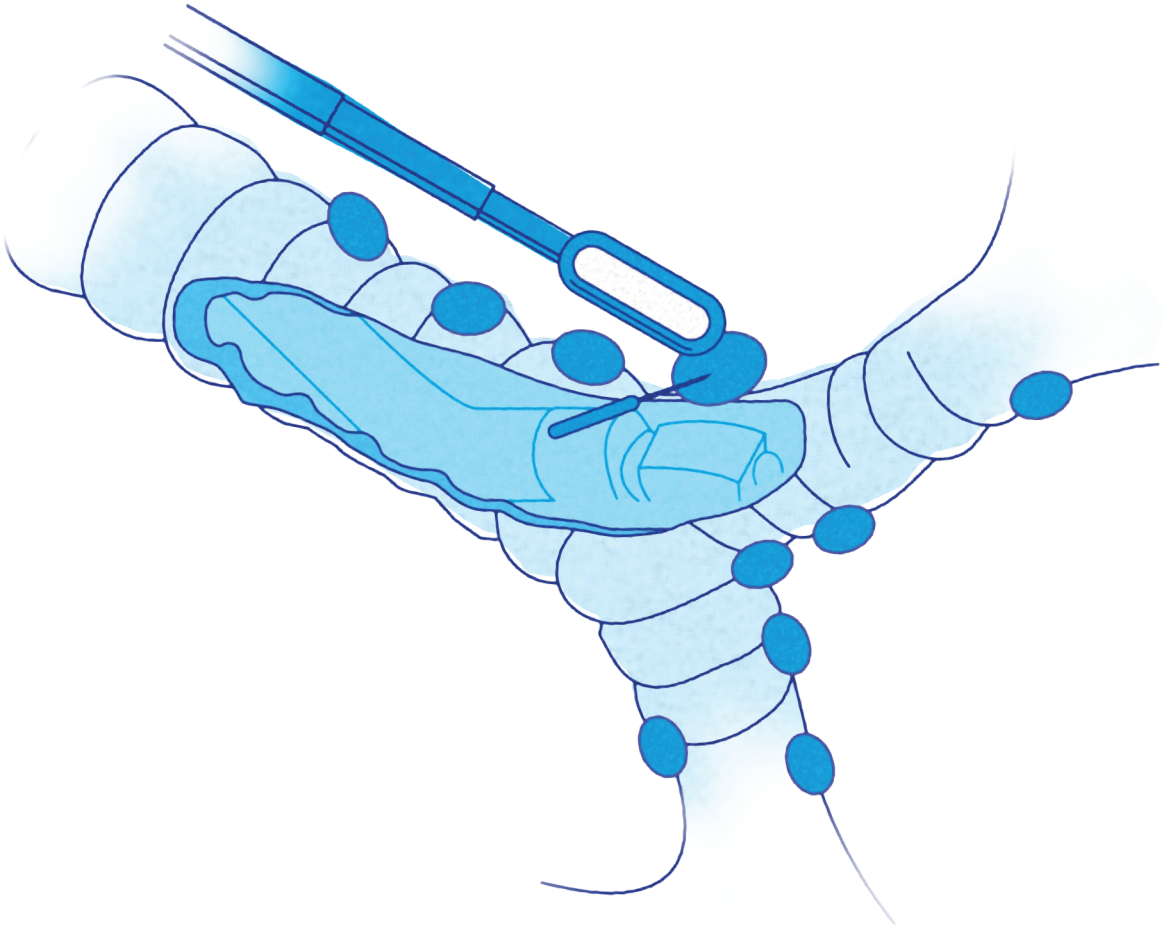
[28] Garelli E, Renaud S, Falcoz P, et al. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2016;50:322-8.

[29] Citak N, Sayar A, Metin M, et al. The Prognostic Significance of Metastasis to Lymph Nodes in Aortopulmonary Zone (Stations 5 and 6) in Completely Resected Left Upper Lobe Tumors. The Thoracic and Cardiovascular Surgeon 2015;63:568-76.

[30] Smeltzer MP, Faris NR, Ray MA, Osarogiagbon RU. Association of Pathologic Nodal Staging Quality With Survival Among Patients With Non–Small Cell Lung Cancer After Resection With Curative Intent. JAMA Oncology 2018;4:80-7.

[31] Edwards T, Balata H, Elshafi M, et al. Adequacy of Intraoperative Nodal Staging during Surgical Resection of NSCLC: Influencing Factors and Its Relationship to Survival. Journal of Thoracic Oncology 2017;12:1845-50.

[32] Rami-Porta R, Wittekind C, Goldstraw P. Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005;49:25-33.



Chapter 4

Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer

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ABSTRACT

Introduction Guidelines for invasive mediastinal nodal staging in resectable non-small cell lung cancer (NSCLC) have changed over the years. The aims of this study were to describe trends in invasive staging and unforeseen N2 (uN2) and to assess a potential effect on overall survival.

Methods A nationwide Dutch cohort study included all clinical stage IA-IIIB NSCLC patients primarily treated by surgical resection between 2005 and 2017 (n=22,555). We assessed trends in invasive nodal staging (mediastinoscopy 2005-2017; endosonography 2011-2017), uN2 and overall survival and compared outcomes in the entire group and in clinical nodal stage (cN)1-3 patients with or without invasive staging.

Results An overall increase in invasive nodal staging from 26% in 2005 to 40% in 2017 was found (p<.01). Endosonography increased from 19% in 2011 to 32% in 2017 (p<.01), while mediastinoscopy decreased from 24% in 2011 to 21% in 2017 (p=.08). Despite these changes, uN2 was stable over the years at 8.7%. Five-year overall survival rate was 41% for pN1 compared to 37% in single node uN2 (p=.18) and 26% with more than one node uN2 (p<.01). Five-year overall survival rate of patients with cN1-3 with invasive staging was 44% *versus* 39% in patients without invasive staging (p=.12).

Conclusion A significant increase in invasive mediastinal nodal staging in patients with resectable NSCLC was found between 2011 and 2017 in the Netherlands. Increasing use of less invasive endosonography prior to (or as substitute for) surgical staging did not lead to more cases of uN2. Performance of invasive staging indicated a possible overall survival benefit in patients with cN1-3 disease.

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LIST OF DEFINITIONS

EBUS(-TBNA) endobronchial ultrasound guided transbronchial needle aspiration. Investigation of mediastinal and hilar lymph nodes with a linear ultrasound probe via the airways with the possibility of nodal sampling under real-time ultrasound control.

EUS(-FNA) endoscopic ultrasound guided fine needle aspiration. Investigation of mediastinal lymph nodes with a linear ultrasound probe via the oesophagus with the possibility of nodal sampling under real-time ultrasound control.

Endosonography Endosonographic examination of mediastinal and hilar lymph nodes by using EBUS-TBNA and/or EUS-FNA.

Mediastinoscopy Surgical procedure under general anaesthesia to examine mediastinal lymph nodes with the possibility to take surgical biopsies.

Invasive mediastinal staging Mediastinal lymph node tissue staging by using EBUS-TBNA, EUS-FNA and/or mediastinoscopy to determine the nodal status of lung cancer.

Surgical lung tumour resection Resection of the primary lung tumour performed by either open thoracotomy or thoracoscopic surgery with assessment of ipsilateral mediastinal lymph nodes.

Unforeseen N2 (uN2) Pathologically proven N2 disease at lung tumour resection and lymph node dissection or sampling when previous mediastinal staging showed N0 or N1 disease.

INTRODUCTION

Adequate staging of patients with non-small cell lung cancer (NSCLC) is important for treatment choice and prognosis. In the absence of mediastinal and distant metastases, surgical lung tumour resection with lymph node dissection is the most appropriate treatment with curative intent.[1] If lymph node dissection reveals unexpected ipsilateral mediastinal lymph node metastases, the nodal stage is called unforeseen N2 disease (uN2). Detecting uN2 after lung tumour resection is deemed undesirable, since patients with N2-3 disease without distant metastases (stage III NSCLC) are generally recommended to undergo definite chemoradiation or trimodality therapy comprising neo-adjuvant chemoradiotherapy and subsequent surgical lung resection. Conversely, upfront surgery in these patients may be associated with worse overall survival.[2]

The European and Dutch guidelines recommend invasive staging in selected patients to minimize the risk of uN2 disease.[1,3] However, these recommendations and daily practice in mediastinal staging have changed following the introduction of endosonography (endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) added by endoscopic ultrasound guided fine needle aspiration (EUS-FNA)). For instance, endosonography followed by surgical staging was found to have greater sensitivity to detect mediastinal nodal metastases compared to surgical staging alone.[4] Therefore, the combined strategy of initial endosonography followed by confirmatory mediastinoscopy is nowadays recommend in NSCLC staging guidelines.[1,3,5]

It is unknown whether these changes in the use of preoperative stratification tools have resulted in a change in outcome. The main objectives of this study were to describe trends in the use of different invasive mediastinal nodal staging techniques and uN2 rates, and to assess a potential effect of invasive nodal staging on overall survival in patients with resectable NSCLC in the Netherlands.

METHODS

Data source

We used data from the population-based Netherlands Cancer Registry which is maintained by the Netherlands Comprehensive Cancer Organisation. The registry includes all newly diagnosed cancer patients residing in the Netherlands. Specialized registration clerks collect data from the medical records in all Dutch hospitals. The quality of the data is high, due to thorough training of the registration clerks and a variety of computerized consistency checks. Completeness is estimated to be at least 95%. During follow-up an

annual connection with the Civil Registry is made to update the vital status of included patients.

Patients

All clinical stage IA-IIIB primary NSCLC patients who underwent primary tumour resection and who were registered in the Netherlands Cancer Registry between January 1, 2005 and December 31, 2017 were included. Patients who received neoadjuvant therapy were excluded.

Data

Information regarding invasive mediastinal staging included the use of mediastinoscopy (registered 2005-2017) and endosonography (EBUS/EUS, registered 2011-2017), reported as positive/negative for metastasis, or not performed. Total number of malignant lymph nodes was reported as number of malignant lymph nodes demonstrated by invasive staging and lymph node dissection (hilar and mediastinal stations) together. However, details on the technique of mediastinal lymph node assessment (i.e. dissection or sampling and which specific lymph node stations were assessed) during surgical lung tumour resection were not available. Follow-up information consisted of the vital state of the patient, but recurrence of the disease or cause of death were unknown. Patients who emigrated were censured. Overall survival was reported as number of days between diagnosis and date of censure or the last Civil Registry update (January 31, 2019).

Data analysis

Patients with cN1-3 disease were analysed as a subgroup having an indication for invasive staging according to the European guideline. Conversely, central tumour location, FDG-avidity of the tumour and exact tumour size as other indications for invasive staging were not available in the registry.[1]

In patients diagnosed between 2005 and 2010, the use of mediastinoscopy was examined. In addition, from 2011 on also the use of endosonography was tabulated. The uN2 rate was calculated as number of patients with pathological N2 stage divided by number of patients with N0 or N1 after invasive staging or without staging. The total number of malignant lymph nodes was used to determine which uN2 patients had just one malignant lymph node. In patients with pN2 having more than one malignant lymph nodes the distribution of these malignant nodes was unknown (e.g. metastases could be located in N1 and N2 lymph node stations), resulting in a ‘more than one lymph node uN2 group’.

Overall survival was assessed using Kaplan Meier estimates assessing differences by the log-rank test. The effect of invasive mediastinal staging on overall survival was assessed in the total population and in the cN1-3 with or without staging subgroups. Univariable and multivariable logistic regression analysis were used for determinants of invasive staging and uN2, whereas Cox regression analysis was used for modelling overall survival. Determinants with a p-value <.1 in univariable analyses were included in multivariable analysis. Adjusted odds ratios (OR) and adjusted hazards ratios (HR) of multivariable analyses were presented with 95% confidence intervals (95%-CI).

Categorical data were calculated as counts and percentages with 95%-CI's by using the Wilson score interval for proportions.[6] Trends for invasive staging were analysed by calculating Spearman's rank correlation coefficient between time and yearly percentages. We reported p-values, and whether a trend was increasing, decreasing or stable. Significance was set at a p-value of less than 0.05 or concluded from the 95%-CI not including 1. All calculations and statistical analyses were performed by using the Statistical Package for the Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients

A total of 22,555 patients with NSCLC primarily treated by surgical lung tumour resection were eligible for analysis of invasive nodal staging. As 1,146 patients did not undergo lymph node dissection during lung tumour resection (pNx) or were already having N2-3 disease at invasive staging, 21,409 patients were included for uN2 and survival analyses (Figure 1). Based on the clinical nodal stage, 13% of patients (3,023/22,555) had an indication for invasive staging (i.e. cN1-3) (Table 1). Excluding 135 patients with pNx or proven N2-3 at invasive staging, a total of 2,888 cN1-3 patients were included in uN2 and survival analyses.

The median age of this cohort was 67 years (IQR 60-73). Age was stable over the years and the proportion of males decreased from 67% in 2005 to 54% in 2017 (p<.01). Location of primary tumours was also stable over the years, although a shift from adenocarcinomas to squamous cell carcinomas as most prevalent histologic subtype was found (Appendix 1). Patient characteristics of the total population and the cN1-3 subgroup were presented in Table 1, whereas patient characteristics and trends per diagnosis year were provided in Appendix 1.

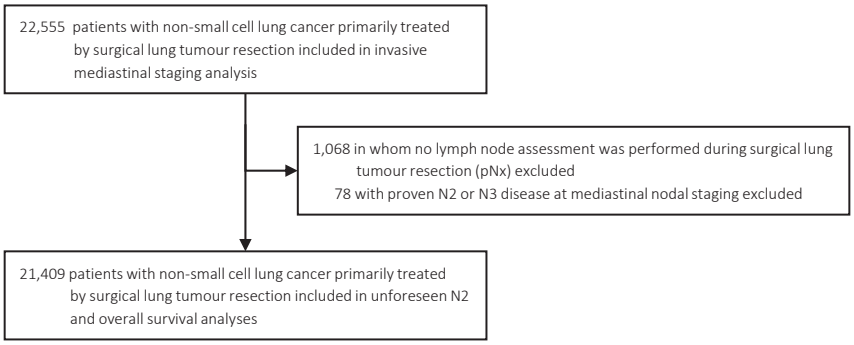

Figure 1. Flowchart of patient selection.

Table 1. Clinical and lung cancer characteristics of all patients and cN1-3 subgroups

	All patients (n=22,555)		Subgroups of patients with cN1-3 (n=2,888)		
	Included for uN2 and survival analyses	Excluded for proven N2-3 at staging or pNx	Without invasive staging	With invasive staging	p-value*
Number of patients	21,409	1,146	1,354	1,534	-
Age, median (IQR), years	67 (60-73)	67 (60-73)	66 (60-72)	66 (60-72)	.01
Gender, No. (%)					
Male	12,751 (60)	615 (54)	862 (64)	969 (63)	.78
Female	8,658 (40)	531 (46)	492 (36)	565 (37)	
Clinical nodal stage, No. (%)					
Nx	807 (4)	101 (9)	0	0	<.01
N0	17,714 (83)	910 (79)	0	0	
N1	2,055 (9)	31 (3)	945 (70)	1,110 (72)	
N2	758 (4)	87 (8)	384 (28)	374 (25)	
N3	75	17 (1)	25 (2)	50 (3)	

Table continues on the next page.

Table 1. Clinical and lung cancer characteristics of all patients and cN1-3 subgroups (*continued*)

	All patients (n=22,555)		Subgroups of patients with cN1-3 (n=2,888)		
	Included for uN2 and survival analyses	**Excluded for proven N2-3 at staging or pNx**	**Without invasive staging**	**With invasive staging**	**p-value***
Tumour location, No. (%)					
Right upper lobe	6,787 (32)	379 (33)	349 (26(	428 (28)	<.01
Right middle lobe	895 (4)	73 (6)	41 (3)	62 (4)	
Right lower lobe	3,753 (18)	240 (21)	247 (18)	285 (19)	
Overlapping right sided lobes	491 (2)	21 (2)	32 (2)	61 (4)	
Left upper lobe	5,754 (27)	216 (19)	442 (33)	418 (27)	
Left lower lobe	3,244 (15)	188 (17)	208 (15)	228 (15)	
Overlapping left sided lobes	316 (1)	13 (1)	29 (2)	38 (2)	
Unknown	169 (1)	16 (1)	6 (1)	14 (1)	
Invasive mediastinal staging, No. (%)					
2005 - 2010					
None	6,689 (74)	539 (94)	707 (100)	0	-
Mediastinoscopy	2,407 (26)	37 (6)	0	390 (100)	
2011 - 2017					
None	7,697 (63)	469 (82)	647 (100)	0	-
Endosonography	1,796 (15)	69 (12)	0	454 (40)	
Endosonography + mediastinoscopy	1,405 (11)	14 (3)	0	355 (31)	
Mediastinoscopy	1,415 (11)	18 (3)	0	335 (29)	
Final histopathology, No. (%)					
Adenocarcinoma	8,862 (41)	551 (48)	522 (39)	539 (35)	<.01
Squamous cell carcinoma	7,934 (37)	283 (25)	545 (40)	729 (47)	
NSCLC not further specified	1,612 (8)	94 (8)	75 (6)	124 (8)	
Neuro endocrine carcinoma	511 (2)	36 (3)	51 (4)	40 (3)	
Large cell carcinoma	633 (3)	38 (4)	71 (5)	42 (3)	
Adenosquamous carcinoma	380 (2)	16 (1)	28 (2)	28 (2)	
Bronchoalveolar cell carcinoma	1,477 (7)	128 (11)	62 (4)	32 (2)	
Adjuvant treatment, No.(%)	6,089 (28)	164 (14)	683 (50)	803 (52)	.31

uN2=unforeseen N2; pNx=unknown pathological nodal stage; cN=clinical nodal stage; No.=number; IQR=interquartile range; NSCLC=non-small cell lung cancer; *p-value of the comparison of cN1-3 subgroups with or without invasive staging by using the Chi-squared test or the independent T-test were appropriate.

Invasive mediastinal nodal staging

Between 2005 and 2017, 32% (7,161/22,555) underwent invasive staging, and an increasing trend was detected (26% to 2017, 40% , p<.01). During this period invasive staging in patients with cN1-3 increased from 40% in 2005 to 73% in 2017 (p<.01).

Between 2005 and 2010 mediastinoscopy was performed in 25% (2,444/9,672). Between 2011 and 2017 endosonography as only invasive staging technique was done in 14% (1,865/12,883), endosonography and confirmatory mediastinoscopy in 11% (1,419/12,883) and 11% (1,433/12,883) underwent only mediastinoscopy (Table 1). An increasing trend was found in endosonography (from 19% in 2011 to 32% in 2017, p<.01), while mediastinoscopy as only staging procedure decreased over the years (15% in 2011 to 8% in 2017, p<.01). Overall performance of mediastinoscopy (individual or combined with endosonography) was stable between 2005 and 2010 (mean 25%, trend p=.26), while it decreased from 24% in 2011 to 21% in 2017 (p=.08). Performance of the combined strategy by using endosonography and confirmatory mediastinoscopy increased from 9% in 2011 to 13% in 2017 (p=.01) (Figure 2).

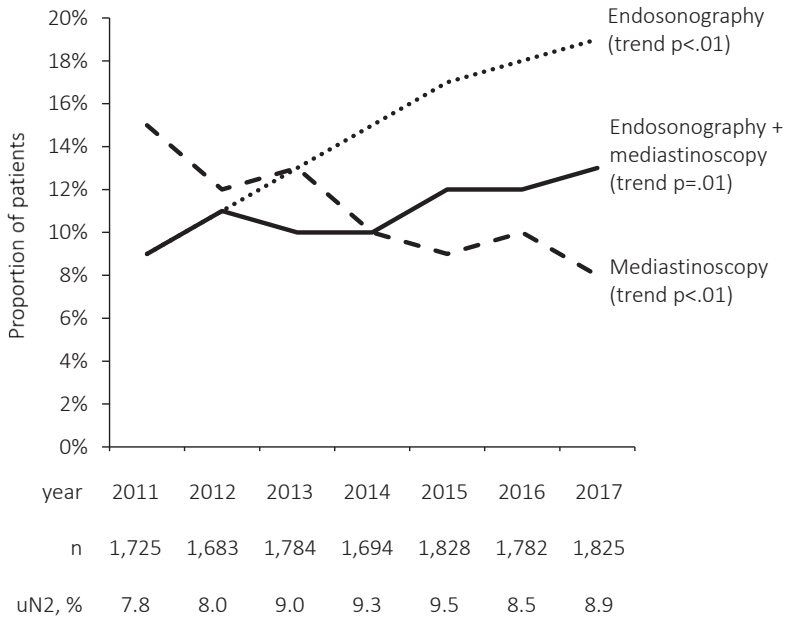

Figure 2. Trends in the use of endosonography and/or mediastinoscopy for mediastinal staging of patients with NSCLC and unforeseen N2 rates between 2011 and 2017. (n=number of patients; uN2=unforeseen N2)

In the entire population performance of invasive staging was more likely in males, left-sided tumours, squamous cell carcinoma compared to adenocarcinoma and cN1-3 compared to cN0 (Table 2). Subanalysis of patients with cN1-3 showed squamous cell histology (compared to adenocarcinoma) and the year of diagnosis as determinants affecting invasive staging (Table 3).

Unforeseen N2 disease

Between 2005 and 2017 a stable uN2 rate of 8.7% (1,865/21,409) was found (Figure 2). The uN2 rate was 11% (798/7,023) in patients with invasive staging *versus* 7.4% (1,067/14,386) in patients without. Between 2011 and 2017 uN2 was found in 12.4% (223/1,796) after endosonography, 11.4% (160/1,405) after endosonography and mediastinoscopy and in 11.0% (156/1,415) after mediastinoscopy only. The proportion of patients with single lymph node uN2 disease was stable at 31% (586/1,865) over the years. No differences in the distribution of single and more than one lymph node uN2 disease was found among the different invasive staging strategies.

Increased risk of uN2 was observed in patients with cN1-3, left sided lung tumours and in patients who underwent invasive mediastinal staging (Table 2).

In the subgroup with cN1-3 disease the uN2 rate decreased from 34% (43/125) in 2005 to 23% (66/289) in 2017 (p=.03). In cN1-3 patients who underwent invasive staging 23% (348/1,534) uN2 was found, while this was 25% (344/1,354) in cN1-3 patients without invasive staging (p=.09). Increased risk of uN2 in the cN1-3 subgroup was found in patients with cN2 or cN3 (compared to cN1) and in patients with left sided tumours (Table 3).

Overall survival

Five-year overall survival rate of patients with pN0 was 61% *versus* 43% and 31% in patients with pN1 and unforeseen pN2, respectively. Five-year overall survival rates of patients with uN2 increased from 23% in 2003 to 40% in 2013 (p=.11). Patients with a single malignant uN2 lymph node had a five-year overall survival rate of 39% compared to 28% in patients with more than one malignant uN2 lymph node (p<.01). Overall survival was comparable among patients with pN1 and single node uN2 (43% *versus* 39%, p=.32).

Table 2. Logistic regression analyses of the use of invasive staging and finding uN2 disease; and cox regression of overall survival of all patients

	Invasive staging n=22,555		Unforeseen N2 n=21,409		Overall survival n=21,409	
	OR	95%-CI	OR	95%-CI	HR	95%-CI
Year of diagnosis	1.1*	1.1-1.1	N/S	N/S	1.0	1.0-1.0
Age at time of diagnosis	1.0	1.0-1.0	1.0	1.0-1.0	1.0	1.0-1.0
Gender						
Female	ref	ref	ref	ref	ref	ref
Male	1.3*	1.2-1.4	0.9	0.9-1.1	1.2*	1.2-1.3
Clinical nodal stage FDG-PET/CT						
cN0	ref	ref	ref	ref	ref	ref
cN1	2.6*	2.4-2.9	3.0*	2.6-3.4	1.4*	1.3-1.5
cN2	2.6*	2.3-3.0	11.3*	9.7-13.4	1.7*	1.5-1.8
cN3	3.5*	2.3-5.3	5.8*	3.5-9.8	1.6*	1.2-2.2
Tumour location						
Right lung	ref	ref	ref	ref	ref	ref
Left lung	0.8*	0.8-0.9	1.4*	1.3-1.5	1.0	1.0-1.0
Histopathology						
Adenocarcinoma	ref	ref	ref	ref	ref	ref
Squamous cell carcinoma	2.0*	1.9-2.1	0.5*	0.5-0.6	1.0	0.9-1.0
NSCLC not further specified	1.3*	1.1-1.4	0.7*	0.6-0.9	1.0	0.9-1.1
Neuro endocrine carcinoma	1.1	0.9-1.3	0.7*	0.5-0.9	1.4*	1.2-1.6
Large cell carcinoma	1.2	1.0-1.4	0.8	0.6-1.0	1.1	1.0-1.2
Adenosquamous carcinoma	1.3	1.0-1.6	1.1	0.8-1.5	1.4*	1.2-1.6
Bronchoalveolar cell carcinoma	0.6*	0.5-0.7	0.8*	0.6-0.9	0.8*	0.7-0.9
Invasive mediastinal staging						
No	N/A	N/A	ref	ref	ref	ref
Yes	N/A	N/A	1.4*	1.3-1.6	1.3*	1.2-1.3
Adjuvant treatment						
No	N/A	N/A	N/A	N/A	ref	ref
Yes	N/A	N/A	N/A	N/A	1.1*	1.1-1.2

OR=adjusted odds ratio; 95%-CI=95% confidence interval; HR=adjusted hazard ratio; ref=reference category; N/A=not applicable. N/S=not significant in univariable analysis and thus not included in multivariable analysis; *indicates significant difference concluded from the 95%-CI not including 1.

Table 3. Logistic regression of the use of invasive staging and finding unforeseen N2 disease in patients with non-small cell lung cancer; and cox regression of overall survival of patients with cN1-3

	Invasive staging n=3,023		Unforeseen N2 n=2,888		Overall survival n=2,888	
	OR	95%-CI	OR	95%-CI	HR	95%-CI
Year of diagnosis	1.1*	1.1-1.2	1.0	1.0-1.0	1.0	1.0-1.0
Age at time of diagnosis	N/S	N/S	1.0	1.0-1.0	1.0	1.0-1.0
Gender						
Female	N/S	N/S	ref	ref	ref	ref
Male	N/S	N/S	0.8	0.7-1.0	1.1*	1.0-1.3
Clinical nodal stage FDG-PET/CT						
cN1	ref	ref	ref	ref	ref	ref
cN2	1.1	0.9-1.3	3.6*	2.9-4.3	1.2*	1.1-1.4
cN3	1.4	0.9-2.2	2.0*	1.2-3.3	1.2	0.9-1.6
Tumour side						
Right lung	ref	ref	ref	ref	ref	ref
Left lung	0.8	0.7-0.9	1.7*	1.4-2.0	0.9	0.9-1.0
Histopathology						
Adenocarcinoma	ref	ref	N/S	N/S	ref	ref
Squamous cell carcinoma	1.3*	1.1-1.6	N/S	N/S	0.9	0.8-1.0
NSCLC not further specified	1.3	0.9-1.8	N/S	N/S	1.1	0.9-1.3
Neuro endocrine carcinoma	0.7	0.5-1.1	N/S	N/S	1.6*	1.2-2.0
Large cell carcinoma	0.9	0.6-1.3	N/S	N/S	1.1	0.9-1.4
Adenosquamous carcinoma	1.0	0.6-1.7	N/S	N/S	1.3	0.9-1.8
Bronchoalveolar cell carcinoma	0.6*	0.4-0.9	N/S	N/S	0.9	0.7-1.2
Invasive mediastinal staging						
No	N/A	N/A	N/S	N/S	ref	ref
Yes	N/A	N/A	N/S	N/S	1.0	0.9-1.1
Adjuvant treatment						
No	N/A	N/A	N/A	N/A	ref	ref
Yes	N/A	N/A	N/A	N/A	0.8*	0.8-0.9

OR=adjusted odds ratio; 95%-CI=95% confidence interval; HR=adjusted hazard ratio; ref=reference category; n=number of patients; N/A=not applicable; N/S=not significant in univariable analysis and thus not included in multivariable analysis; *indicates significant difference concluded from the 95%-CI not including 1.

Five-year overall survival rate of patients who underwent invasive staging was 48% compared to 58% in patients who did not undergo invasive staging (p<.01). Increased mortality rates were observed in males, cN1-3 patients (compared to cN0), neuro endocrine carcinoma or adenosquamous carcinomas (compared to adenocarcinomas) and in patients who underwent invasive mediastinal staging (Table 2).

In the cN1-3 subgroup five-year overall survival rate was 44% in patients who underwent invasive staging *versus* 39% in patients who did not (p=.12). Increased mortality hazard were found in males, cN2 patients (compared to cN1) and in patients with neuro endocrine carcinomas (compared to adenocarcinomas), while adjuvant treatment was protective (Table 3).

DISCUSSION

A significant increase in rates of invasive mediastinal nodal staging in patients with resectable NSCLC was found between 2011 and 2017 in the Netherlands. Increasing use of less invasive endosonography prior to or substituting surgical staging did not lead to an increase in uN2 disease. Performance of invasive mediastinal staging led to a clinically relevant overall survival benefit in patients with clinical N1-3 disease.

After introduction of registration of endosonography in the Netherlands Cancer Registry in 2011 a significant increase in invasive mediastinal staging in patients with potentially resectable NSCLC in the Netherlands was found. Between 2005 and 2010 only the use of mediastinoscopy was registered, which could have possibly induced overestimation of the increase in use of endosonography from 2011 on. It could however be expected that endosonography was not used on a large scale in the Netherlands before 2011. The 2007 European Society for Thoracic Surgeons (ESTS) guideline described endosonography as an optional new technique with high specificity but low negative predictive value, requiring confirmatory invasive surgical technique in case of negative endosonography. After publication of the 2007 ESTS guideline recommending mediastinoscopy, the availability and experience with endosonography has tremendously increased. In the ASTER-1 trial comparable sensitivity for mediastinal nodal metastases detection was found by endosonography (85%) and surgical staging alone (79%). When adding confirmatory mediastinoscopy to endosonography a significant increase in sensitivity to 94% was found (p=.02 compared to 79% with surgical staging alone).[4] Largely based on these facts, the 2015 conjoint European Society of Gastrointestinal Endoscopy (ESGE), European Respiratory Society (ERS) and ESTS guideline recommended to perform EBUS, preferably added by EUS, as initial staging technique followed by confirmatory

mediastinoscopy in case no metastases were proven by pathology.[1] The increase in endosonography that we demonstrated in this study was probably based on these publications.

The increase in invasive staging over the years did not result in a decrease in uN2 disease. Adequate selection of patients who might benefit from invasive staging seems therefore important. A nationwide study including 3,263 Dutch patients who underwent NSCLC resection in 2017-2018 showed that 69% of these patients had an indication for invasive staging according to the ERS-ESTS-ESGE guideline.[7] With only 32% patients undergoing invasive staging in our analysis it appears that not all patients with an indication actually underwent invasive staging. Additionally, only 11% of patients underwent combined endosonography and confirmatory mediastinoscopy, suggesting significant non-adherence to the guidelines. Although not deducible from our dataset, possible reasons for this non-adherence could be doctors or historical preferences, limited experience with endosonography or limited availability of equipment and endosonography suites. In addition, it may be possible that increasing experience with endosonography led to higher confidence about its negative predictive value resulting in omitting confirmatory mediastinoscopy Information on medical decision making and detailed data (except the clinical nodal stage) to determine if patients had an indication for invasive staging were however lacking in the Netherlands Cancer Registry.

Obviously, higher clinical nodal stages were associated with an increased risk of uN2 and worse overall survival, underlining the importance of invasive staging in patients with cN1-3. The survival difference among cN1-3 subgroups with or without invasive staging was 5%. Interview based studies indicated that survival was the most important attribute in lung cancer treatment.[8,9] Discrete choice experiments showed that lung cancer patients accepted 2% mortality of lung cancer treatment (surgery or radiotherapy) for one additional year of life or would trade survival for short- or long term side effects of therapies.[10,11] Therefore, with limited morbidity and mortality of invasive mediastinal staging a 5% increase in overall survival in this population appears to be defined as clinically relevant by patients. Survival analyses of an observational cohort study of eleven North American hospitals showed significant survival benefit of performance of invasive nodal staging in patients with cN1-3 disease (only Kaplan Meier figure provided, no absolute data). Selection bias in this study has however to be taken into account.[12]

Squamous cell histology was found to increase the use of invasive staging compared to adenocarcinomas. This could be influenced by clinical features such as fast grow, cavitation with necrosis possibly inducing reactivity in lymph nodes and compromised

prognosis of squamous cell carcinomas.[13,14] Next to the histology, tumour location also determined whether invasive staging was used and affected uN2 outcomes. We found patients with left sided lung tumours to be less likely to undergo invasive staging (in the entire population), while left sided lung tumours were associated with increased risk of uN2. It is known that approximately 25% of all N2 metastases are located in the aortopulmonary stations, which cannot be reached by either EBUS, EUS or cervical mediastinoscopy.[5,15,16] The challenging anatomic position as well as the uncertain clinical relevance of aortopulmonary N2 metastases in patients with left upper lobe tumours might have influenced the decision whether to perform invasive staging. Survival of these patients after all seems to be significantly better compared to patients with metastases in the subcarinal station.[17] No information of the affected lymph node stations however was available in the Netherlands Cancer Registry, making it impossible to interpret and analyse reasons for less adherence to the guideline and the effect of nodal metastatic distribution on survival.

Although detection of unforeseen N2 after definite surgery seems undesirable, the question remains whether upfront detection of N2 leads to improved survival. Garelli et al. also demonstrated a significant survival difference between patients with microscopic (<2 mm) and macroscopic (≥2 mm) uN2 and Yoo et al. showed significant overall survival differences among patients with 1, 2-4 and ≥5 malignant N2 lymph nodes. [18,19] These results correspond with several retrospective studies reporting on better overall survival in patients with minimal N2 disease.[20-22] Since details on the affected lymph node stations and size of metastases were lacking in the Netherlands Cancer Registry we were not able to describe details on nodal spread, other than number of affected nodes. Constrained by the available data we were forced to use a very strict cut-off between minimal and extensive uN2 disease. Based on the above mentioned studies the proportion of patients with minimal uN2 disease in our analysis may therefore be underestimated as more than one affected lymph nodes might all have been micrometastases and/or located in a single lymph node station as well as distribution of affected nodes among hilar and mediastinal lymph node stations with only minimal spread in N2 stations.

In patients with stage III NSCLC the choice and timing of treatment (neo-adjuvant or adjuvant chemotherapy with or without surgery) may influence survival. Analysis of the American National Cancer Database comprising approximately 65% of all lung cancer patients in the United States showed 34% five-year overall survival in patients with stage III NSCLC who underwent primary surgical resection and adjuvant treatment (2004-2012, n=3,721, all pN2).[23] From the Netherlands Cancer Registry analysis of patients with clinical stage IIIA NSCLC (2010-2013, n=4,816, 67% cN2, 23% cT4) we found 4-year overall survival of 39% in patients primarily treated by surgical lung tumour resection,

while 4-year overall survival was 51% in patients receiving neo-adjuvant therapy and subsequent surgical lung tumour resection.[24] The ESPATUE trial showed 5-year-overall survival of 44% in patients with cytologically proven stage IIIA or IIIB (n=81, 70% N2-3, 30% T4) treated by induction chemotherapy and subsequent surgical lung tumour resection.[25]. Only patients with sufficient response to neo-adjuvant therapy and good clinical condition will generally proceed to surgical lung tumour resection, and thus selection bias should be taken into account assessing these outcomes. Based on these results adequate mediastinal nodal staging of patients with resectable NSCLC remains important.

In our study, performance of invasive nodal staging even indicated to possibly improve overall survival with 5% in patients with cN1-3 disease undergoing primary surgical lung tumour resection. Future research should determine whether this survival benefit persists and should evaluate which subgroups especially benefit from the different invasive mediastinal staging strategies. Patients with extensive N2 disease might benefit from neo-adjuvant therapy instead of primary surgical lung tumour resection, whereas minimal N2 disease may accurately be treated by surgery and adjuvant systemic therapy.

The results of this study should be interpreted with the limitation that the Netherlands Cancer Registry lacks detailed information. No information was available on quality of staging techniques (e.g number of lymph node stations visualized or sampled; use of conventional or video mediastinoscopy; combined use of EBUS and EUS), precluding the assessment of impact of quality on uN2 rates or survival. Except the pathological nodal stage and number of affected lymph nodes, no details on lymph node level and extensiveness of spread with a lymph node or level were available. This also precluded us from dividing uN2 cases in detection errors (lymph node metastasis not detected by FDG-PET/CT nor endosonography and mediastinoscopy if performed) or sampling errors (metastasis missed despite lymph node sampling during endosonography and/or mediastinoscopy of a suspicious station on imaging). Additionally, during follow-up no details on recurrence of the disease or causes of death were reported, limiting the survival analysis to overall survival only. Despite these limitations, this is the first study showing long-term nationwide trends in invasive mediastinal nodal staging of NSCLC and its effect on uN2 disease and overall survival.

CONCLUSION

A significant increase in the use of invasive mediastinal staging in patients with potentially resectable NSCLC was found between 2011 and 2017 in the Netherlands. Increas-

ing use of less invasive endosonography prior to or substituting surgical staging did not lead to an increase in uN2 disease. Performance of invasive mediastinal staging led to a possible overall survival benefit in patients with clinical N1-3 disease. Further research should focus on which subgroup of patients will benefit most from which invasive mediastinal staging strategy.

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CONFLICT OF INTEREST

JB, MA, MD and FvdB have nothing to disclose. JA received non-financial support from Hitachi Medical systems, non-financial support from Pentax, grants from Cook medical and Mauna Kea Technologies, outside the submitted work.

AUTHOR CONTRIBUTIONS

JB, MA, MD, JA and FvdB have been involved in the design of the study. JB analysed the data and interpreted the results together with MA and FvdB. JB drafted the manuscript which was critically revised by MA, MD, JA and FvdB. All authors gave approval of the final version to be published.

REFERENCES

1. Vilmann P, Clementsen PF, Colella S, Siemsen M, de Leyn P, Dumonceau J, Herth FJ, Larghi A, Vazquez-Sequeiros E, Vasquez-Sequeiros E, Hassan C, Crombag L, Korevaar DA, Konge L, Annema JT. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). *Endoscopy* 2015; 47: 546-560.
2. Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, Escriu C, Peters S. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2017; 28: iv1-iv21.
3. Landelijke Werkgroep Longtumoren. Landelijke richtlijn niet kleincellig longcarcinoom. 2015.
4. Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, De Leyn P, Braun J, Carroll NR, Praet M, de Ryck F, Vansteenkiste J, Vermassen F, Versteegh MI, Veseliç M, Nicholson AG, Rabe KF, Tournoy KG. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. *JAMA* 2010; 304: 2245-2252.
5. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, Turna A, Schil PV, Venuta F, Waller D, Weder W, Zielinski M. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *European Journal of Cardio-Thoracic Surgery* 2014; 45: 787-798.
6. Lawrence D. Brown, T. Tony Cai, Anirban DasGupta. Interval Estimation for a Binomial Proportion. *Statistical Science* 2001; 16: 101-117.
7. Bousema JE, Heineman DJ, Dijkgraaf MGW, Annema JT, van den Broek, Frank J.C. Adherence to the mediastinal staging guideline and unforeseen N2 disease in patients with resectable non-small cell lung cancer: Nationwide results from the Dutch Lung Cancer Audit - Surgery. *Lung Cancer* 2020; 142: 51-58.
8. Sun H, Wang H, Xu N, Li J, Shi J, Zhou N, Ni M, Hu X, Chen Y. Patient Preferences For Chemotherapy In The Treatment Of Non-Small Cell Lung Cancer: A Multicenter Discrete Choice Experiment (DCE) Study In China. *Patient preference and adherence* 2019; 13: 1701-1709.
9. Mühlbacher AC, Bethge S. Patients' preferences: a discrete-choice experiment for treatment of non-small-cell lung cancer. *Eur J Health Econ* 2015; 16: 657-670.
10. Sullivan DR, Eden KB, Dieckmann NF, Golden SE, Vranas KC, Nugent SM, Slatore CG. Understanding patients' values and preferences regarding early stage lung cancer treatment decision making. *Lung cancer (Amsterdam, Netherlands)* 2019; 131: 47-57.
11. Janssen EM, Dy SM, Meara AS, Kneuertz PJ, Presley CJ, Bridges JF. Analysis of Patient Preferences in Lung Cancer – Estimating Acceptable Tradeoffs Between Treatment Benefit and Side Effects. *Patient preference and adherence* 2020; 14: 927-937.
12. Osarogiagbon RU, Lee Y, Faris NR, Ray MA, Ojeabulu PO, Smeltzer MP. Invasive mediastinal staging for resected non–small cell lung cancer in a population-based cohort. *The Journal of Thoracic and Cardiovascular Surgery* 2019; 158: 1220-1229.e2.
13. Socinski MA, Obasaju C, Gandara D, Hirsch FR, Bonomi P, Bunn P, Kim ES, Langer CJ, Natale RB, Novello S, Paz-Ares L, Pérol M, Reck M, Ramalingam SS, Reynolds CH, Spigel DR, Stinchcombe TE, Wakelee H, Mayo C, Thatcher N. Clinicopathologic Features of Advanced Squamous NSCLC. *Journal of Thoracic Oncology* 2016; 11: 1411-1422.

14. Wang B, Huang J, Chen H, Lin C, Lin S, Hung W, Cheng Y. The comparison between adenocarcinoma and squamous cell carcinoma in lung cancer patients. *Journal of Cancer Research and Clinical Oncology*. 2020 Jan;146(1):43-52
15. Bousema JE, van Dorp M, Noyez VJJM, Dijkgraaf MGW, Annema JT, van den Broek, Frank J.C. Unforeseen N2 Disease after Negative Endosonography Findings with or without Confirmatory Mediastinoscopy in Resectable Non–Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. *Journal of Thoracic Oncology* 2019; 14: 979-992.
16. von Bartheld, Martin B., BSc, Rabe, Klaus F., MD, PhD, Annema, Jouke T., MD, PhD. Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. *Gastrointestinal Endoscopy* 2009; 69: 345-349.
17. Citak N, Sayar A, Metin M, Büyükkale S, Kök A, Solak O, Yurt S, Gürses A. The Prognostic Significance of Metastasis to Lymph Nodes in Aortopulmonary Zone (Stations 5 and 6) in Completely Resected Left Upper Lobe Tumors. *The Thoracic and Cardiovascular Surgeon* 2015; 63: 568-576.
18. Garelli E, Renaud S, Falcoz P, Weingertner N, Olland A, Santelmo N, Massard G. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. *European Journal of Cardio-Thoracic Surgery* 2016; 50: 322-328.
19. Yoo, Changhoon|Yoon, Shinkyo|Lee, Dae Ho|Park, Seung-Il|Kim, Dong Kwan|Kim, Yong-Hee|Kim, Hyeong Ryul|Choi, Se Hoon|Kim, Woo Sung|Choi, Chang-Min|Jang, Se Jin|Song, Si Yeol|Kim, Su Ssan|Choi, Eun Kyung|Lee, Jae Cheol|Suh, Cheolwon|Lee, Jung-Shin|Kim, Sang-We. Prognostic Significance of the Number of Metastatic pN2 Lymph Nodes in Stage IIIA-N2 Non–Small-Cell Lung Cancer After Curative Resection. *Clinical Lung Cancer* 2015; 16: e203-e212.
20. Cerfolio RJ, Bryant AS. Survival of Patients With Unsuspected N2 (Stage IIIA) Nonsmall-Cell Lung Cancer. *The Annals of Thoracic Surgery* 2008; 86: 362-367.
21. Deok Heon Lee, Jae Bum Kim, Dong Yoon Keum, Ilseon Hwang, Chang Kwon Park. Long Term Survival of Patients with Unsuspected N2 Disease in Non-Small Cell Lung Cancer. *Korean J Thorac Cardiovasc Surg* 2013; 46: 49-55.
22. Obiols C, Call S, Rami-Porta R, Trujillo-Reyes JC, Saumench R, Iglesias M, Serra-Mitjans M, Gonzalez-Pont G, Belda-Sanchís J. Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. *The Annals of thoracic surgery* 2014; 97: 957-964.
23. Thomas D, Thomas D, Arnold B, Arnold B, Rosen J, Rosen J, Salazar M, Salazar M, Detterbeck F, Detterbeck F, Blasberg J, Blasberg J, Boffa D, Boffa D, Kim A, Kim A. The Significance of Upfront Knowledge of N2 Disease in Non-small Cell Lung Cancer. *World J Surg* 2018; 42: 161-171.
24. Dickhoff C, Dahele M, de Langen AJ, Paul MA, Smit EF, Senan S, Hartemink KJ, Damhuis RA. Population-Based Patterns of Surgical Care for Stage IIIA NSCLC in the Netherlands between 2010 and 2013. *Journal of Thoracic Oncology* 2016; 11: 566-572.
25. Eberhardt WEE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H, Westeel V, Stahel R, Felip E, Peters S. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* 2015; 26: 1573-1588.

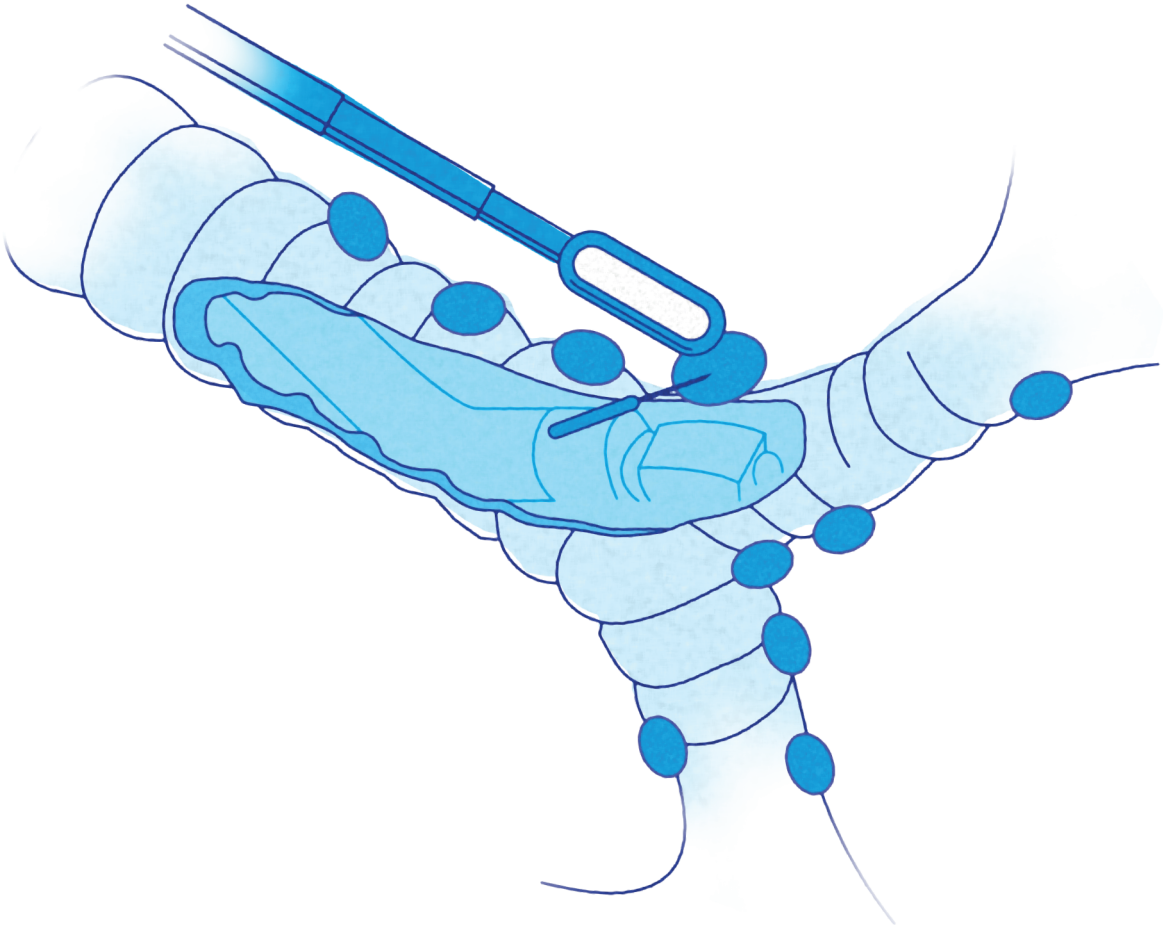
Appendix 1. Clinical and lung cancer characteristics of patients included in unforeseen N2 and survival analyses per diagnosis year (n=21,409)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	x^2	Trend	Spearman
Number of patients	1,434	1,442	1,536	1,481	1,593	1,610	1,725	1,681	1,783	1,694	1,827	1,779	1,824	-	-	-
Age, median	66	66	66	66	67	67	66	66	66	67	67	67	68	-	-	-
Male gender, %	67	63	64	61	63	62	60	57	58	57	56	54	54	-	↓	<.01
Clinical nodal stage, %																
cN0	86	82	82	82	81	84	84	84	83	83	82	82	83		-	.56
cN1	5	7	8	8	10	9	9	9	10	11	12	13	12		↑	.01
cN2	3	4	4	4	4	4	3	4	4	3	3	3	3	<.01	-	.09
cN3	0	0	1	0	0	0	1	0	0	0	0	0	1		-	.75
cNx	6	7	7	6	5	3	3	3	3	2	3	2	1		↓	<.01
Tumour location, %																
Right upper lobe	32	36	31	34	32	33	34	34	36	33	32	33	32		-	.82
Right middle lobe	4	4	4	5	4	4	5	4	4	5	5	5	5		↑	.02
Right lower lobe	19	17	18	18	20	18	18	18	18	17	19	18	20	.13	-	.55
Left upper lobe	30	27	30	28	27	27	28	29	28	30	28	27	27		-	.35
Left lower lobe	15	15	16	15	16	19	15	14	14	16	15	17	17		-	.54

Appendix 1. Clinical and lung cancer characteristics of patients included in unforeseen N2 and survival analyses per diagnosis year (n=21,409) (*continued*)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	x^2	Trend	Spearman
Histopathology, %																
Adenocarcinoma	37	37	37	39	38	41	41	45	46	45	46	48	35		↑	.04
Squamous cell carcinoma	40	42	41	38	40	39	40	36	36	33	35	33	31		↓	<.01
NSCLC not further specified	4	5	5	5	5	5	5	8	7	11	9	8	19		↑	<.01
Neuro endocrine	2	2	2	2	2	2	2	3	3	3	2	3	2	<.01	-	.09
Large cell carcinoma	8	8	6	6	4	2	2	1	1	1	1	1	0		↓	<.01
Adenosquamous carcinoma	2	2	2	2	2	2	2	1	1	2	1	2	2		-	.25
Bronchoalveolar cell	6	6	7	8	9	9	7	5	5	6	5	6	11		-	.88
Mediastinal nodal staging, %																
No invasive staging	74	71	76	74	77	75	67	66	64	65	61	60	60		↓	<.01
Endosonography only	N/A	N/A	N/A	N/A	N/A	N/A	9	11	13	15	17	18	19		↑	<.01
Endosonography + mediastinoscopy	N/A	N/A	N/A	N/A	N/A	N/A	9	11	10	10	12	12	13	<.01	-	.01
Mediastinoscopy only	26	29	24	26	23	25	15	12	13	10	10	10	8		↓	<.01
Adjuvant therapy, %	22	25	25	29	32	33	35	32	28	29	28	25	27	-	-	.54

x2 =Chi-squared test p-value; trend=↑=increasing trend; ↓=decreasing trend; – =stable trend; Spearman=Spearman's rank correlation coefficient p-value; cN=clinical nodal stage; N/A=not available;



Chapter 5

Patients' preferences regarding invasive mediastinal nodal staging of resectable lung cancer

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ABSTRACT

Background Variability in practice and ongoing debate on optimal invasive mediastinal staging of patients with resectable non-small cell lung cancer (NSCLC) is widely described in literature. Patients' preferences on this topic have however been underexposed so far.

Methods An internet-based questionnaire was distributed among MEDIASTrial participants (NTR6528, randomization of patients to mediastinoscopy or not in the case of negative endosonography). Literature, expert opinion and patient interviews resulted in five attributes; the risk of a futile lung resection (oncological futile in case of unforeseen N2 disease), the length of the staging period, resection of the primary tumor, complications of staging procedures and the mediastinoscopy scar. The relative importance (RI) of each attribute was assessed by using adaptive-conjoint-analysis and Hierarchical Bayes estimation. A treatment-trade-off was used to examine the acceptable proportion of avoided futile lung resections to cover the burden of confirmatory mediastinoscopy.

Results Ninety-seven patients completed the questionnaire (57%). The length of the staging period was significantly the most important attribute (RI 26.24; 95%-CI: 25.05-27.43), followed by the risk of a futile surgical lung resection (RI 23.44; 95%-CI: 22.28-24.60) and resection of the primary tumor (RI 22.21; 95%-CI: 21.09-23.33). Avoidance of 7% (IQR 1- >14%) futile lung resections would cover the burden of confirmatory mediastinoscopy, with a dichotomy among patients always (39%) or never (38%) willing to undergo confirmatory mediastinoscopy after N2 and N3 negative endosonography.

Conclusions Although a strong dichotomy among patients always or never willing to undergo confirmatory mediastinoscopy was found, the length of the staging period was the most important attribute in invasive mediastinal staging according to patients with resectable NSCLC.

LIST OF DEFINITIONS

EBUS(-TBNA) endobronchial ultrasound guided transbronchial needle aspiration. Investigation of mediastinal and hilar lymph nodes with a linear ultrasound probe via the airways with the possibility of nodal sampling under real-time ultrasound control.

EUS(-FNA) endoscopic ultrasound guided fine needle aspiration. Investigation of mediastinal lymph nodes with a linear ultrasound probe via the oesophagus with the possibility of nodal sampling under real-time ultrasound control.

Futile surgical lung tumor resection A surgical lung tumor resection was deemed oncological futile in case unforeseen N2 (macro metastases or multi-level) disease was detected after surgery, as overall survival of these patients is generally not extended as results of the surgery.

Mediastinal staging Invasive mediastinal nodal staging to determine the nodal status of lung cancer by using EBUS, EUS and/or mediastinoscopy.

Mediastinoscopy Surgical procedure under general anaesthesia to examine mediastinal lymph nodes, located paratracheal and subcarinal, with the possibility to take surgical biopsies.

Negative endosonography Endosonographic examination of mediastinal lymph nodes by using EBUS-TBNA and/or EUS-FNA showing no pathologically proven N2 or N3 lymph node metastases.

Unforeseen N2 Pathologically proven N2 disease resulting from mediastinal lymph node dissection at time of tumor resection, not detected by clinical staging including endosonography nor mediastinoscopy (if performed).

INTRODUCTION

Non-small cell lung cancer (NSCLC) is a common disease with 9,623 new Dutch cases in 2020.(1) Only 23% of patients are potential candidates for intended curative surgical treatment in the Netherlands, since the remaining 77% already have locoregional or distant metastases at time of diagnosis.(2) Potential surgical candidates with increased risk of locoregional metastases are recommended to undergo invasive mediastinal staging prior to surgical lung tumor resection.(3) Adequate staging of these patients is important, as patients with N2 or N3 disease (stage III NSCLC) generally undergo definite chemoradiation or multimodality therapy that consists of neo-adjuvant chemoradiotherapy and subsequent surgical lung tumor resection. Upfront surgery in these patients seems to be associated with worse overall survival.(4) Recent studies showed that

The additional value of confirmatory mediastinoscopy after N2 and N3 negative endosonography results is under debate. In a randomised trial published in 2010 only 9% N2 or N3 metastases after negative endosonography were detected.(5) This results in a number needed to test of eleven, while mediastinoscopy is associated with significant risk of complications, hospital admission, general anaesthesia and delay in definite lung cancer treatment.(6-11) A recent meta-analysis including studies until 2019 revealed comparable unforeseen N2 rates after invasive mediastinal nodal staging by endosonography with or without mediastinoscopy, underlining the suggested limited additional diagnostic value of confirmatory mediastinoscopy.(11)

Despite extensive research on the value and accuracy of endosonography and cervical mediastinoscopy in NSCLC staging, patients' preferences have, in this era of shared decision making, never been investigated before. Therefore, we aimed to determine patients' preferences on invasive mediastinal staging addressing the burden of care, burden of complications and prognostic uncertainties of staging strategies with or without confirmatory mediastinoscopy.

PATIENTS AND METHODS

Research questions

1. What are the most important attributes of invasive mediastinal nodal staging according to patients with resectable NSCLC?
2. What do NSCLC patients consider a minimum proportion of avoided futile surgical lung tumor resections (defined as demonstrating unforeseen N2 after surgery) to

accept the burden of confirmatory mediastinoscopy after N2 and N3 negative endosonography?

Design

An internet-based questionnaire consisting of adaptive conjoint analysis (ACA) and treatment trade-off method (TTM) was developed using Sawtooth Software Lighthouse Studio version 9.8.0. Background information about mediastinal nodal staging by using endosonography (conscious sedation, 1% complications) and cervical mediastinoscopy (general anaesthesia, scar, 3% complications, laryngeal recurrent nerve palsy) as well as surgical lung tumor resection with mediastinal lymph node dissection (18% minor complications, 2% major complications, 2% mortality) was provided in the introduction of the questionnaire. After the introduction the ACA was used to determine the most important attributes of invasive mediastinal staging. The considered minimum proportion of avoided futile surgical lung tumor resections to accept the burden of confirmatory mediastinoscopy after N2 and N3 negative endosonography was determined by the TTM.

Study population

All patients participating in the randomised MEDIASTrial (NTR6528) were potentially eligible for participation in this study. Depending on randomisation patients underwent surgical lung tumor resection and lobe-specific mediastinal lymph node dissection with or without prior cervical mediastinoscopy after negative endosonography.(12) At least three months after lung surgery all patients received a written invitation to participate in this patients' preferences study. In case the questionnaire was not completed within three weeks a written reminder was sent. Patients who already withdrew consent of the MEDIASTrial were not invited.

Collection of attributes

We used literature to collect possible attributes associated with invasive mediastinal staging. The most reported outcomes were listed and sent to 20 local investigators of the MEDIASTrial (10 pulmonologists and 10 lung surgeons) in order to get an 'expert opinion' of the most important attributes. The experts selected all attributes they thought to be important on the list and were able to add important attributes, which resulted in a list of 13 attributes as displayed in Table 1. These attributes were integrated in semi-structured interviews with five patients from the Dutch lung cancer patients' association (Longkanker NL). The interviews consisted of three parts; background information, open questions to identify additional attributes and ranking of the attributes listed by the experts. Taking the feasibility of the final questionnaire into account we aimed to select five attributes. Therefore, all patients were asked to rank the attributes resulting in the following five most important attributes from the interviews: the risk of

a futile surgical lung tumor resection (with its inherent morbidity and mortality), the risk of complications of staging procedures, the length of the staging period, a scar in the neck from the mediastinoscopy, and actual resection of the primary lung tumor. These five attributes were included in the ACA to determine their relative importance. The lay-out and formulations of the created questionnaire were pilot tested by another five patients from the Dutch lung cancer patients' association before it was distributed among included patients.

Table 1. Attributes based on literature and expert opinion

Clinical relevance of mediastinal staging (e.g. treatment choice)
Cost-effectiveness of mediastinal staging
Effect of unforeseen N2 disease on survival
Maximum accuracy of mediastinal staging
Negative predictive value of endosonography
Negative predictive value of mediastinoscopy
Patients' comfort during staging procedures
Risk of complications of futile surgical lung tumor resection
Risk of complications of staging procedures
Sensitivity of endosonography
Sensitivity of mediastinoscopy
The total length of the staging period
The total number of staging procedures

Adaptive Conjoint Analysis

After determining the ACA attributes we adjusted realistic levels to them based on literature and clinical practice (Table 2). Before the start of the ACA an explanation of the attributes was provided (Table 2), including an ACA example task. The first part of the ACA consisted of questions to indicate the relevance of the difference between the highest and lowest level within each attribute on a four-point scale; not important at all – a little bit important – important – very important. Based on the results of the attribute relevance questions individualized trade-offs between two scenarios were constructed. The minimum number of trade-offs needed for accurate estimations of probability utilities was 12, based on the following formula: 3 x (N – n – 1) – N, where N is the total number of levels and n is the number of attributes.(13) Patients were exposed to six considerations of scenarios with two attributes and six considerations of scenarios with three attributes. Patients indicated which scenario they preferred and the strength of their preference (seven-point scale) by making trade-offs between preferred

and adverse outcomes. Probabilities were described in frequency formats to facilitate understanding (example ACA task in Figure 1).(14) To prevent patients from clinically irrelevant or impossible considerations some restrictions were made (e.g. scar in the neck if mediastinoscopy was omitted).

Table 2. Adaptive conjoint analysis attributes with their levels and explanation to the patients

Attribute	Explanation to patients	Levels
Futile surgical lung tumor resection	Surgical lung tumor resection was futile in case unforeseen N2 disease is detected after surgery. Your survival will not be extended as result of the surgery, while surgical lung tumor resection is associated with 30% overall complications (18% mild complications, 10% severe complications, 2% mortality). The levels represent the proportion of futile surgical lung tumor resections.	3% 6% 9% 12%
Complications of staging procedures	During the invasive mediastinal nodal staging procedures complications could occur. However, complications are rare, some could be severe.	0% 4% 6% 8%
Length of staging period	The process of scheduling, performing and pathology investigation of confirmatory mediastinoscopy takes time. This process has to be completed before lung cancer treatment can start, and therefore this will be prolonged by performing confirmatory mediastinoscopy. On the other hand, confirmatory mediastinoscopy can prevent you from futile lung surgery.	1 week 3 weeks 5 weeks
Resection of the lung tumor	When confirmatory mediastinoscopy is omitted you will directly be referred for surgical lung tumor resection. When confirmatory mediastinoscopy is not omitted, the surgical lung tumor resection will only be performed if mediastinoscopy does not show mediastinal lymph node metastases. If mediastinal lymph node metastases are detected at mediastinoscopy, generally no surgical lung tumor resection will be performed.	Always Only if mediastinoscopy is N2-3 negative
Mediastinoscopy scar in the neck	Cervical mediastinoscopy is performed through an incision in the neck. A scar of approximately 3-4 centimeter just above the sternum will be created.	Yes No

In the ASTER-trial unforeseen N2 rates of 6.9% after endosonography and mediastinoscopy versus 14.3% after mediastinoscopy only were found.(5) Despite this difference in unforeseen N2 disease the five-year survival was 35% in both groups.(15) Based on these results we suggested that up to 14% futile surgical lung tumor resections would not compromise long-term survival. The TTM contained several choice sets between two scenarios: a scenario with mediastinoscopy (scenario A) and without mediastinoscopy (scenario B) and its effect on the proportion of avoided futile surgical lung tumors resections. It was stated that survival was similar in both scenarios.

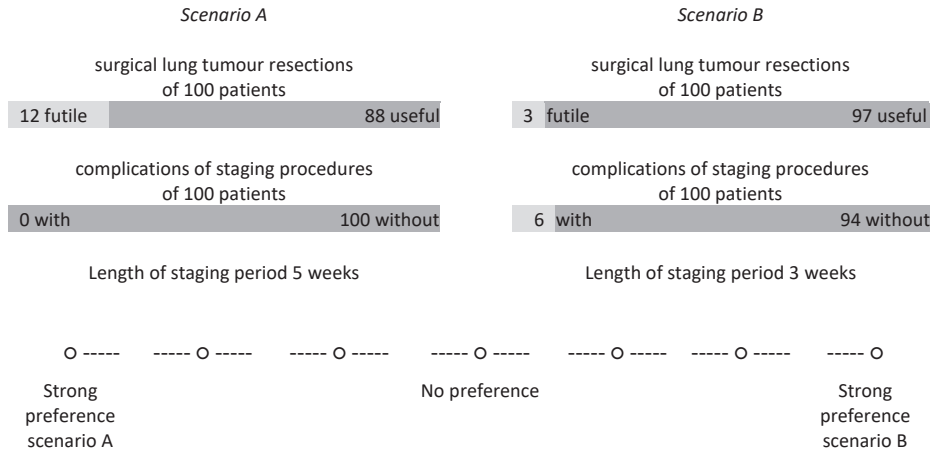

Figure 1. Example adaptive conjoint analysis trade-off containing three attributes.
Treatment Trade-off Method

We started with a choice set in which scenario A included 100 patients in whom confirmatory mediastinoscopy was performed, resulting in 14 avoided futile surgical lung tumor resections at the cost of six patients with complications of mediastinoscopy (three patients with mild complications and three patients with severe life-threatening complications). Scenario B was a fixed scenario including 100 patients not undergoing mediastinoscopy and thus no patients suffering from complications of mediastinoscopy, resulting in zero avoided futile surgical lung tumor resections (corresponding with an unforeseen N2: 14%). When patients chose scenario A (with mediastinoscopy) the number of avoided futile surgical lung tumor resections in scenario A decreased in order to determine whether a decreased value of mediastinoscopy would still cover the burden of mediastinoscopy. When patients chose scenario B (without mediastinoscopy) in this first choice set, they were asked again with additional explanation. If they maintained their preference for scenario B, the TTM ended for them; these patients were classified as 'would never undergo mediastinoscopy'. In subsequent choice sets (for patients choosing scenario A in the first choice set) the number of avoided futile surgical lung tumor resections in scenario A (with mediastinoscopy) decreased or increased when patients respectively chose scenario A or B in order to determine whether the decreased or increased value of mediastinoscopy would cover the burden (example TTM task in Figure 2). In this way an acceptable proportion of avoided futile surgical lung tumor resections to cover the burden of confirmatory mediastinoscopy was established for all patients.

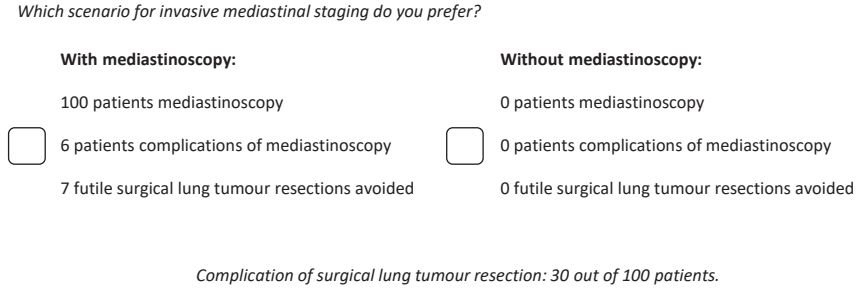

Figure 2. Example treatment trade-off.

Data analysis

Randomisation allocation, age and gender of included patients were retrieved from the MEDIASTrial database. Hierarchical Bayes Estimation was used to calculate the relative importance (RI) of all attributes from the ACA, by using the maximum difference in the average overall utility levels within an attribute.(16) The RI of an attribute represents its weight compared to the other attributes, since the sum of the RI's is always 100. The mean RI's of the attributes were compared to each other by using the paired T-test. Subgroup analysis to assess whether different groups assigned different RI's to specific attributes was done using the independent T-test based on the accepted proportion of avoided futile lung tumor resections obtained from the TTM (below/equal or above the median), MEDIASTrial randomisation allocation (i.e. mediastinal staging with or without confirmatory mediastinoscopy), age at time of diagnosis (below/equal or above the median) and on gender. All analyses were performed by using Sawtooth Software Lighthouse Studio 9.8.0 (Sawtooth Software, Inc., Sequim, WA, USA) and the Statistical Package for Social Sciences, version 22.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients

A total of 97 patients completed the questionnaire and were included for analysis (response rate: 57%). The median age of included patients was 67 years (IQR 61-72) and 55% (53/97) were males. As result of randomisation in the MEDIASTrial 52 patients underwent endosonography only and 45 patients underwent endosonography and confirmatory mediastinoscopy prior to surgical lung tumor resection. Responders were younger than non-responders (67 years (IQR 61-72) vs 71 years (IQR 64-75), p=.012). No differences were found among responders and non-responders in randomisation outcome and gender.

Relative importance of attributes

The most important attribute of invasive mediastinal nodal staging of NSCLC was the length of the staging period (RI 26.24; 95%-CI: 25.05-27.43), followed by the risk of a futile surgical lung tumor resection (RI 23.44; 95%-CI: 22.28-24.60), actual resection of the primary lung tumor (RI 22.21; 95% CI: 21.09-23.33), complications of staging procedures (RI 20.65; 95% CI: 20.09-21.20) and the mediastinoscopy scar (RI 7.46; 95% CI: 6.87-8.05) (Table 3). The length of the staging period was more important than all other attributes (futile lung tumor resection p=.009, other attributes p=.000). The risk of a futile surgical lung tumor resection and actual resection of the primary lung tumor were evenly important (p=.199), while both were more important than complications of staging procedures (p=.000 and p=.044 respectively). The scar from the mediastinoscopy was the least important attribute (p=.000 compared to all other attributes).

Table 3. Adaptive conjoint analysis results (n=97)

Attributes and levels	Average utility (SD)	Average relative importance (95%-CI)
Length of the staging period		26.24 (25.05-27.43)
1 week	63.74 (13.71)	
3 weeks	3.72 (5.84)	
5 weeks	-67.46 (16.35)	
Futile surgical lung tumor resection		23.44 (22.28-24.60)
3%	58.32 (13.25)	
6%	23.85 (8.68)	
9%	-23.28 (6.89)	
12%	-58.88 (15.68)	
Resection of the lung tumor		22.21 (21.09-23.33)
Always	55.53 (13.84)	
If mediastinoscopy N2-3 negative	-55.53 (13.84)	
Complications of staging procedures		20.65 (20.09-21.20)
0%	50.78 (5.84)	
4%	18.14 (4.04)	
6%	-16.46 (2.48)	
8%	-52.46 (8.07)	
Mediastinoscopy scar in the neck		7.46 (6.87-8.05)
Yes	-18.65 (7.30)	
No	18.65 (7.30)	

SD=standard deviation; CI=confidence interval

Mediastinoscopy Treatment Trade Method

The minimum acceptable proportion of avoided futile surgical lung resections to accept the burden of confirmatory mediastinoscopy was 7% (IQR 1 - >14%). A dichotomy in patients' preferences was however found; 39% (38/97) of patients would always undergo mediastinoscopy, even if it avoids only 1% futile surgical lung tumor resections. On the other hand, 38% (37/97) of patients would never undergo mediastinoscopy, even if it avoids 14% futile surgical lung tumor resections (Figure 3). The TTM preferences (tending towards omitting or performing confirmatory mediastinoscopy) were in concordance with the randomisation allocation in 73% of patients who underwent mediastinoscopy and 67% in whom mediastinoscopy was omitted (p=.522).

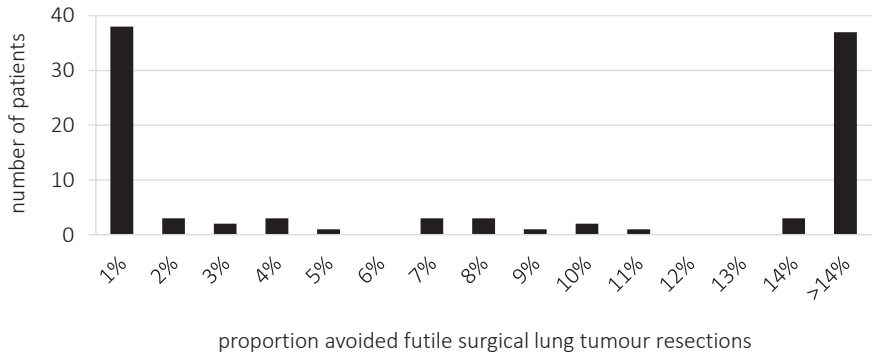

Figure 3. Minimum proportion of avoided futile surgical lung tumor resections to accept the burden of confirmatory mediastinoscopy after N2 and N3 negative endosonography based on TTM (n=97).

Subgroup analysis

Comparison of the ACA results of MEDIASTrial randomisation allocation subgroups showed that patients in whom confirmatory mediastinoscopy was omitted assigned the length of the staging period as single most important attribute, with actual resection of the primary tumor as second attribute. Patients who underwent confirmatory mediastinoscopy ranked the risk of a futile lung tumor resection, length of the staging period, and actual resection of the primary tumor respectively as most important attributes, without significant differences among them (Table 4).

When comparing patients based on age at time of diagnosis (≤67 years vs >67 years) the length of the staging period was ranked as most important attribute in both groups. Older patients found the risk of a futile surgical lung tumor resection however evenly important as the length of the staging period. In the other attributes no differences among age subgroups were found. (Table 4) Subgroup analysis based on gender showed no differences in RI's of all attributes.

When comparing patients based on the outcome of the TTM we found that patients tending towards the use of confirmatory mediastinoscopy (TTM ≤7 avoided futile surgical lung resections) ranked the risk of a futile lung tumor resection, length of the staging period, and actual resection of the primary tumor respectively as most important attributes, without significant differences among them. Patients tending towards omitting confirmatory mediastinoscopy (TTM >7 avoided futile surgical lung resections) ranked the length of the staging period as single most important attribute (Table 4).

Table 4. Relative importance and rank of attributes subgroup analyses

	TTM using confirmatory mediastinoscopy (n=50)		TTM omitting confirmatory mediastinoscopy (n=47)		p value
Length of the staging period	2	25.01 (23.30-26.71)	1	27.56 (25.91-29.20)	.033
Futile surgical lung tumor resection	1	25.19 (23.59-26.77)	3	21.59 (20.00-23.17)	.002
Resection of the lung tumor	3	22.50 (20.81-24.20)	2	21.89 (20.40-23.40)	.593
Complications of staging procedures	4	20.59 (19.80-21.38)	4	20.71 (19.91-21.51)	.833
Mediastinoscopy scar	5	6.71 (6.09-7.34)	5	8.25 (7.25-9.24)	.009

	Randomisation: with mediastinoscopy (n=45)		Randomisation: without mediastinoscopy (n=52)		p value
Length of the staging period	2	24.17 (22.33-26.01)	1	28.03 (26.60-29.46)	.001
Futile surgical lung tumor resection	1	25.93 (24.18-27.69)	3	21.28 (19.96-22.61)	.000
Resection of the lung tumor	3	22.19 (20.39-23.99)	2	22.23 (20.79-23.67)	.974
Complications of staging procedures	4	20.96 (20.14-21.78)	4	20.38 (19.62-21.14)	.301
Mediastinoscopy scar	5	6.75 (5.95-7.41)	5	8.08 (7.23-8.91)	.025

	Age below/equal median (≤67 years) (n=49)		Age above median (>67 years) (n=48)		p value
Length of the staging period	1	26.96 (25.38-28.55)	1	25.50 (23.68-27.33)	.227
Futile surgical lung tumor resection	3	22.21 (20.69-23.73)	2	24.69 (22.96-26.44)	.032
Resection of the lung tumor	2	22.94 (21.46-24.42)	3	21.47 (19.76-23.17)	.192
Complications of staging procedures	4	20.10 (19.31-20.89)	4	21.21 (20.44-21.97)	.047
Mediastinoscopy scar	5	7.79 (6.73-8.85)	5	7.12 (6.59-7.65)	.265

DISCUSSION

The present study indicated that NSCLC patients with an indication for invasive mediastinal staging determined the length of the staging period the most important attribute of

invasive staging, while futile surgical lung resections (e.g. unforeseen N2 after resection) and actual resection of the primary lung tumor were the second most important attributes. On average, avoidance of 7% futile surgical lung tumor resections would cover the burden of confirmatory mediastinoscopy. However, a dichotomy among patients always or never willing to undergo confirmatory mediastinoscopy was found.

The European guidelines on invasive mediastinal nodal staging in selected patients are clear about the preference of endosonography over surgical staging as initial staging technique. However, in case of negative endosonography results (no pathologically proven N2 or N3 metastases) confirmatory mediastinoscopy is recommended in patients with cN1-3 and should be considered in patients with centrally located, FDG-non-avid or peripheral tumors >3 cm. This leaves room for doctors preferences and/or shared decision making, resulting in an ongoing debate in scientific forums in literature and variation in daily practice.(6-11) Significant variability in the use of invasive staging was already described in the United States, Canada and the Netherlands.(17-19) Shared decision making is currently upcoming and would, in our opinion, perfectly fit in the abovementioned knowledge gap, awaiting further research on this topic. Our results suggest that lung cancer patients have explicit ideas about invasive mediastinal staging, unless the period diagnosing and staging lung cancer is generally very emotional and precarious. Patient preferences on invasive mediastinal lung cancer staging have however never been investigated before. Several interview based studies on treatment preferences showed that lung cancer patients had clear ideas about efficacy and burden of lung cancer treatment.(20-24) These findings were strengthened by the results of a study including stage I-II NSCLC patients showing that most of these patients found it important to be involved in treatment decision making.(25) In this era of shared decision making physicians should therefore consider to invite patients to participate in their staging process.

Key element of shared decision making is providing patients from sufficient information.(26) Up to one-fifth of patients in the abovementioned stage I-II NSCLC study reported lack of knowledge about the treatment options.(25) Added by the assumption that cancer patients in general are at risk to overestimate their life expectancy and expectations about medical treatment, an important role is reserved for the information providing doctor.(27)

When considering to omit confirmatory mediastinoscopy after negative endosonography it is important to inform patients about the potential oncological consequences. Patients with extensive mediastinal lymph node metastases (stage III NSCLC), detected at mediastinal staging, are generally treated by definitive chemoradiotherapy or a mul-

timodality strategy of induction therapy followed by surgery. The randomised PACIFIC trial showed that application of Durvalumab after chemoradiotherapy in patients with locally advanced NSCLC (stage III) improved overall survival.(28). However, patients with minimal N2 disease (metastases <2mm and/or metastases in 1 lymph node station only) are thought not to have compromised survival by primary surgical treatment followed by adjuvant chemoradiotherapy. (4,29-31)

Most unforeseen N2 metastases turned out to be minimal N2 in previous studies, thereby asking ourselves whether resection of unforeseen N2 should be defined as 'futile' after all. Since best treatment of N2 disease is an ongoing debate among physicians, inclusion of this minimal N2 issue in the informed consent conversation with patients may make it even more complicated for patients. Therefore we chose a more conservative approach in the present study to investigate the patients' opinion about 'futile' resection.

Against our expectations, the risk of complications by mediastinoscopy was not considered as important as the attributes 'period of staging', 'futile lung resection' and 'actual resection of the primary tumor'. Moreover, the accuracy of mediastinoscopy (as overall accuracy, sensitivity, or negative predictive value) was not considered by our patient panel at all to include this as attribute in de adaptive conjoint analysis. Although, the risk of a futile lung resection may be an equivalent (according to patients) of diagnostic accuracy. Evaluation of mediastinoscopy in the Netherlands from 2012 to 2016 demonstrated that only half of the mediastinoscopies was performed according to the Dutch guideline (requiring biopsies of two ipsilateral stations, one contralateral station and N7). This may have resulted in the significant more unforeseen N2 disease in the non-adherence group compared to patients who underwent complete mediastinoscopy.(32) A meta-analysis including studies until September 2019 showed comparable unforeseen N2 rates after invasive mediastinal nodal staging by endosonography with or without mediastinoscopy.(11) When evaluating complications as well as accuracy in our treatment trade-off method, we found a clear dichotomy in our study results, with approximately 40% always choosing for mediastinoscopy and 40% always choosing for omitting mediastinoscopy. Whether the occurrence of complications or a futile resection have attributed to their choices remains unclear, but we cannot ignore the fact that 70% of patients answered the TTM conform their randomisation allocation suggesting that cognitive dissonance reduction could have influenced patients' choices. This psychologic phenomenon is based on the assumption that patients who have experienced a certain treatment or disease assign higher utilities to that treatment or disease.(33)

One of the shortcomings of the present study may be that the included patients have been a selected sample, as it were patients who already underwent invasive staging

(endosonography with or without mediastinoscopy according to randomisation) and surgical lung tumor resection. In advance, we suggested that a certain knowledge and experience with lung cancer staging and treatment was required to properly judge which attributes were most important. For patients without this experience it would have been very hard to acknowledge the effects of the disease and its staging and surgical treatment. Moreover, the time between lung cancer diagnosis, invasive staging and surgery is as result of the guideline recommendations very short in the Netherlands. Since this period is generally very precarious for patients, we thought it would not be ethical to present this questionnaire to them in this period.

As cognitive dissonance reduction could have influenced patients' choices, it may therefore be valuable to assess patients in whom mediastinal nodal staging is not yet performed. Special attention for detailed background information and patients' well-being should hereby be taken into account.

Also, the strong dichotomy in the TTM results might be (partly) a result of insufficient understanding of the considerations to be made or the method used to do so (TTM), despite a confirmatory question that was added to the questionnaire. Therefore, in future research it could be considered to use an interview setting instead of an internet-based questionnaire. Availability of this study as internet-based questionnaire only, could also have induced the age difference among responders and non-responders. However, in subgroup analysis based on age the length of the staging period remained the most important attribute. The increased RI of the risk of a futile lung resection in older patients could be explained by older patients probably being more prudent of futile major surgery based on an inferior general condition compared to younger patients. The actual length of the staging period of included patients was not available, subanalysis for this attribute was therefore not possible.

In the end this is the first study on patients' preferences on invasive nodal staging of NSCLC. The results of this study show that patients have preferences on this topic, taking the burden of care, burden of complications and prognostic uncertainties of different staging strategies and dependent treatments into account.

CONCLUSIONS

Although a strong dichotomy among patients always or never willing to undergo confirmatory mediastinoscopy was found, the length of the staging period was the most important attribute in invasive mediastinal staging according to patients with resectable

NSCLC. Awaiting further research on the optimal strategy for invasive mediastinal nodal staging, local staging logistics could already be optimized and shared decision making could be considered to fulfil patient preferences.

LIST OF ABBREVIATIONS

NSCLC=non-small cell lung cancer; RI=relative importance; EBUS=endobronchial ultrasonography, EUS=endoscopic ultrasonography; ACA=adaptive conjoint analysis; TTM=treatment trade-off method; IQR=interquartile range; CI=confidence interval.

DECLARATIONS

Ethics approval and consent to participate

This study was performed in accordance with the declaration of Helsinki, 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO, the Netherlands). The medical ethical committee of Máxima MC approved the study protocol and written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

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AUTHOR CONTRIBUTIONS

JB, FH, MD, JA, FvdB and EvdA have been involved in the design on the study. JB, FH and EvdA have been involved in designing the questionnaire and acquisition of data. JB and EvdA analysed and interpreted the data and JB drafted the manuscript. All authors critically revised the manuscript and all authors and the MEDIASTrial study group members gave approval for publication of the final version.

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REFERENCES

(1) Integraal Kanker Centrum Nederland, (IKNL). Cijfers over Kanker (Dutch Cancer Registry). 2019; Available at: http://www.cijfersoverkanker.nl/selecties/Dataset_2/img5a4b6b6782289. Accessed 30-10-, 2019.

(2) Heineman DJ, Hoeijmakers F, Beck N, Dickhoff C, Daniels JM, Schreurs WH, et al. Impact of health care organization on surgical lung cancer care. Lung Cancer 2019 Sep;135:181-187.

(3) Vilmann P, Clementsen PF, Colella S, Siemsen M, de Leyn P, Dumonceau J, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015;47(6):546-560.

(4) Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017 Jul 1,;28(4):iv1-iv21.

(5) Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, et al. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. JAMA 2010 Nov 24,;304(20):2245-2252.

(6) Rusch VW. Mediastinoscopy: An obsolete procedure? The Journal of Thoracic and Cardiovascular Surgery 2011 Dec;142(6):1400-1402.

(7) Annema JT, de Leyn P, Clementsen P, Siemsen M, Vilmann P. Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European respiratory journal 2015;46(6):1848-1849.

(8) Li WWL, Heijden, H F M van der, Verhagen AF. Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European Respiratory Journal 2015;46(6):1846-1848.

(9) Kim H. Reply to “Are We at the Dusk of Mediastinoscopy in Modern Clinical Practice?”: An Irresistible Trend. Journal of Thoracic Oncology 2015 Sep;10(9):e91-e92.

(10) Verhagen, A F T M, Schuurbiers OCJ, Looijen-Salamon MG, Heide, S M van der, Swieten HAv, Heijden, E H M van der. Mediastinal staging in daily practice: endosonography, followed by cervical mediastinoscopy. Do we really need both? Interactive Cardiovascular and Thoracic Surgery 2013;17(5):823-828.

(11) Bousema JE, van Dorp M, Noyez VJJM, Dijkgraaf MGW, Annema JT, van den Broek, Frank J.C. Unforeseen N2 Disease after Negative Endosonography Findings with or without Confirmatory Mediastinoscopy in Resectable Non–Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Journal of Thoracic Oncology 2019 Jun;14(6):979-992.

(12) Bousema JE, Dijkgraaf MGW, Papen-Botterhuis NE, Schreurs HW, Maessen JG, van der Heijden, Erik H, et al. MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a multicenter randomised controlled trial. BMC surgery 2018 May 18,;18(1):27.

(13) Sawtooth Software. ACA Technical Paper V6.0. 2007.

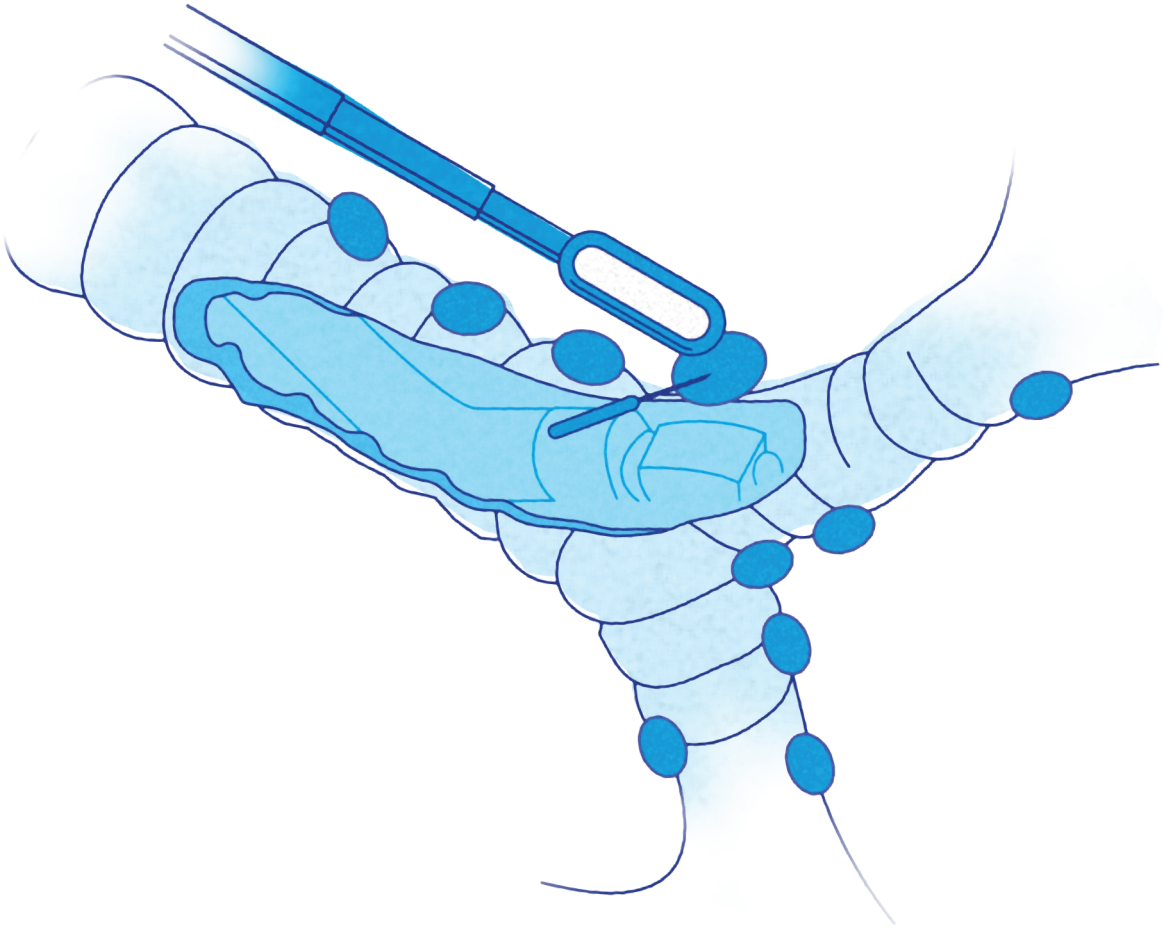
(14) Gerd Gigerenzer. The psychology of good judgment: Frequency formats and simple algorithms. Medical Decision Making 1996 Jul 1,;16(3):273.

(15) Kuijvenhoven JC, Korevaar DA, Tournoy KG, Malfait TLA, Dooms C, Rintoul RC, et al. Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer. JAMA 2016 Sep 13,;316(10):1110-1112.

(16) Orme B. Hierarchical Bayes: Why All the Attention? Sawtooth Software Inc. 2000.

(17) Turner SR, Seyednejad N, Nasir BS. Patterns of Practice in Mediastinal Lymph Node Staging for Non-Small Cell Lung Cancer in Canada. The Annals of Thoracic Surgery 2018 Aug;106(2):428-434.
(18) Thornblade LW, Wood DE, Mulligan MS, Farivar AS, Hubka M, Costas KE, et al. Variability in invasive mediastinal staging for lung cancer: A multicenter regional study. The Journal of Thoracic and Cardiovascular Surgery 2018 Jun;155(6):2658-2671.e1.
(19) Bousema JE, van Dorp M, Hoeijmakers F, Huijbregts IA, Barlo NP, Bootsma GP, et al. Guideline adherence of mediastinal staging of non-small cell lung cancer: A multicentre retrospective analysis. Lung Cancer 2019 Aug;134:52-58.
(20) Schmidt K, Damm K, Prenzler A, Golpon H, Welte T. Preferences of lung cancer patients for treatment and decision-making: a systematic literature review. European journal of cancer care 2016;25(4):580-591.
(21) Sun H, Wang H, Xu N, Li J, Shi J, Zhou N, et al. Patient Preferences For Chemotherapy In The Treatment Of Non-Small Cell Lung Cancer: A Multicenter Discrete Choice Experiment (DCE) Study In China. Patient preference and adherence 2019 Jan 1,;13:1701-1709.
(22) Axel C. Mühlbacher, Susanne Bethge. Patients' preferences: a discrete-choice experiment for treatment of non-small-cell lung cancer. Eur J Health Econ 2015 Jul 1,;16(6):657-670.
(23) Sullivan DR, Eden KB, Dieckmann NF, Golden SE, Vranas KC, Nugent SM, et al. Understanding patients' values and preferences regarding early stage lung cancer treatment decision making. Lung cancer (Amsterdam, Netherlands) 2019;131:47-57.
(24) Janssen EM, Dy SM, Meara AS, Kneuertz PJ, Presley CJ, Bridges JF. Analysis of Patient Preferences in Lung Cancer – Estimating Acceptable Tradeoffs Between Treatment Benefit and Side Effects. Patient preference and adherence 2020 Jan 1,;14:927-937.
(25) Mokhles S, Nuyttens, J. J. M. E, de Mol M, Aerts, J. G. J. V, Maat, A. P. W. M, Birim Ö, et al. Treatment selection of early stage non-small cell lung cancer: the role of the patient in clinical decision making. BMC cancer 2018;18(1):79.
(26) Abbett SK, Urman RD, Bader AM. Shared decision-making – Creating pathways and models of care. Best practice & research. Clinical anaesthesiology 2020 Jun;34(2):297-301.
(27) Weeks JC, Catalano PJ, Cronin A, Finkelman MD, Mack JW, Keating NL, et al. Patients' Expectations about Effects of Chemotherapy for Advanced Cancer. The New England journal of medicine 2012;367(17):1616-1625.
(28) Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. The New England journal of medicine 2017 Nov 16,;377(20):1919-1929.
(29) Dickhoff C, Dahele M, de Langen AJ, Paul MA, Smit EF, Senan S, et al. Population-Based Patterns of Surgical Care for Stage IIIA NSCLC in the Netherlands between 2010 and 2013. Journal of Thoracic Oncology 2016 Apr;11(4):566-572.
(30) Thomas D, Thomas D, Arnold B, Arnold B, Rosen J, Rosen J, et al. The Significance of Upfront Knowledge of N2 Disease in Non-small Cell Lung Cancer. World J Surg 2018 Jan;42(1):161-171.
(31) Eberhardt WEE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H, et al. 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2015 Aug;26(8):1573-1588.
(32) Hoeijmakers F, Heineman DJ, Beck N, Klamer J, Tollenaar RAEM, Wouters MWJM, et al. Mediastinoscopy for staging of Non-Small Cell Lung Cancer: surgical performance in the Netherlands. The Annals of Thoracic Surgery 2018 Dec 14,.

(33) A. M. Stiggelbout, J. C.J.M. de Haes. Patient Preference for Cancer Therapy: An Overview of Measurement Approaches. Journal of Clinical Oncology 2001 Jan 1,;19(1):220-230.



Chapter 6

Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis

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ABSTRACT

Introduction Confirmatory mediastinoscopy after negative endosonography findings is advised by the guidelines on patients with resectable NSCLC and suspected intrathoracic nodes fluorodeoxyglucose F 18 positron emission tomography-computed tomography. Its role however is under debate owing to its limited nodal metastasis detection rate, morbidity, associated treatment delay and unknown impact on survival.

Methods Systematic review and meta-analysis of studies on invasive mediastinal staging in patients with (suspected) NSCLC. MEDLINE, EMBASE and Cochrane databases were searched without year or language restrictions till September 19, 2018. QUADAS-2 was used to evaluate the risk of bias and applicability of included studies. Unforeseen N2 disease rates were assessed for EBUS and/or EUS staging strategies with or without confirmatory mediastinoscopy. Additionally, complication rates of cervical video-mediastinoscopy for mediastinal staging of NSCLC were investigated.

Results A total of 5073 articles were found, of which 42 studies or subgroups (covering 3248 patients undergoing the surgical reference standard of treatment) were considered in the analysis. Random effects meta-analysis of endosonography with or without confirmatory mediastinoscopy showed unforeseen N2 rates of 9.6% (95% confidence interval [CI]: 7.8%-11.7%; I^2=30%) versus 9.9% (95% CI: 6.3%-15.2%; I^2=73%) respectively. Random effects meta-analysis of mediastinoscopy (eight studies; 1245 patients in total) showed a complication rate of 6.0% (95% CI: 4.8%-7.5%), with laryngeal nerve palsy accounting for 2.8% (95% CI: 2.0%-4.0%).

Conclusion The rate of unforeseen N2 disease after negative endosonography findings was similar in patients undergoing immediate lung tumor resection to those undergoing confirmatory mediastinoscopy first, at the cost of 6.0% rate of complications by mediastinoscopy.

LIST OF DEFINITIONS

Centrally located lung tumor A lung tumor located within the inner third of the chest. (1)

EBUS-TBNA An acronym for endobronchial ultrasound guided transbronchial needle aspiration. Investigation of mediastinal and hilar lymph nodes with a linear ultrasound probe from the airways with the possibility of nodal sampling under real-time ultrasound control.

EUS-FNA An acronym for endoscopic ultrasound guided fine needle aspiration. Investigation of mediastinal lymph nodes with a linear ultrasound probe from the esophagus with the possibility of nodal sampling under real-time ultrasound control.

EUS-B-FNA An acronym for endoscopic ultrasound guided fine needle aspiration using the EBUS scope.

Mediastinoscopy Surgical procedure to examine mediastinal lymph nodes with the possibility to take surgical biopsies.

Mediastinal nodal dissection Surgical reference standard of mediastinal lymph node staging. A lobe-specific mediastinal, hilar and interlobar lymph node dissection is recommended together with an anatomical lung parenchyma resection of the primary tumor.

Unforeseen N2 Pathologically proven N2 disease at final lung tumor resection and lymph node dissection when previous mediastinal staging showed N0 or N1 disease.

INTRODUCTION

Accurate mediastinal lymph node staging of non-small cell lung cancer (NSCLC) is crucial in guiding treatment choice and determining prognosis. In case Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and Computed Tomography (CT) do not show any signs of distant metastases (M1 disease), mediastinal nodal status determines treatment options. The current European guideline recommends invasive mediastinal lymph node staging in patients with clinical N1-3 (cN), a centrally located primary tumor, a FDG-non-avid primary tumor or a peripheral tumor >3 centimeter.(1,2) Invasive mediastinal staging is indicated in approximately 30% of patients with (suspected) NSCLC. In the presence of mediastinal nodal (N2/N3 disease) metastases, chemo-radiation therapy is advised.(3,4) In the absence (N0) of or just hilar mediastinal node involvement (N1) surgical resection of the lung tumor is the most appropriate treatment. False negative results of mediastinal staging results in unforeseen N2 disease, which is defined as proven N2 disease at lung tumor resection and lymph node dissection when previous mediastinal staging showed N0 or N1 disease. Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) and endoscopic ultrasound (EUS)-guided fine-needle aspiration (FNA) are recommended over surgical staging (cervical mediastinoscopy) as initial tissue staging procedure.(5) A mediastinal nodal evaluation using a procedure combining EBUS and EUS results in the optimal nodal assessment.(6) In patients with an indication for mediastinal staging and no signs of mediastinal nodal involvement at endosonography, cervical mediastinoscopy is advised to rule out false negative endosonography staging results.(1) Its role however, is under debate, due to its limited nodal metastases detection rate, its morbidity, associated treatment delay and questionable impact on survival. This debate results in wide practice variation and deviance of guideline advises in clinical practice.

The aim of this systematic review and meta-analysis was to assess the rate of unforeseen N2 in lung cancer patients with or without mediastinoscopy following negative endosonography. Additionally, complication rate of cervical mediastinoscopy for mediastinal staging of NSCLC was assessed.

MATERIAL AND METHODS

Eligible studies

Eligible studies included clinical (non)randomized trials or observational studies assessing the performance of EBUS and/or EUS, as well as the performance of mediastinoscopy in case of negative EBUS and/or EUS, for the detection of mediastinal lymph node

metastases (i.e. N2/N3 disease) in patients with potentially resectable NSCLC with an indication for preoperative invasive mediastinal staging. Included patients underwent EBUS and/or EUS; after negative findings, patients subsequently underwent mediastinoscopy and/or pulmonary resection with lymph node dissection or sampling. Studies evaluating morbidity and mortality of video-mediastinoscopy as staging procedure for NSCLC were eligible for inclusion as well.

Search strategy and selection criteria

Studies were identified through electronic searches of MEDLINE, EMBASE and Cochrane databases without calendar year or language restrictions. In addition, reference lists of included studies were scanned for additional relevant papers (citation tracking). The search strategies consisted of a combination of index terms and free text words related to non-small cell lung cancer, mediastinoscopy and endosonography. The last search was provided on September 19, 2018. The full search strategy and database information are provided in Appendix A.

Two authors (JB and MvD) independently screened the titles and abstracts of all studies identified by the abovementioned search strategy and obtained full articles for all potentially relevant studies. Titles and abstracts that definitely reported on T4 tumors, distant metastases, small cell lung cancer, chemotherapy, radiotherapy, case-reports or series of <20 patients were excluded.

The same two authors (JB and MvD) independently read the full text of studies selected after title and abstract screening. The following studies were excluded: studies evaluating EBUS, EUS and mediastinoscopy for other diagnoses (e.g. solitary mediastinal masses) or in heterogeneous populations (e.g. diagnosing lung cancer, mediastinal metastases of other origin, tuberculosis, sarcoidosis, lymphomas, or restaging after induction therapy) in which transparent reporting on NSCLC staging was lacking; studies using other operative techniques for staging (such as video-assisted mediastinoscopic lymphadenectomy (VAMLA), transcervical extended mediastinal lymphadenectomy (TEMLA), and conventional transbronchial needle aspiration); studies reporting on conventional (nonvideo) mediastinoscopy or studies that reported insufficiently on complications of video mediastinoscopy; and conference abstracts repeating results of included studies, editorial reviews, guidelines and data-sets. Finally, studies with insufficient methods (such as clear selection bias, no representative patient group or no surgical reference standard) and studies that reported non-transparent data precluding calculation of unforeseen N2 rates were excluded.

Studies reporting transparently on data of patients undergoing mediastinal staging by various staging strategies were included to process the data. Patients in included studies with negative EBUS and/or EUS results without any surgical reference standard were excluded for analysis. Patients from studies on staging with endosonography and mediastinoscopy who did not undergo mediastinoscopy after negative endosonography were divided in subgroups and analysed for unforeseen N2 after endosonography only. Studies reporting on multiple staging strategies (i.e. EBUS and/or EUS with or without mediastinoscopy) were also divided in subgroups for analysis. According to our exclusion criterium of studies below 20 patients we decided to exclude study subgroups below 10 patients. Any disagreement between the two assessors in abstract, title and full text phase were resolved by consulting the senior author (FvdB).

Data extraction

A data collection form was developed to extract relevant information from each included study. Two authors (JB, MvD) extracted the data separately and resolved differences by discussion with the senior author (FvdB) until consensus was achieved. Data were extracted concerning study design, focus of study (EBUS, EUS and/or mediastinoscopy), patient characteristics (age and sex) and inclusion criteria, radiological staging (FDG-PET/CT), allocation method and sources of bias. The number of patients with positive and negative histology (for N2/N3 disease) at EBUS, EUS and mediastinoscopy were extracted. With respect to these index test results, the ideal reference standard is histopathological evaluation of a complete surgical mediastinal lymph node dissection in each patient (irrespective of positive or negative findings at EBUS, EUS and mediastinoscopy). It is anticipated however, that tumor positive findings at EBUS, EUS and mediastinoscopy generally will not be proven by the reference standard as this is extremely rare. The used reference standard was noted, which can be systematic surgical mediastinal lymph node dissection or sampling. Finally, the distribution of unforeseen N2 disease among different lymph node stations was extracted. Studies reporting on the morbidity and mortality of cervical video-mediastinoscopy were assessed to extract the mean number of assessed lymph node stations, the mean number of sampled lymph nodes and details on how often individual lymph node stations were sampled. To assess morbidity and mortality the number of patients with postoperative complications, recurrent laryngeal nerve palsy, re-interventions (endoscopic, surgical or radiological) or related mortality were collected.

Assessment of methodological quality

The Quality Assessment Tool for Diagnostic Accuracy Studies – version 2 (QUADAS-2) was used to assess the risk of bias and applicability concerns of included studies. For adequate assessment of methodological quality of included studies we consulted an

epidemiologist (D.A. Korevaar) who advised on the methodological part of this project. To optimize the methodological assessment of included studies we tailored the QUADAS-2. We divided the index test domain in two parts to assess the methodological quality of both endosonography and mediastinoscopy as index test. Also the reference test domain was tailored for risk of bias and assessment of applicability concerns for this study. Studies which excluded over 10% of patients with negative index test results for reference standard were deemed to have high risk of bias on the flow domain. Two authors (JB and MvD) independently applied the tailored QUADAS-2 to the included studies, and resolved disagreement by discussion with the senior author (FvdB). Based on the tailored QUADAS-2 studies with a retrospective design or high/unclear risk of bias on patient selection, index test, reference standard or flow domain were judged to have high risk of bias. The complete tailored QUADAS-2 description and results are included in Appendix B.

Data analysis

Descriptive statistics were analysed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Version 22.0, Armonk, NY). Continuous data were reported as medians and interquartile range (IQR) and/or total range (non-parametric data) or as means and standard deviation (SD) and/or total range (parametric data). Categorical data were reported as numbers with percentages. After construction of 2x2 tables the proportion of unforeseen N2 disease (i.e. 1 minus negative predictive value) following the different staging strategies (EBUS and/or EUS with or without mediastinoscopy) were calculated. We calculated standard errors and 95%-confidence intervals (95%-CI) around the unforeseen N2 proportions using The Wilson interval for individual studies.(7) We then logit transformed the unforeseen N2 proportions and performed univariate random effects meta-analysis according to the DerSimonian and Laird method using the meta package in R (version 3.5.1).(8) This analysis provided summary estimates of the unforeseen N2 rate after either EBUS or EUS only, EBUS and EUS combined or after EBUS and/or EUS with additional mediastinoscopy. Since the guidelines advise either EBUS only or EBUS combined with EUS as endosonographic procedure, summary estimates of combinations of strategy including EBUS or EBUS and EUS are also provided. From the random-effects meta-analysis, we report the summary estimates as proportions with their 95%-CIs. We additionally calculated I^2 statistics with 95%-CIs, presenting the percentage of variability that is attributable to between-study heterogeneity. We used $I^2 \geq 50\%$ as cut-off indicating significant heterogeneity between studies.(9)

Methodological as well as clinical characteristics could be possible sources of heterogeneity and may have impact on the proportion unforeseen N2 disease. Therefore, we additionally calculated unforeseen N2 rates for studies with low or high risk of bias. We

also calculated unforeseen N2 rates for subgroups based on use of preoperative FDG-PET (below or above median), radiological suspicion on clinical N2/N3 disease (cN2/3) and on the prevalence of pathologically proven N2/N3 (pN2/3). We used the same method for univariate random effects meta-analysis on complications of cervical video-mediastinoscopy. Meta-analysis was done on the number of complications, mortality, recurrent laryngeal nerve palsy and morbidity classified as Clavien-Dindo grade III-IV (necessitating additional surgical, endoscopic or radiological intervention or needing intensive care unit admission).(10) Finally, we used the Pearson correlation coefficient to assess the correlation between the occurrence of complications and the mean number of sampled lymph node stations and lymph nodes, and the correlation between laryngeal recurrent nerve palsy and left paratracheal lymph node stations sampling.

RESULTS

Description of studies

4,770 unique studies were identified of which 32 were included in the unforeseen N2 meta-analysis (Figure 1).(5,11-41) The included studies contained 6,513 patients, with an age range of 56 to 70 years (median 65 years) and a proportion of males of 72% (range 46-89). All patients in the included studies had suspected or proven NSCLC, and were possible surgical candidates. The studies were performed in Europe (n=18), Asia (n=9), North America (n=4) and Southern-America (n=1). After excluding patients with negative EBUS and/or EUS without undergoing the surgical reference standard 6,049 patients remained for meta-analysis. A total of 2,801 (46%) patients had tumor positive mediastinal nodal results at endosonography or mediastinoscopy. The remaining 3,248 patients (54%) underwent additional surgical reference standard and were included in the final unforeseen N2 meta-analysis. Details on studies and exclusion of patients are provided in Appendix C in the Supplementary data. Six of 32 unique studies reported transparently on subgroups of patients undergoing mediastinal staging by different staging strategies (i.e. EBUS and/or EUS with or without mediastinoscopy) within one study.(13,24,29,31-33) To assess rates of unforeseen N2 disease for the various different staging strategies these studies were subdivided in subgroups according to the used strategy. Details on the subdivided studies are provided in Appendix D in the Supplementary data. A total of eight studies were included in the mediastinoscopy complications meta-analysis (Figure 1).(5,42-48)

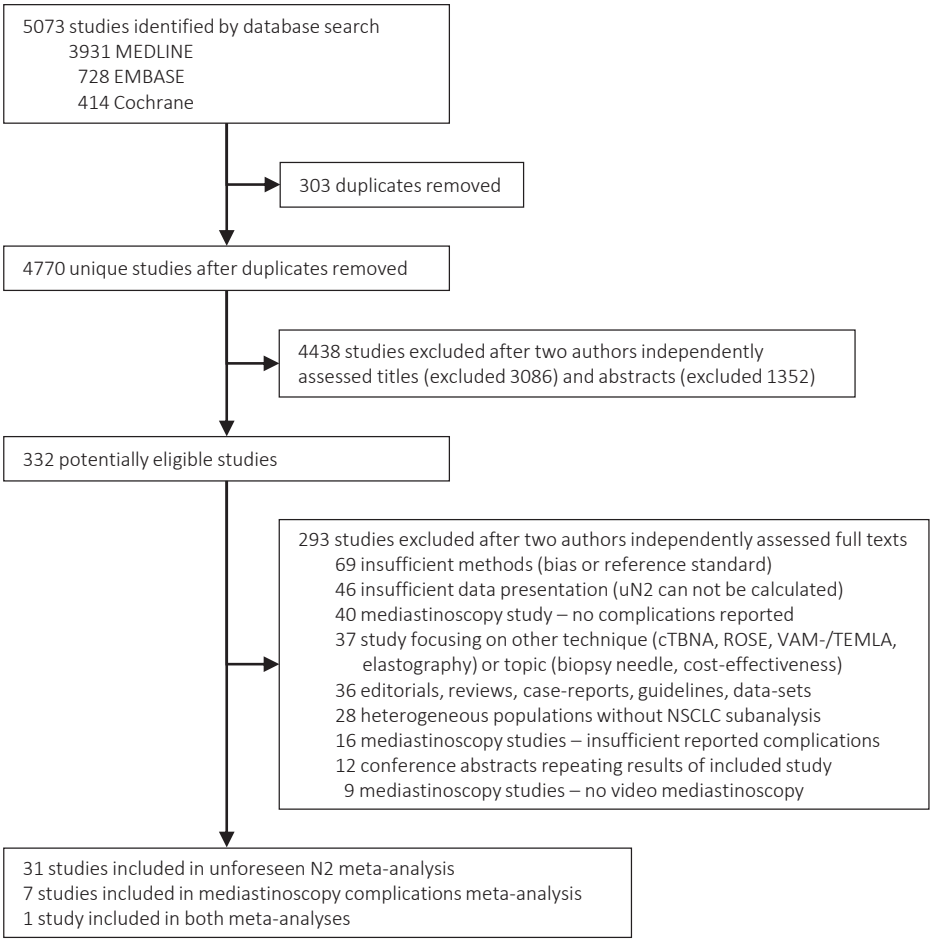

Figure 1. Flow diagram of study selection
uN2= unforeseen N2; cTBNA= conventional transbronchial needle aspiration; ROSE=rapid on side evaluation; VAMLA=: video-assisted mediastinoscopic lymphadenectomy; TEMLA=transcervical extended mediastinal lymphadenectomy; NSCLC= non-small cell lung cancer.

Unforeseen N2 after EBUS and/or EUS as only staging technique

A total of 31 studies or subgroups with use of endosonography only (without additional surgical staging) were included (Table 1). Of these studies, 12 evaluated EBUS(11-22), seven evaluated EUS(13,23-28) and 12 evaluated combined EBUS and EUS as staging method.(13,29-37) One study was a randomized controlled trial (RCT) comparing staging by EBUS followed by EUS versus EUS followed by EBUS and one study was an observational study comparing EBUS plus EUS versus EBUS plus EUS using the EBUS-scope. These studies were divided into four subgroups for meta-analysis.(31,33) The remaining were observational studies (15 prospective, 12 retrospective). The surgical reference standard was mediastinal lymph node dissection in twenty-one studies, mediastinal

lymph node sampling in two studies and in six studies the operation was not specified. In two studies the surgical reference standard was TEMLA with anatomical resection in case of negative TEMLA results.(20,36)

The proportion unforeseen N2 disease after negative EBUS findings (847 patients) was 9.3% (95% CI: 6.9%-12.6%; I^2=39%), after negative EUS findings (384 patients) 13.4% (95% CI: 10.3%-17.2%; I^2=0%) and after negative findings of EBUS plus EUS (671 patients) it was 9.7% (95% CI: 7.2%-12.9%; I^2=26%) (Figure 2). The current guidelines recommend EBUS, preferably combined with EUS as initial staging method. If only EBUS or EBUS plus EUS studies were included (1,518 patients) the rate of unforeseen N2 was 9.6% (95% CI: 7.8%-11.7%; I^2=30%). Of 187 patients with unforeseen N2 disease after only endosonography, the affected lymph node station was mentioned in 97 cases. The metastases were located in the lower paratracheal station in 32% of patients (20% right, 7% left and 5% unknown), in the subcarinaal station in 30% and in the aortopulmonary stations in 22%.

Unforeseen N2 after EBUS and/or EUS with subsequent mediastinoscopy

Of the included studies or subgroups, 11 described the accuracy of mediastinoscopy following negative or inconclusive endosonography findings. Four evaluated EBUS plus mediastinoscopy(13,38-40), three evaluated EUS plus mediastinoscopy(13,24,41) and four evaluated EBUS plus EUS, followed by mediastinoscopy.(5,13,29,32) Two studies were RCTs, only one of them reporting adequate concealment of allocation and no blinding was used in both trials. Both RCTs compared endosonography plus mediastinoscopy with surgical staging only, therefore only the endosonography randomisation groups of both studies were included for analysis.(5,41) The remaining were observational studies (7 retrospective and 2 prospective). Five subgroups included patients with negative endosonography without mentioning detailed information on the indication for mediastinal staging.(13,32,40) The surgical reference standard was mediastinal lymph node dissection in 10 studies and mediastinal lymph node sampling in one study (Table 2).

	Index test		Included patients					Reference standard			
Study (subgroup)	Test	Bias	n total	Selection bias	% FDG-PET	Clinical N2/3 prevalence	Pathologic N2/3 prevalence	Type	n ref	Bias	uN2
Zhang, et al., 2018[11]	EBUS	☺	55	☺	100%	100%	41%	MLND	55	☺	10.9%
Coutinho, et al., 2017[12]	EBUS	☺	52	☺	75%	21%	60%	MLND	22	☺	4.6%
Talebian, et al., (1) 2015[13]	EBUS	☺	73	☺	78%	39%	15%	MLND	73	☺	15.1%
Figueiredo, et al., 2015[14]	EBUS	☺	107	?	N/S	67%	79%	N/S	27	?	14.8%
Clementsen, et al., 2014[15]	EBUS	☺	80	☺	36%	27%	21%	N/S	67	?	6.0%
Sakairi, et al., 2013[16]	EBUS	?	459	☺	N/S	72%	58%	N/S	215	?	9.3%
Lee, et al., 2012[17]	EBUS	☺	69	☺	84%	58%	62%	MLND	27	☺	3.7%
Sanz-Santos, et al., 2012[18]	EBUS	☺	222	☺	0%	62%	70%	MLND	72	?	6.9%
Hwangbo, et al., 2009[19]	EBUS	☺	117	☺	100%	48%	26%	N/S	90	☺	3.3%
Szlubowski, et al., 2009[20]	EBUS	☺	226	☺	N/S	N/S	73%	TEMLA/ MLND	97	☺	16.5%
Lee, et al., 2008[21]	EBUS	☺	95	☺	N/S	100%	34%	MLND	65	☺	3.1%
Yasufuku, et al., 2005[22]	EBUS	☺	101	☺	0%	100%	67%	MLND	37	☺	10.8%
Talebian, et al., (3) 2015[13]	EUS	☺	182	☺	64%	34%	15%	MLND	182	☺	14.8%
Srinivasan, et al., 2012[23]	EUS	?	64	☹	N/S	74%	58%	N/S	26	?	11.5%
Talebian, et al., (1) 2010[24]	EUS	☺	31	☺	N/S	68%	19%	MLND	31	☺	19.4%
Craanen, et al., 2007[25]	EUS	☹	16	☹	100%	50%	44%	MLND	10	☺	10.0%
Fernandez, et al., 2006[26]	EUS	☺	47	☺	0%	0%	21%	MLND	42	☺	11.9%
Fritscher, et al., 2003[27]	EUS	☺	30	☺	100%	45%	53%	MLNS	15	?	6.7%
Laudanski, et al., 2001[28]	EUS	?	92	☺	0%	58%	23%	MLND	78	☺	9.0%
Talebian, et al., (5) 2015[13]	EBUS+EUS	☺	38	☺	48%	97%	5%	MLND	38	☺	5.3%
Dooms, et al., (1) 2015[29]	EBUS+EUS	☺	10	☺	100%	100%	10%	MLND	10	☺	10.0%
Oki, et al., 2014[30]	EBUS+EUS	☺	131	☺	N/S	N/S	24%	MLND	107	?	6.5%
Kang, et al., (1) 2014[1]	EBUS+EUS	☺	80	☺	54%	100%	43%	MLND	45	☺	11.1%
Kang, et al., (2) 2014[31]	EUS+EBUS	☺	80	☺	54%	100%	31%	MLND	51	☺	3.9%
Verhagen, et al., (1) 2013[32]	EBUS+EUS	☺	23	☺	39%	100%	17%	MLND	23	☺	17.4%
Szlubowski, et al., (1) 2012[33]	EBUS+EUS	☺	107	☺	N/S	N/S	53%	MLND	55	☺	9.1%
Szlubowski, et al., (2) 2012[33]	EBUS+EUS-B	☺	97	☺	N/S	N/S	55%	MLND	53	☺	17.0%
Ohnishi, et al., 2011[34]	EBUS+EUS	☺	105	☺	32%	100%	36%	N/S	79	?	15.2%
Hwangbo, et al., 2010[35]	EBUS+EUS	☺	143	☺	N/S	N/S	31%	MLND	102	☺	3.9%
Szlubowski, et al., 2010[36]	EBUS + EUS	☺	118	☺	N/S	N/S	24%	TEMLA/ MLND	101	☺	8.9%
Vilmann, et al., 2005[37]	EBUS+EUS	☹	27	☹	42%	6%	74%	MLNS	7	☺	0.0%

Figure 2. Characteristics of studies on mediastinal lymph node staging with endosonography.
Index test bias refers to risk of bias in endosonography results based on the tailored QUADAS-2. Patient selection bias refers to the risk of selection bias based on the tailored QUADAS-2. Reference standard bias refers to the risk of bias in the reference standard results based on the tailored QUADAS-2. Happy face indicates low risk, and sad face indicates high risk. Question mark indicates unclear risk. % FDG-PET refers to the proportion of patients who underwent fludeoxyglucose F 18 positron emission tomography; N2/3 refers to the proportion of patients in the study population with N2 or N3 metastases. Abbreviations: MLND, mediastinal lymph node dissection; MLNS, mediastinal lymph node sampling; TEMLA, transcervical extended mediastinal lymphadenectomy; uN2, unforeseen N2 disease; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; EUS-B, endoscopic ultrasound using the endobronchial ultrasound scope.

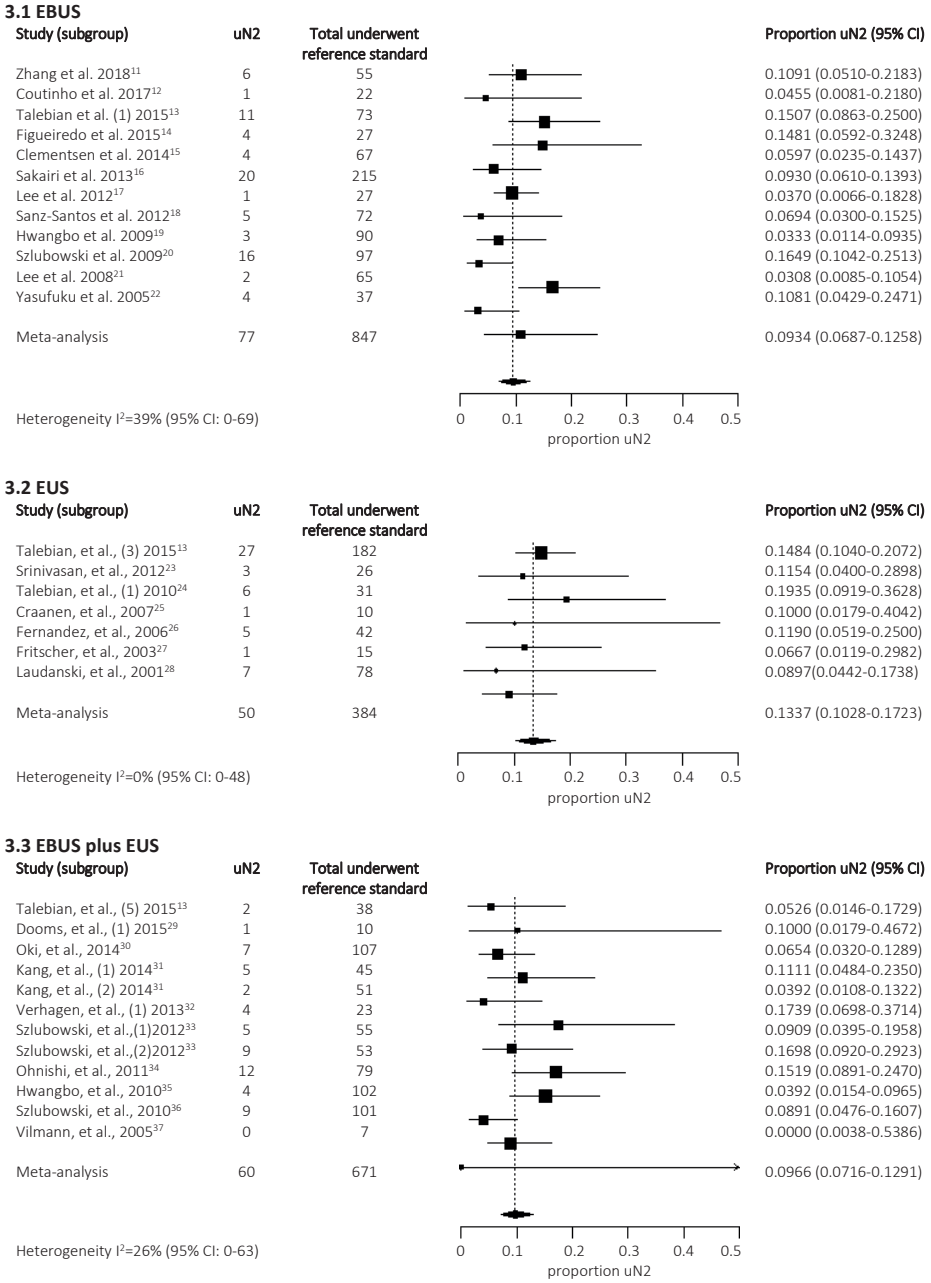

Figure 3. Meta-analysis of proportion unforeseen N2 disease after endosonography. (3.1.) After negative EBUS. (3.2) After negative EUS. (3.3) After negative EBUS plus EUS. Proportion uN2=proportion unforeseen N2 disease; SE=standard error; 95%-CI=95% confidence interval; EBUS=endobronchial ultrasonography; EUS=endoscopic ultrasonography.

	Index texts				Included patients					Mediastinoscopy		Reference standard			
Study (subgroup)	Test 1	Bias	Test 2	Bias	n total	Selection bias	% FDG-PET	clinical N2/3 prevalence	pathologic N2/3 prevalence	n MED	% N2/N3 MED	Type	n ref	Bias	% uN2
Warren&Hagaman 2016[38]	EBUS	☹	MED	☺	236	☹	100%	70%	85%	44	9%	MLND	40	?	10.0%
Dziedzic, et al., 2015[39]	EBUS	?	MED	☺	1841	☺	36%	100%	66%	730	11%	MLND	647	☺	4.6%
Talebian, et al., (2) 2015[13]	EBUS	☺	MED	☺	106	☺	78%	39%	39%	109	24%	MLND	80	☺	18.8%
Defranchi, et al., 2010[40]	EBUS	?	MED	☺	29	☺	90%	56%	41%	29	28%	MLND	21	☺	19.1%
Talebian, et al., (4) 2015[13]	EUS	☺	MED	☺	276	☺	64%	34%	31%	289	18%	MLND	225	☺	15.1%
Talebian, et al., (2) 2010[24]	EUS	☺	MED	☺	109	☺	N/S	68%	57%	40	15%	MLND	34	☺	14.7%
Tournoy, et al., 2008[41]	EUS	?	MED	☺	19	☺	95%	100%	74%	6	17%	MLNS	5	☺	0.0%
Talebian, et al., 2015[13]	EBUS+EUS	☺	MED	☺	78	☺	97%	48%	21%	84	11%	MLND	69	☺	10.1%
Dooms, et al., (2) 2015[29]	EBUS+EUS (lobe specific)	?	MED	☺	84	☺	100%	100%	27%	75	9%	MLND	67	☺	9.0%
Verhagen, et al., 2013[32]	EBUS+EUS	☺	MED	☺	114	☺	100%	39%	21%	124	11%	MLND	100	☺	10.0%
Annema, et al., 2010[5]	EBUS+EUS	☺	MED	☺	120	☺	100%	76%	54%	65	9%	MLND	58	☺	6.9%

Figure 4. Characteristics of studies on mediastinal lymph node staging with endosonography plus mediastinoscopy. Index test bias refers to risk of bias in endosonography results based on the tailored QUADAS-2. Patient selection bias refers to the risk of selection bias based on the tailored QUADAS-2. Reference standard bias refers to the risk of bias in the reference standard results based on the tailored QUADAS-2. Happy face indicates low risk, and sad face indicates high risk. Question mark indicates unclear risk. % FDG-PET refers to the proportion of patients who underwent fludeoxyglucose F 18 positron emission tomography; N2/3 refers to the proportion of patients in the study population with N2 or N3 metastases. N2/N3 MED refers to the number of patients with N2 or N3 disease, as proved by mediastinoscopy (MED). Abbreviations: MLND, mediastinal lymph node dissection; MLNS, mediastinal lymph node sampling; uN2, unforeseen N2 disease; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound.

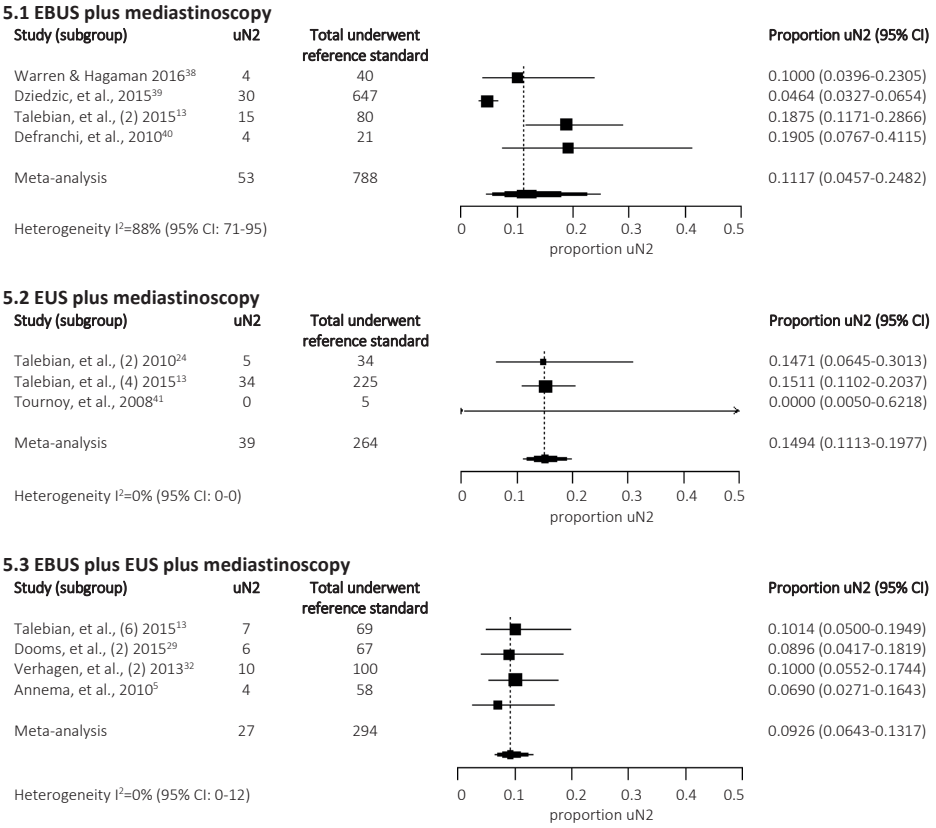

Figure 5. Meta-analysis of proportion unforeseen N2 disease after endosonography plus mediastinoscopy (5.1.) After negative EBUS plus mediastinoscopy. (5.2) After negative EUS plus mediastinoscopy. (5.3) After negative EBUS plus EUS plus mediastinoscopy. uN2=proportion unforeseen N2 disease; SE=standard error; 95%-CI=95% confidence interval; EBUS=endobronchial ultrasonography; EUS=endoscopic ultrasonography.

The proportion of unforeseen N2 after negative findings of EBUS plus mediastinoscopy (788 patients) was 11.2% (95% CI: 4.6%-24.8%; I^2=88%), after negative findings of EUS plus mediastinoscopy (264 patients) it was 14.9% (95% CI: 11.1%-19.8%; I^2=0%) and after negative findings of EBUS plus EUS plus mediastinoscopy (294 patients) it was 9.3% (95% CI: 6.4%-13.2%; I^2=0%) (Figure 3). A meta-analysis of the combined strategy that is recommended by the guideline (i.e. EBUS or EBUS plus EUS with subsequent mediastinoscopy) (1082 patients) showed an unforeseen N2 rate of 9.9% (95% CI: 6.3%-15.2%; I^2=73%). The affected lymph node stations were mentioned in 63 of 119 patients with unforeseen N2 disease after endosonography plus mediastinoscopy. The metastases were located in the subcarinaal station in 35% of patients, the lower paratracheal station in 21% (right) and 5% (left) and in the aortopulmonary station in 28%.

Subgroup analysis based on risk of bias

Nine subgroups (29%) undergoing endosonography only(19-21,26,29,33,35,36) and two subgroups (18%) undergoing endosonography plus mediastinoscopy(5,29) were deemed to have low risk of bias based on QUADAS-2 (Table 1). Random effects meta-analysis of studies with low risk of bias showed rates of unforeseen N2 of 8.9% (95% CI: 5.7%-13.4%; I^2=56%) in the endosonography only group (9 studies; 615 patients) and 8.1% (95% CI: 4.4%-14.3%; I^2=0%) in the endosonography plus mediastinoscopy groups (2 studies; 125 patients). In studies with a high risk of bias, the respective rates of unforeseen N2 disease were 11.1% (95% CI 9.4%-13.0%; I^2=0%) (22 studies; 1,287 patients) and 11.5% (95% CI: 7.4%-17.3%; I^2=77%) (9 studies; 1,221 patients).

Subgroup analysis based on clinical characteristics

The median percentage of patients who underwent preoperative FDG-PET was 96% (IQR 57-100) (Table 1). Information on preoperative FDG-PET was not provided in eleven endosonography only studies(14,16,20,21,23,24,30,33,35,36) and in one endosonography plus mediastinoscopy study(24); hence, we excluded these studies from this analysis. The rates of unforeseen N2 disease of studies in which more than 96% of patients underwent preoperative FDG-PET were 9.8% (95% CI 6.8%-13.8%; I^2=16%) for endosonography only (10 studies; 416 patients) versus 9.4% (95% CI: 6.7%-13.0%; I^2=0%) for endosonography plus mediastinoscopy (5 studies; 334 patients). In studies with preoperative FDG-PET use below 96% the unforeseen N2 rates were 11.3% (95% CI: 8.9%-14.3%; I^2=4%) for endosonography only (10 studies; 607 patients) versus 12.0% (95% CI: 5.8%-23.5%; I^2=88%) for endosonography plus mediastinoscopy (5 studies; 978 patients).

The median cN2/3 prevalence in all studies was 55% (IQR 39-74) (Table 1). Information on radiological mediastinal lymph node staging was not provided in six endosonography only studies(20,30,33,35,36); again, we excluded these studies from this sub analysis. Random effects meta-analysis of studies with cN2/3 prevalence below 55% showed unforeseen N2 rates of 10.8% (95% CI: 8.2%-14.1%; I^2=24%) for endosonography only (14 studies; 744 patients) versus 14.0% (95% CI: 10.7%-18.2%; I^2=22%) for endosonography plus mediastinoscopy (4 studies; 474 patients). In studies with a cN2/3 prevalence above the median, the unforeseen N2 rates were 9.8% (95% CI: 7.7%-12.5%; I^2=0%) for endosonography only (11 studies; 643 patients) versus 8.9% (95% CI: 5.5%-14.1%; I^2=55%) for endosonography plus mediastinoscopy (7 studies; 872 patients).

The median pN2/N3 prevalence in studies included in the unforeseen N2 meta-analysis was 40% (IQR 22-58) (Table 1). Random effects meta-analysis of studies with a pN2/3 prevalence below the median shows unforeseen N2 rates of 9.4% (95% CI: 7.0%-12.3%;

I^2=71%) for endosonography only (16 studies; 1,139 patients) versus 13.3% (95% CI: 10.2%-17.2%; I^2=23%) for endosonography plus mediastinoscopy (5 studies; 541 patients). When the pN2/3 prevalence is above the median the unforeseen N2 rates were 11.2% (95% CI: 9.1%-13.8%; I^2=0%) for endosonography only (15 studies; 763 patients) and 9.1% (95% CI: 5.1%-15.7%; I^2=61%) for endosonography plus mediastinoscopy (6 studies; 805 patients).

Cervical video-mediastinoscopy complications

A total of 72 studies included mediastinoscopy in their mediastinal lymph node staging procedures, but only 23 reported on morbidity and mortality related to cervical video-mediastinoscopy for mediastinal lymph node staging. However, 15 studies did not describe methods of retrieval of complications or did not define complications (e.g. deemed insufficient) and hence were excluded from analysis. Six studies also included patients who underwent VAMLA, TEMLA or conventional mediastinoscopy, so these patients were excluded from meta-analysis.(42,43,45-48) The remaining eight studies included 1,245 patients who underwent video-mediastinoscopy for mediastinal staging of NSCLC.(5,42-48) The median overall age was 63 years (range 55-68) and the median proportion of male patients of 82% (range 61-100). The eight studies were two randomized trials, one prospective and five retrospective observational studies with adequate definitions, retrieval and reporting of complications. All studies at least assessed the left and right paratracheal and the subcarinal lymph node stations as recommended by the guideline.(2) The mean number of assessed lymph node stations ranged from 2.8 to 4.3 with a mean number of biopsied lymph nodes ranging from 7.0 to 12.0 (Table 3). Four studies described more detailed information on the location of sampled lymph nodes. (42,43,45,46) The left upper paratracheal station was the least sampled location with only samples in 16% to 57% of the reported cases. We found no significant correlation between mean number of assessed lymph node stations or sampled lymph nodes and the occurrence of complications. Also no correlation between laryngeal nerve palsy and sampling of the left paratracheal stations was found. Meta-analysis showed an overall complication rate of 6.0% (95% CI: 4.8%-7.5%) with a procedure related mortality of 0.5% (95% CI: 0.2%-1.2%). Morbidity classified as Clavien-Dindo grade III or IV occurred in 1.9% (95% CI: 1.1%-3.2%) of patients and laryngeal recurrent nerve palsy was reported in 2.8% (95% CI: 2.0%-4.0%) (Table 3).

Table 1. Random effects meta-analysis of complications of cervical video-mediastinoscopy

Study	Lymph node stations aimed to assess	Mean number of stations biopsied	Mean number of lymph nodes biopsied	n	Complications			Mortality
					Overall	Laryngeal recurrent nerve palsy	Clavien Dindo grade III-IV	
Decaluwe 2017 [42]	4R-7-4L	3.9 (SD 1.2)	N/S	82	4.9%	2.4%	1.2%	0.0%
Sayar 2016 [43]	2R-4R-7-4L-2L	4.3 (SD 0.8)	7.9 (SD 2.0)	261	7.7%	1.2%	0.8%	0.0%
Steunenberg 2015 [44]	2R-4R-7-4L-2L	2.8 (SD 1.1)	12.0 (SD 7.0)	102	6.9%	2.9%	3.9%	1.0%
Citak 2014 [45]	2R-4R-7-4L-2L	4.2 (SD 0.8)	7.7 (SD 1.7)	260	5.4%	4.2%	1.2%	0.0%
Annema 2010 [5]	2R-4R-7-4L-2L	4.0 (range 0-5)	N/S	182	6.6%	3.3%	3.3%	0.0%
Anraku 2010 [46]	2R-4R-7-4L-2L	3.6 (SD 1.1)	7.0 (SD 3.2)	104	3.9%	1.0%	1.9%	0.0%
Leschber 2007 [47], *	2R-4R-7-4L-2L	N/S	7.6 (range 3-25)	234	4.3%	2.1%	1.3%	0.0%
Kuzdzal 2007 [48]	2R-4R-7-4L-2L	4.3 (SD N/S)	N/S	20	10.0%	0.0%	0.0%	0.0%
			Meta-analysis 95% CI Heterogeneity		**6.0% (4.8-7.5) I^2=0%**	**2.8% (2.0-4.0) I^2=0%**	**1.9% (1.1-3.2) I^2=21%**	**0.5% (0.2-1.2) I^2=0%**

VAM=Video-assisted mediastinoscopy; n= number of patients who underwent cervical video-mediastinoscopy; N/S=not specified;

*combined patient group of mediastinal staging for proven NSCLC (57%), mediastinal lymph node assessment in suspected NSCLC (30%) and a small amount of other benign or malignant indications (13%).

DISCUSSION

In this meta-analysis comprising 3,248 patients, the rate of unforeseen N2 disease in patients with resected NSCLC was similar in patients staged with endosonography alone versus those who underwent additional surgical staging with mediastinoscopy. Overall morbidity was reported in 6.0% of patients undergoing mediastinoscopy.

Despite the lack of studies that solely focus on the additional value of mediastinoscopy after negative endosonography, debate on omitting confirmatory mediastinoscopy after negative endosonography is very actual.(32,49-51) Important in the discussion whether or not confirmatory mediastinoscopy can be omitted following negative endosonography is the acceptable rate of unforeseen N2. Even in studies were all staging methods

are used (integrated FDG-PET/CT, EBUS, EUS and mediastinoscopy) rate of unforeseen N2 is around 7%.(5) The question at stake is the extent to which the survival of patients with lung tumors and single-level N2 disease treated surgically followed by adjuvant therapy differs from the survival of patient treated with definite or neoadjuvant chemoradiation. Several studies including a meta-analysis comparing surgery with definite chemoradiation for stage III-N2 NSCLC showed no difference in overall survival between the treatment strategies.(52,53) In the randomized ASTER trial the rate of unforeseen N2 disease after accurate staging with both endosonography and mediastinoscopy was 6.9% whereas this rate after surgical staging by mediastinoscopy only was 14.3%.(5) Despite of the difference in unforeseen N2 disease, five year survival was exactly the same in both groups (35% versus 35%).(54) The unforeseen N2 rates after endosonography without mediastinoscopy in our meta-analysis were 9.3% (EBUS) and 9.7% (combined EBUS and EUS) and therefore below the 14.3% that did not compromise survival in the ASTER trial. In addition, several studies showed comparable five year overall survival rates in patients with occult single level N2 disease treated with intended curative resection and adjuvant chemoradiotherapy compared with patients with N1 disease.(55,56) The extensiveness of N2 nodal metastasis however remains important since significant differences in overall survival were found between patients with single and multiple station N2 disease and between patients with microscopic (0.2 to 2 mm) and macroscopic N2 disease.(57,58) In the ASTER trial, mediastinoscopy diagnosed N2/N3 disease after negative endosonography in 9.2% of patients. These nodal spread however were micro metastases (<2 mm) or single level N2 disease in two third of patients, while the metastases in the last third of patients were located in the aortopulmonary lymph node stations. In this meta-analysis approximately 25% of unforeseen N2 disease was located in the aortopulmonary lymph node stations. The majority however in both groups (with or without mediastinoscopy) was located in the lower paratracheal and subcarinal lymph node stations. Therefore, when considering to omit confirmatory mediastinoscopy, accurate and systematic endosonographic staging is crucial. Korevaar et al. found a significant increase in sensitivity and detection rate for the combined use of EBUS and EUS compared with either test alone in a meta-analysis.(6) Recently Crombag et al. showed a 9% higher sensitivity on detection of mediastinal lymph node metastases by a systemic combined endosonographic approach (EBUS and EUS) compared to a targeted EBUS approach in a prospective staging trial.(59) Despite of the primary focus of these studies on diagnosing mediastinal lymph node metastases instead of excluding them, these results are in concordance with our results. EUS as only endosonographic staging technique demonstrated higher unforeseen N2 rates compared with endosonographic staging by EBUS or combined EBUS and EUS.

Besides the doubtful additional value of mediastinoscopy it is associated with significant complications such as laryngeal nerve palsy and requires general anaesthesia and hospital admission.(5,44) The number and type of complications is possibly influenced by which specific lymph node stations are assessed and by the extent of sampling. Although the mean number of assessed lymph node stations (range 2.8-4.3) seemed adequate and in line with the guideline, a precise description of assessed individual lymph node stations was lacking in half of the included studies. Therefore, we were not able to assign complications to specific lymph node stations. We found an overall complication rate of 6% for video-mediastinoscopy for mediastinal staging of NSCLC. Another meta-analysis, including both conventional and video-mediastinoscopy, found an even higher complication rate; 35 of 445 (7.9%) patients with a major complication including bleeding, esophageal perforation or tracheal injury.(60) The presumed benefit of detecting single level nodal N2 disease by mediastinoscopy in 9% of patients has to be weighed against the 6% of serious complications, health economic costs and the burden of undergoing diagnostic surgery and treatment delay for all.

When selecting patients for omitting mediastinoscopy it could be valuable to select specific subgroups based on tumor or FDG-PET/CT imaging characteristics that are known to be at risk for false negative endosonography outcomes. One may consider patients with cN1 disease as a possible high risk subgroup since the prevalence of occult N2 disease is known to be approximately 25% in this subgroup. Dooms et al. found a sensitivity for detecting N2 metastases of only 38% in cN1 NSCLC by endosonography only.(29) However, in this study just one out of fourteen patients with false negative endosonography results underwent both EBUS and EUS. In ten of these fourteen patients, the addition of EUS might have prevented these patients from false negative results since the missed metastases where within reach of EUS (lymph node station 4L, 5, 7 and 8). With addition of EUS to EBUS the sensitivity may theoretically have been increased to >70%.(61) Moreover, Decaluwé et al. provided a prospective multicenter study on cN1 NSCLC patients. Primary use of video-mediastinoscopy or VAMLA resulted in a sensitivity of 73% for detecting N2 metastases.(42) In our current meta-analysis we were not able to do subgroup analysis of cN1 patients due to insufficient data description in the included studies. We found increased unforeseen N2 rates in subgroups with low percentage of preoperative FDG-PET and in subgroups with low cN2/3 prevalence. However, we could not demonstrate differences in unforeseen N2 rates between staging strategies with or without mediastinoscopy in these subgroups. Therefore, surgical staging does not seem to reduce unforeseen N2 in these subgroups as well, whereas it still exposes patients to complications and treatment delay. Combined (EBUS and EUS) systematic (examining all nodes reachable by EBUS and EUS) endosonography appears to be key in considering to omit mediastinoscopy.

The main limitations of available studies for this systematic review and meta-analysis were insufficient methodology and lack of detailed data description. Due to significant heterogeneity between studies a direct comparison between different staging strategies with or without mediastinoscopy was not possible. However, despite the difference in unforeseen N2 rates between studies with high or low risk of bias, no difference was found between studies with or without mediastinoscopy in these categories. Strong points of the current study are the rigorous methodological approach and careful assessment of the included studies using the tailored QUADAS-2 which were guided by an experienced epidemiologist (D.A. Korevaar).

Further research is needed to determine whether confirmatory mediastinoscopy can safely be omitted following negative endosonography. Tumor characteristics, FDG-PET/CT imaging data, and extent of endosonography performance are important factors to take into account. It would be best to identify a small subgroup of patients staged negative by endosonography in which confirmatory mediastinoscopy results in a high rate of missed metastases by endosonography. The MEDIASTrial, a multicenter randomised trial evaluating the impact on unforeseen N2 disease by comparing mediastinal staging strategies with or without confirmatory mediastinoscopy might shed light on this issue (MEDIASTrial, NTR6528).(62)

CONCLUSION

The rate of unforeseen N2 disease after negative endosonography findings was similar in patients undergoing immediate lung tumor resection to those undergoing confirmatory mediastinoscopy first. With a complication rate of 6.0%, the role of confirmatory mediastinoscopy is under debate.

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AUTHOR'S CONTRIBUTIONS

JB, MvD, VN and FvdB have been involved in acquisition of data. JB and FvdB analysed and interpreted the data and JB drafted the manuscript. MvD, VN, MD, JA and FvdB critically revisited the manuscript and gave final approval of the version to be published.

CONFLICT OF INTEREST

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REFERENCES

(1) Vilmann P, Clementsen PF, Colella S, Siemsen M, de Leyn P, Dumonceau J, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015;47(6):546-560.

(2) De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2014 May;45(5):787-798.

(3) Meerbeeck J, Kramer G, Schil P, Legrand C, Smit E, Schramel F, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. National Cancer Institute. Journal (Print) 2007 Mar 21,;99(6):442-450.

(4) Postmus PE, Kerr KM, Oudkerk M, Senan S, Waller DA, Vansteenkiste J, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2017 Jul 1,;28(4):iv21.

(5) Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, et al. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. JAMA 2010 Nov 24,;304(20):2245-2252.

(6) Korevaar DA, Crombag LM, Cohen JF, Spijker R, Bossuyt PM, Annema JT. Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: a systematic review and meta-analysis. The Lancet Respiratory Medicine 2016 Dec;4(12):960-968.

(7) Lawrence D. Brown, T. Tony Cai, Anirban DasGupta. Interval Estimation for a Binomial Proportion. Statistical Science 2001 May 1,;16(2):101-117.

(8) DerSimonian R, Nan. Meta-analysis in clinical trials revisited. Contemporary Clinical Trials 2015;45(Pt A):139-145.

(9) Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in medicine 2002 Jun 15,;21(11):1539-1558.

(10) Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 2004 Aug;240(2):205-213.

(11) Zhang R, Ma Y, Xu G, Gao X, Luo G, Lin Q, et al. Endobronchial ultrasound-guided transbronchial needle aspiration and cervical mediastinoscopy for mediastinal staging of non-small cell lung cancer: a retrospective comparison study. Journal of thoracic disease 2018 Mar;10(3):1951-1959.

(12) Coutinho, D.|Oliveira, A.|Campainha, S.|Neves, S.|Guerra, M.|Miranda, J.|Furtado, A.|Tente, D.|Sanches, A.|Almeida, J.|Moura e Sá, J. Endobronchial ultrasound-guided transbronchial needle aspiration for nodal staging in non-small cell lung carcinoma. Portuguese Review of Pneumology (Revista Portuguesa de Pneumologia, English Edition) 2017;23(2):85-89.

(13) Talebian Yazdi, Mehrdad|Egberts, Joost|Schinkelshoek, Mink S.|Wolterbeek, Ron|Nabers, Johannes|Venmans, Ben J.W.|Tournoy, Kurt G.|Annema, Jouke T. Endosonography for lung cancer staging: predictors for false-negative outcomes. Lung Cancer 2015;90(3):451-456.

(14) Figueiredo VR, Cardoso PFG, Jacomelli M, Demarzo SE, Palomino ALM, Rodrigues AJ, et al. Endobronchial ultrasound-guided transbronchial needle aspiration for lung cancer staging: early experience in Brazil. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia 2015 Jan;41(1):23-30.

(15) Clementsen PF, Skov BG, Vilmann P, Krasnik M. Endobronchial ultrasound-guided biopsy performed under optimal conditions in patients with known or suspected lung cancer may render mediastinoscopy unnecessary. Journal of bronchology & interventional pulmonology 2014 Jan;21(1):21-25.

(16) Sakairi Y, Hoshino H, Fujiwara T, Nakajima T, Yasufuku K, Yoshida S, et al. Validation of EBUS-TBNA-integrated nodal staging in potentially node-positive non-small cell lung cancer. Gen Thorac Cardiovasc Surg 2013 Sep;61(9):522-527.

(17) Lee, Benjamin E., MD|Kletsman, Elaine, PA|Rutledge, John R., MAS|Korst, Robert J., MD. Utility of endobronchial ultrasound–guided mediastinal lymph node biopsy in patients with non–small cell lung cancer. Journal of Thoracic and Cardiovascular Surgery, The 2012;143(3):585-590.

(18) Sanz-Santos, J.|Andreo, F.|Castellà, E.|Llatjós, M.|López de Castro, P.|Astudillo, J.|García-Luján, R.|Serra, P.|Monsó, E. Representativeness of Nodal Sampling With Endobronchial Ultrasonography in Non–Small-Cell Lung Cancer Staging. Ultrasound in Medicine & Biology 2012;38(1):62-68.

(19) Hwangbo B, Kim MS, Kim H, Kim SK, Lee G, Lee JM, et al. Application of Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration Following Integrated PET/CT in Mediastinal Staging of Potentially Operable Non-small Cell Lung Cancer. Chest 2009 May;135(5):1280-1287.

(20) Szlubowski A, Kuzdzal J, Kolodziej M, Soja J, Pankowski J, Obrochta A, et al. Endobronchial ultrasound-guided needle aspiration in the non-small cell lung cancer staging. Eur J Cardiothorac Surg 2009 Feb 1,;35(2):332-336.

(21) Lee HS, Lee GK, Lee H, Kim MS, Lee JM, Kim HY, et al. Real-time endobronchial ultrasound-guided transbronchial needle aspiration in mediastinal staging of non-small cell lung cancer: how many aspirations per target lymph node station? Chest 2008 Aug;134(2):368.

(22) Yasufuku K, Chiyo M, Koh E, Moriya Y, Iyoda A, Sekine Y, et al. Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. Lung Cancer 2005;50(3):347-354.

(23) Srinivasan R, Bhutani MS, Thosani N, Săftoiu A, Rice DC, Ioncică AM, et al. Clinical impact of EUS-FNA of mediastinal lymph nodes in patients with known or suspected lung cancer or mediastinal lymph nodes of unknown etiology. Journal of gastrointestinal and liver diseases : JGLD 2012 Jun;21(2):145.

(24) Talebian, M.|von Bartheld, M.B.|Braun, J.|Versteegh, M.I.M.|Dekkers, O.M.|Rabe, K.F.|Annema, J.T. EUS-FNA in the preoperative staging of non-small cell lung cancer. Lung Cancer 2010;69(1):60-65.

(25) Craanen ME, Comans EFI, Paul MA, Smit EF. Endoscopic ultrasound guided fine-needle aspiration and 18FDG-positron emission tomography in the evaluation of patients with non-small cell lung cancer. Interactive CardioVascular and Thoracic Surgery 2007 Aug 1,;6(4):433-436.

(26) Fernández-Esparrach G, Ginès A, Belda J, Pellisé M, Solé M, Marrades R, et al. Transesophageal ultrasound-guided fine needle aspiration improves mediastinal staging in patients with non-small cell lung cancer and normal mediastinum on computed tomography. Lung Cancer 2006;54(1):35-40.

(27) Fritscher-Ravens A, Bohuslavizki KH, Brandt L, Bobrowski C, Lund C, Knöfel WT, et al. Mediastinal lymph node involvement in potentially resectable lung cancer: comparison of CT, positron emission tomography, and endoscopic ultrasonography with and without fine-needle aspiration. Chest 2003 Feb;123(2):442.

(28) Laudanski J, Kozlowski M, Nikliński J, Chyczewski L. The preoperative study of mediastinal lymph nodes metastasis in lung cancer by endoscopic ultrasonography (EUS) and helical computed tomography (CT). Lung Cancer 2001;34:S126.

(29) Dooms C, Tournoy KG, Schuurbiers O, Decaluwe H, Ryck FD, Verhagen A, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest 2015;147(1):209-215.

(30) Oki, Masahide, MD|Saka, Hideo, MD|Ando, Masahiko, MD|Kitagawa, Chiyoe, MD|Kogure, Yoshihito, MD|Seki, Yukio, MD. Endoscopic ultrasound-guided fine needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration: Are two better than one in mediastinal staging of non–small cell lung cancer? Journal of Thoracic and Cardiovascular Surgery, The 2014;148(4):1177.e1.

(31) Kang HJ, Hwangbo B, Lee G, Nam B, Lee H, Kim MS, et al. EBUS-centred versus EUS-centred mediastinal staging in lung cancer: a randomised controlled trial. Thorax 2014 Mar;69(3):261-268.

(32) Verhagen, A F T M, Schuurbiers OCJ, Looijen-Salamon MG, Heide, S M van der, Swieten HAv, Heijden, E H M van der. Mediastinal staging in daily practice: endosonography, followed by cervical mediastinoscopy. Do we really need both? Interactive Cardiovascular and Thoracic Surgery 2013;17(5):823-828.

(33) Szlubowski A, Soja J, Koco P, Talar P, Czajkowski W, Rudnicka-Sosin L, et al. A comparison of the combined ultrasound of the mediastinum by use of a single ultrasound bronchoscope versus ultrasound bronchoscope plus ultrasound gastroscope in lung cancer staging: a prospective trial. Interactive CardioVascular and Thoracic Surgery 2012 Sep;15(3):442-446.

(34) Ohnishi R, Yasuda I, Kato T, Tanaka T, Kaneko Y, Suzuki T, et al. Combined endobronchial and endoscopic ultrasoundguided fine needle aspiration for mediastinal nodal staging of lung cancer. Endoscopy 2011;43:1082-1089.

(35) Hwangbo B, Lee HS, Lee G, Lee HS, Lee JM, Lee S, et al. Transbronchial and Transesophageal Fine-Needle Aspiration Using an Ultrasound Bronchoscope in Mediastinal Staging of Potentially Operable Lung Cancer. Chest 2010 Oct;138(4):795-802.

(36) Szlubowski A, Zieliński M, Soja J, Annema JT, Sośnicki W, Jakubiak M, et al. A combined approach of endobronchial and endoscopic ultrasound-guided needle aspiration in the radiologically normal mediastinum in non-small-cell lung cancer staging--a prospective trial. Eur J Cardiothorac Surg 2010;37(5):1175-1179.

(37) Vilmann P, Krasnik M, Larsen SS, Jacobsen GK, Clementsen P. Transesophageal Endoscopic Ultrasound-Guided Fine-Needle Aspiration (EUS-FNA) and Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) Biopsy: a Combined Approach in the Evaluation of Mediastinal Lesions. Endoscopy 2005 Sep;37(9):833-839.

(38) Whittney A Warren, Jared T Hagaman. Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration for Mediastinal Staging in a Community Medical Center. Annals of the American Thoracic Society 2016 Oct 1,;13(10):1802.

(39) Dziedzic D, Peryt A, Szolkowska M, Langfort R, Orlowski T. Endobronchial ultrasound–guided transbronchial needle aspiration in the staging of lung cancer patients. SAGE Open Medicine 2015 Oct 1,;3.

(40) Defranchi, Sebastian A., MD|Edell, Eric S., MD|Daniels, Craig E., MD|Prakash, Udaya B.S., MD|Swanson, Karen L., DO|Utz, James P., MD|Allen, Mark S., MD|Cassivi, Stephen D., MD|Deschamps, Claude, MD|Nichols, Francis C., MD|Shen, K. Robert, MD|Wigle, Dennis A., MD, PhD. Mediastinoscopy in Patients With Lung Cancer and Negative Endobronchial Ultrasound Guided Needle Aspiration. Annals of Thoracic Surgery 2010;90(6):1753-1757.

(41) Tournoy KG, De Ryck F, Vanwalleghem LR, Vermassen F, Praet M, Aerts JG, et al. Endoscopic Ultrasound Reduces Surgical Mediastinal Staging in Lung Cancer: A Randomized Trial. American Journal of Respiratory and Critical Care Medicine 2008 Mar 1,;177(5):531-535.

(42) Decaluwé Herbert, Dooms Christophe, D'Journo Xavier Benoit, Call Sergi, Sanchez David, Haager Benedikt, et al. Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study. The European Respiratory Journal 2017 Dec 1,;50(6):1701493.

(43) Sayar A, Citak N, Buyukkale S, Metin M, Kok A, Celikten A, et al. The incidence of hoarseness after mediastinoscopy and outcome of video-assisted versus conventional mediastinoscopy in lung cancer staging. Acta Chirurgica Belgica 2016;116:23-29.

(44) Steunenberg B, Aerts J, Aerts B, De Groot H, Boot C, Romme P, et al. Quality Assessment of Video Mediastinoscopy Performed for Staging in Non-Small Cell Lung Cancer. Thorac cardiovasc Surg 2016 Sep;64(6):520-525.

(45) Citak N, Buyukkale S, Kok A, Celikten A, Metin M, Sayar A, et al. Does Video-Assisted Mediastinoscopy Offer Lower False-Negative Rates for Subcarinal Lymph Nodes Compared with Standard Cervical Mediastinoscopy? Thorac cardiovasc Surg 2014 Oct;62(7):624-630.

(46) Anraku, Masaki, MD|Miyata, Ryo, MD|Compeau, Christopher, MD|Shargall, Yaron, MD. Video-Assisted Mediastinoscopy Compared With Conventional Mediastinoscopy: Are We Doing Better? Annals of Thoracic Surgery 2010;89(5):1577-1581.

(47) Leschber G, Sperling D, Klemm W, Merk J. Does video-mediastinoscopy improve the results of conventional mediastinoscopy? Eur J Cardiothorac Surg 2008 Feb 1,;33(2):289-293.

(48) Kuzdzal J, Zielinski M, Papla B, Urbanik A, Wojciechowski W, Narski M, et al. The transcervical extended mediastinal lymphadenectomy versus cervical mediastinoscopy in non-small cell lung cancer staging. Eur J Cardiothorac Surg 2007 Jan 1,;31(1):88-94.

(49) Rusch VW. Mediastinoscopy: An obsolete procedure? The Journal of Thoracic and Cardiovascular Surgery 2011 Dec;142(6):1400-1402.

(50) Annema JT, de Leyn P, Clementsen P, Siemsen M, Vilmann P. Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European respiratory journal 2015;46(6):1848-1849.

(51) Kim H. Reply to "Are We at the Dusk of Mediastinoscopy in Modern Clinical Practice?": An Irresistible Trend. Journal of Thoracic Oncology 2015 Sep;10(9):e92.

(52) Pöttgen C, Eberhardt W, Stamatis G, Stuschke M. Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence. Oncotarget 2017 Jun 20,;8(25):41670-41678.

(53) Van Schil PE, Lauwers P, Yogeswaran SK, Berzenji L, Hendriks JM. Surgical Management of Stage IIIA Non-Small Cell Lung Cancer. Frontiers in Oncology 2017 Oct 26,;7.

(54) Kuijvenhoven JC, Korevaar DA, Tournoy KG, Malfait TLA, Dooms C, Rintoul RC, et al. Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer. JAMA 2016 Sep 13,;316(10):1110-1112.

(55) Kirmani BH, Volpi S, Aresu G, Peryt A, Win T, Coonar AS. Long term and disease-free survival following surgical resection of occult N2 lung cancer. Journal of thoracic disease 2018 Aug;10(8):4806-4811.

(56) Tezel C, Dogruyol T, Alpay L, Akyıl M, Evman S, Metin S, et al. Prognostic Importance of the Lymph Node Factor in Surgically Resected non-small Cell Lung Cancer. The Thoracic and Cardiovascular Surgeon 2018 Nov 2,.

(57) Yoo, Changhoon|Yoon, Shinkyo|Lee, Dae Ho|Park, Seung-Il|Kim, Dong Kwan|Kim, Yong-Hee|Kim, Hyeong Ryul|Choi, Se Hoon|Kim, Woo Sung|Choi, Chang-Min|Jang, Se Jin|Song, Si Yeol|Kim, Su Ssan|Choi, Eun Kyung|Lee, Jae Cheol|Suh, Cheolwon|Lee, Jung-Shin|Kim, Sang-We. Prognostic

Significance of the Number of Metastatic pN2 Lymph Nodes in Stage IIIA-N2 Non–Small-Cell Lung Cancer After Curative Resection. Clinical Lung Cancer 2015;16(6):e212.

(58) Garelli E, Renaud S, Falcoz P, Weingertner N, Olland A, Santelmo N, et al. Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2016 Aug;50(2):322-328.

(59) Crombag LMM, Dooms C, Stigt JA, Tournoy KG, Schuurbiers OCJ, Ninaber MK, et al. Systematic and combined endosonographic staging of lung cancer (SCORE Study). The European respiratory journal 2018 Dec 21,:1800800.

(60) Sehgal, Inderpaul Singh, MD, DM|Dhooria, Sahajal, MD, DM|Aggarwal, Ashutosh Nath, MD, DM|Behera, Digambar, MD|Agarwal, Ritesh, MD, DM. Endosonography Versus Mediastinoscopy in Mediastinal Staging of Lung Cancer: Systematic Review and Meta-Analysis. Annals of Thoracic Surgery 2016;102(5):1747-1755.

(61) Annema, Jouke T., MD, PhD. Endosonographic Staging for N1 Disease. Chest 2015;147(3):e122.

(62) Bousema JE, Dijkgraaf MGW, Papen-Botterhuis NE, Schreurs HW, Maessen JG, van der Heijden, Erik H, et al. MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a multicenter randomised controlled trial. BMC surgery 2018 May 18,;18(1):27.

SUPPLEMENTARY MATERIAL

Appendix A. Search strategy

MEDLINE (PubMed):

("Lung Neoplasms"[Mesh] OR Lung Neoplasm*[Tiab] OR Pulmonary Neoplasm*[Tiab] OR Lung Cancer*[Tiab] OR Pulmonary Cancer*[Tiab] OR Cancer of the Lung[Tiab] OR Cancer of Lung[Tiab] OR Bronchogenic Carcinoma*[Tiab] OR Bronchial Carcinoma*[Tiab] OR Lung Carcinoma*[Tiab]) AND (("Mediastinoscopy"[Mesh] OR Mediastinoscop*[Tiab] OR Mediastinal Staging[Tiab] OR Mediastinum Staging[Tiab]) OR ("Endosonography"[Mesh] OR Endosonograph*[Tiab] OR Echo Endoscop*[Tiab] OR Ultrasonic Endoscop*[Tiab] OR Endoscopic Ultrasonograph*[Tiab] OR Endoscopic Ultrasound[Tiab] OR Endobronchial Ultrasonograph*[Tiab] OR Endobronchial Ultrasound*[Tiab] OR EBUS*[Tiab] OR EUS*[Tiab]))

EMBASE (Ovid):

ID	Search	Hits
1	exp lung tumor/	314587
2	(Lung Neoplasm* or Pulmonary Neoplasm* or Lung Cancer* or Pulmonary Cancer* or Cancer of the Lung or Cancer of Lung or Bronchogenic Carcinoma* or Bronchial Carcinoma* or Lung Carcinoma*).ab,ti.	225142
3	1 or 2	376593
4	exp mediastinoscopy/	4319
5	(Mediastinoscop* or Mediastinal Staging or Mediastinum Staging).ab,ti.	4265
6	4 or 5	5860
7	exp endoscopic ultrasonography/ or exp endobronchial ultrasonography/	8045
8	(Endosonograph* or Echo Endoscop* or Ultrasonic Endoscop* or Endoscopic Ultrasonograph* or Endoscopic Ultrasound or Endobronchial Ultrasonograph* or Endobronchial Ultrasound* or EBUS* or EUS*).ab,ti.	37132
9	7 or 8	39178
10	6 or 9	43672
11	3 and 10	6402
12	limit 11 to exclude medline journals	728

Cochrane Library (Wiley):

ID	Search	Hits
#1	MeSH descriptor: [Lung Neoplasms] explode all trees	6056
#2	lung neoplasm*:ti,ab,kw or pulmonary neoplasm*:ti,ab,kw or lung cancer*: ti,ab,kw or pulmonary cancer*:ti,ab,kw or cancer of the lung:ti,ab,kw (Word variations have been searched)	17256
#3	Bronchogenic Carcinoma*:ti,ab,kw or Bronchial Carcinoma*:ti,ab,kw or Lung Carcinoma*:ti,ab,kw (Word variations have been searched)	6363
#4	#1 or #2 or #3	17707
#5	MeSH descriptor: [Mediastinoscopy] explode all trees	40
#6	Mediastinoscop*:ti,ab,kw or Mediastinal Staging:ti,ab,kw or Mediastinum Staging:ti,ab,kw (Word variations have been searched)	566
#7	#5 or #6	566
#8	MeSH descriptor: [Endosonography] explode all trees	419
#9	Endosonograph*:ti,ab,kw or Echo Endoscop*:ti,ab,kw or Ultrasonic Endoscop*: ti,ab,kw or Endoscopic Ultrasonograph*:ti,ab,kw or Endoscopic Ultrasound: ti,ab,kw (Word variations have been searched)	1350
#10	Endobronchial Ultrasonograph*:ti,ab,kw or Endobronchial Ultrasound*:ti,ab,kw or EBUS*:ti,ab,kw or EUS*:ti,ab,kw (Word variations have been searched)	965
#11	#8 or #9 or #10	1792
#12	#7 or #11	2276
#13	#4 and #12	414

Appendix B. QUADAS-2 assessment of included endosonography only studies

		Patient selection				Index test – Endosonography		Reference standard		Flow and timing	
Study	Type endoscopy	**Bias:** Was a retrospective inclusion of patients avoided?	**Bias:** Was non-consecutive inclusion of patients avoided?	**Bias:** Was a case-control design avoided?	**Applicability:** Is there concern that the included patients do not match the review question?	**Bias:** Was the endosonography plan systematically and complete? (described in methods)	**Bias:** Were endoscopists blinded to the results of the reference standard?	**Bias:** Was the reference standard performed systematically according to the ESTS guideline?	**Applicability:** Is there concern that N2 disease will not be diagnosed adequately by the reference standard?	**Bias:** Did >90% of patients with negative index tests receive surgical reference standard?	**Bias:** Were all patients included in the analysis?
Zhang 2018	EBUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺
Coutinho 2017	EBUS	☺	☺	☺	☺	☺	☺	☺	☺	☹	☺
Talebian 2015 (1)	EBUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺
Figueiredo 2015	EBUS	☹	?	☺	?	☺	☺	?	?	☹	☹
Clementsen 2014	EBUS	☹	☺	☺	☺	☺	☺	?	?	☹	☹
Sakairi 2013	EBUS	☹	☺	☺	☺	?	☺	?	?	☺	☹
Lee 2012 (1)	EBUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺
Sanz-Santos 2012	EBUS	☹	☺	☺	☺	☺	☺	?	?	☹	☹
Hwangbo 2009	EBUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹
Szlubowski 2008	EBUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Lee 2008	EBUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹
Yasufuku 2005	EBUS	☺	☺	☺	☺	☺	☺	☺	☺	☹	☹
Talebian 2015 (3)	EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺
Srinivasan 2012	EUS	☹	☹	☺	☺	?	☺	?	?	☹	☹
Talebian 2010 (1)	EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺
Craanen 2007	EUS	☺	☹	☺	☹	☺	☺	☺	☺	☹	☹
Fernandez 2006	EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹
Fritscher 2003	EUS	☺	☺	☺	☺	☺	☺	?	?	☺	☺
Laudanski 2001	EUS	☺	☺	☺	☺	?	☺	☺	☺	☺	☺
Talebian 2015 (5)	EBUS+EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺
Dooms 2015 (1)	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹
Oki 2014	EBUS+EUS	☺	☺	☺	☺	☺	☺	?	?	☺	☺
Kang 2014 (1)	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☹	☹
Kang 2014 (2)	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☹	☹
Verhagen 2013 (1)	EBUS+EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☹
Szlubowski '12 (1)	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Szlubowski '12 (2)	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Ohnishi 2011	EBUS+EUS	☺	☺	☺	☺	☺	☺	?	?	☹	☹
Hwangbo 2010	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹
Szlubowski 2010	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Vilmann 2005	EBUS+EUS	☺	☹	☺	?	?	☺	☺	☺	☹	☹

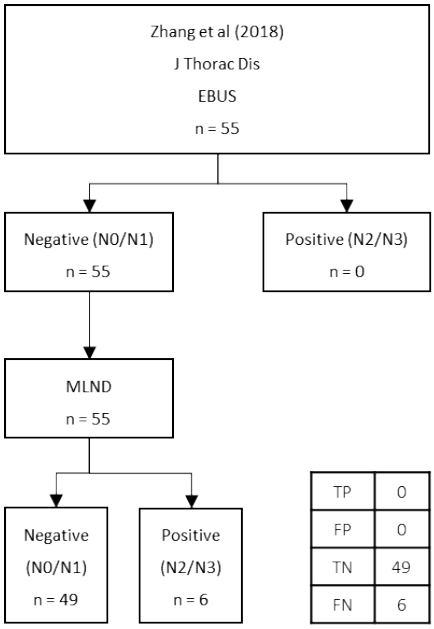
☺ Low risk of bias / no applicability concerns, ☹ High risk of bias / high applicability concerns, ? Unclear risk of bias / unclear applicability concerns

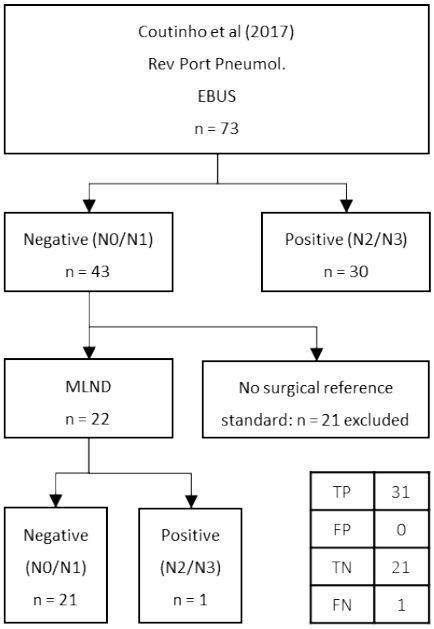
QUADAS-2 assessment of included endosonography and mediastinoscopy studies

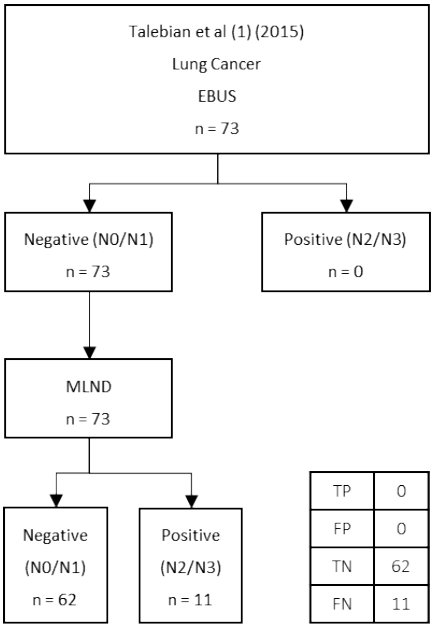
		Patient selection				Index test - Endosonography		Index test - Mediastinoscopy		Reference standard		Flow and timing		
Study	**Type endoscopy**	**Bias:** Was a retro-spective inclusion of patients avoided?	**Bias:** Was non-consecutive inclusion of patients avoided?	**Bias:** Was a case-control design avoided?	**Applicability** Is there concern that the included patients do not match the review question?	**Bias:** Was the endo-sonography plan systematically and complete? (described in methods)	**Bias:** Were endoscopists blinded to the results of the reference standard?	**Bias:** Were at least lymph node stations 4R, 7 and 4L biopsied?	**Bias:** Were surgeons blinded to the result of the reference standard?	**Bias:** Was the reference standard performed systematically according to the ESTS guideline?	**Applicability** Is there concern that N2 disease will not be diagnosed adequately by the reference standard?	**Bias:** Did all patient with negative endo-sonography receive a medias-tinoscopy?	**Bias:** Did >90% of patients with negative index tests receive surgical reference standard?	**Bias:** Were all patients included in the analysis?
Warren 2016	EBUS	☹	☹	☺	☺	?	☹	☺	☺	?	?	☹	☺	☹
Dziedzic 2015	EBUS	☺	☺	☺	☺	?	☺	☺	☺	☺	☺	☹	☺	☺
Talebian 2015 (2)	EBUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Defranchi 2010	EBUS	☹	☺	☺	☺	?	☺	☺	☺	☺	☺	☺	☺	☺
Talebian 2015 (4)	EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Talebian 2010 (2)	EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹	☺	☺
Tournoy 2008	EUS	☺	☺	☺	☺	?	☺	☺	☺	☺	☺	☺	☺	☺
Talebian 2015 (6)	EBUS+EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺
Dooms 2015 (2)	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹	☺	☹
Verhagen 2013 (2)	EBUS+EUS	☹	☺	☺	☺	☺	☺	☺	☺	☺	☺	☹	☺	☹
Annema 2010	EBUS+EUS	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺	☺

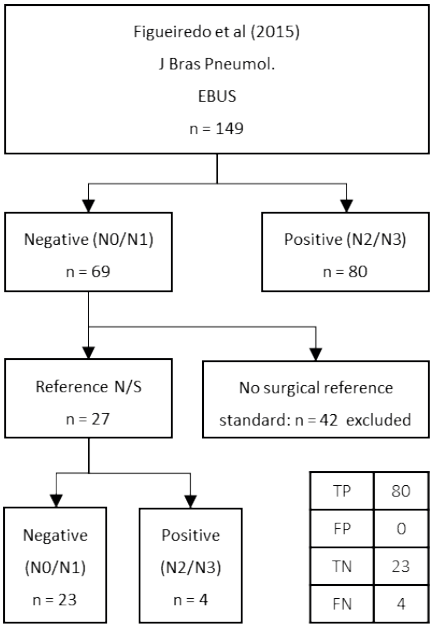
☺ Low risk of bias / no applicability concerns, ☹ High risk of bias / high applicability concerns, ? Unclear risk of bias / unclear applicability concerns

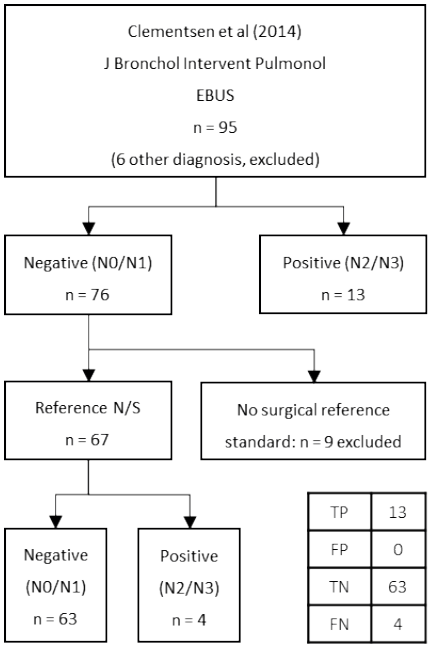
Appendix C. Details on included studies and excluded patients

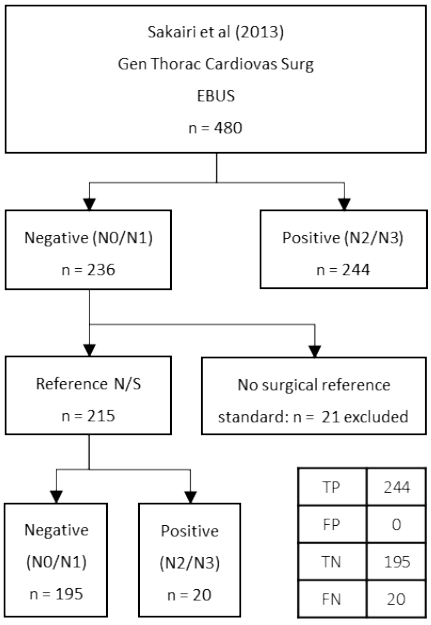


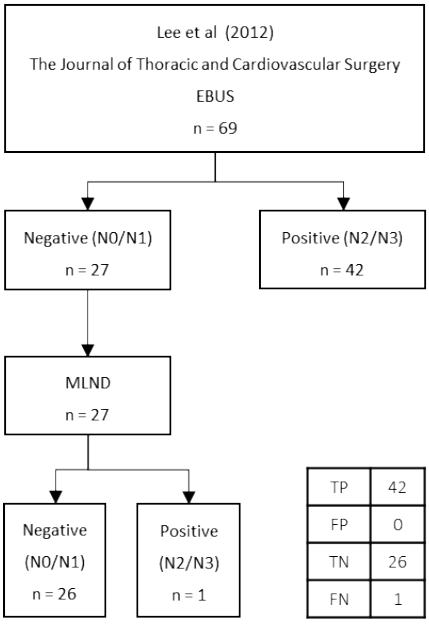


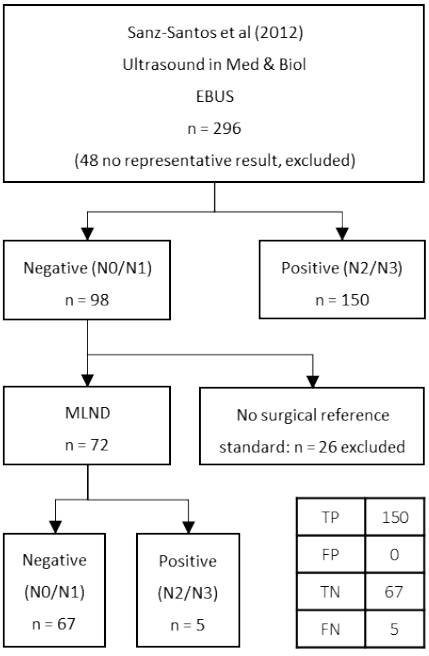


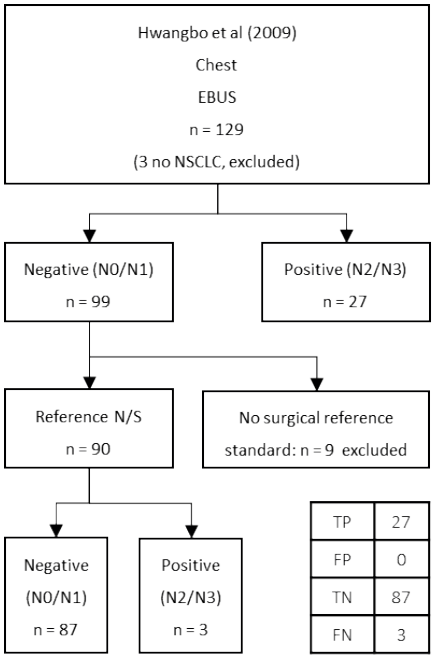


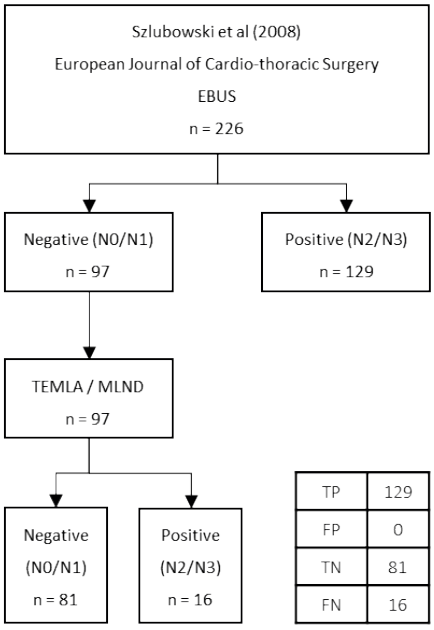

Clementsen et al (2014)
J Bronchol Intervent Pulmonol
EBUS
n = 95
(6 other diagnosis, excluded)
Negative (N0/N1)
n = 76
Positive (N2/N3)
n = 13
Reference N/S
n = 67
No surgical reference standard: n = 9 excluded
Negative (N0/N1)
n = 63
Positive (N2/N3)
n = 4
TP 13
FP 0
TN 63
FN 4

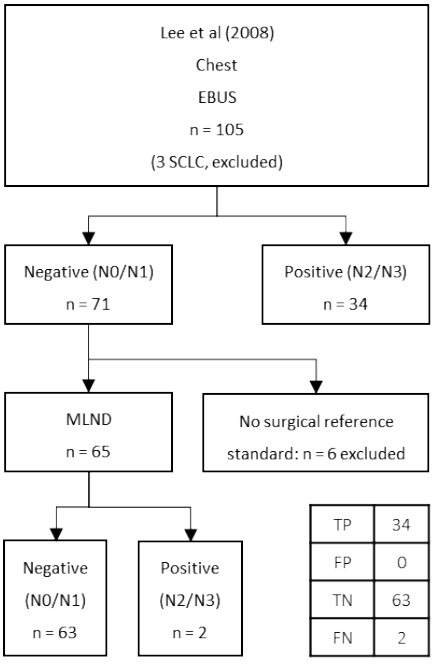

Sakairi et al (2013)
Gen Thorac Cardiovas Surg
EBUS
n = 480
Negative (N0/N1)
n = 236
Positive (N2/N3)
n = 244
Reference N/S
n = 215
No surgical reference standard: n = 21 excluded
Negative (N0/N1)
n = 195
Positive (N2/N3)
n = 20
TP 244
FP 0
TN 195
FN 20

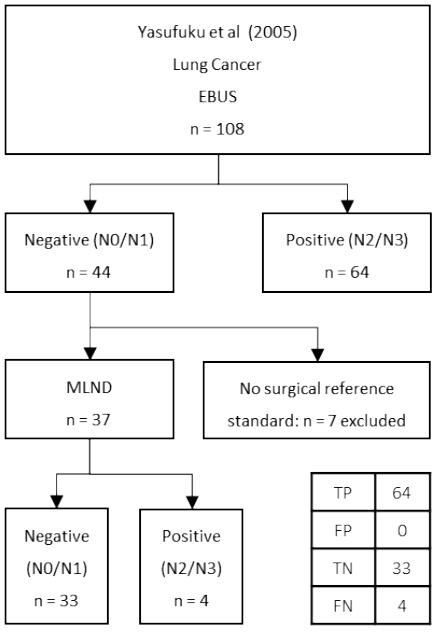

Lee et al (2012)
The Journal of Thoracic and Cardiovascular Surgery
EBUS
n = 69
Negative (N0/N1)
n = 27
Positive (N2/N3)
n = 42
MLND
n = 27
Negative (N0/N1)
n = 26
Positive (N2/N3)
n = 1
TP 42
FP 0
TN 26
FN 1

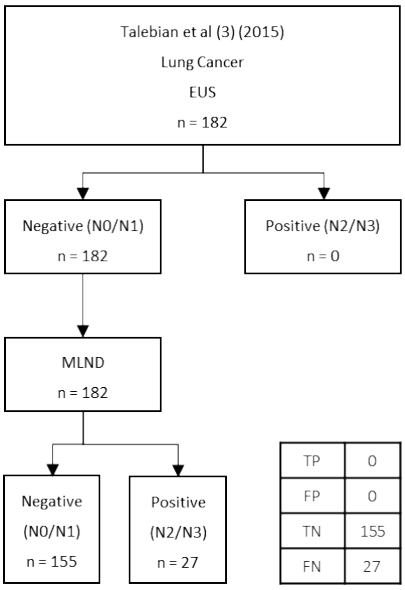

Sanz-Santos et al (2012)
Ultrasound in Med & Biol
EBUS
n = 296
(48 no representative result, excluded)
Negative (N0/N1)
n = 98
Positive (N2/N3)
n = 150
MLND
n = 72
No surgical reference standard: n = 26 excluded
Negative (N0/N1)
n = 67
Positive (N2/N3)
n = 5
TP 150
FP 0
TN 67
FN 5

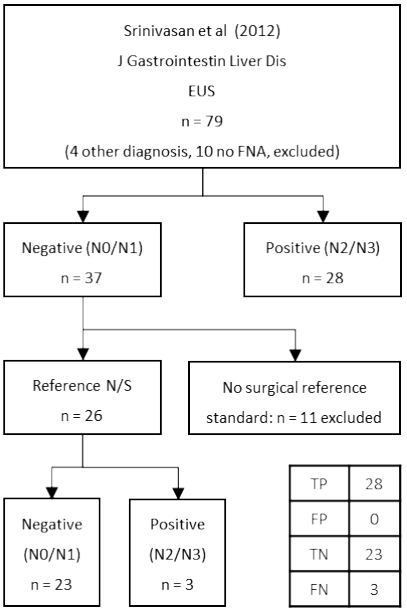

Hwangbo et al (2009)
Chest
EBUS
n = 129
(3 no NSCLC, excluded)
Negative (N0/N1)
n = 99
Positive (N2/N3)
n = 27
Reference N/S
n = 90
No surgical reference standard: n = 9 excluded
Negative (N0/N1)
n = 87
Positive (N2/N3)
n = 3
TP 27
FP 0
TN 87
FN 3

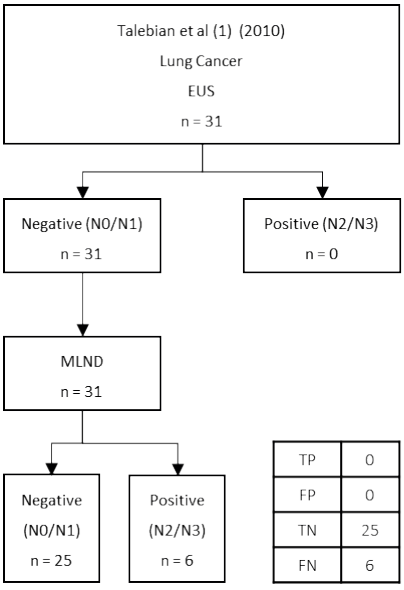

Szlubowski et al (2008)
European Journal of Cardio-thoracic Surgery
EBUS
n = 226
Negative (N0/N1)
n = 97
Positive (N2/N3)
n = 129
TEMLA / MLND
n = 97
Negative (N0/N1)
n = 81
Positive (N2/N3)
n = 16
TP 129
FP 0
TN 81
FN 16

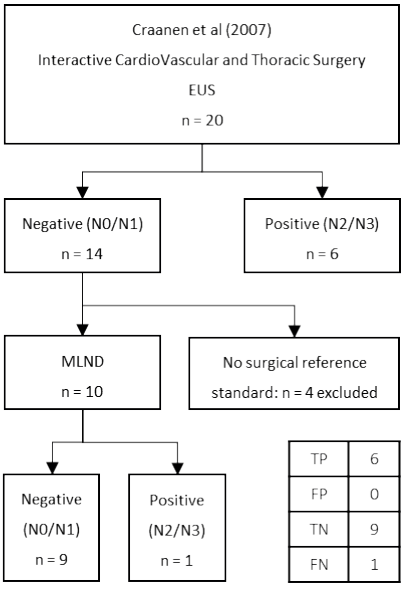

Lee et al (2008)
Chest
EBUS
n = 105
(3 SCLC, excluded)
Negative (N0/N1)
n = 71
Positive (N2/N3)
n = 34
MLND
n = 65
No surgical reference standard: n = 6 excluded
Negative (N0/N1)
n = 63
Positive (N2/N3)
n = 2
TP 34
FP 0
TN 63
FN 2

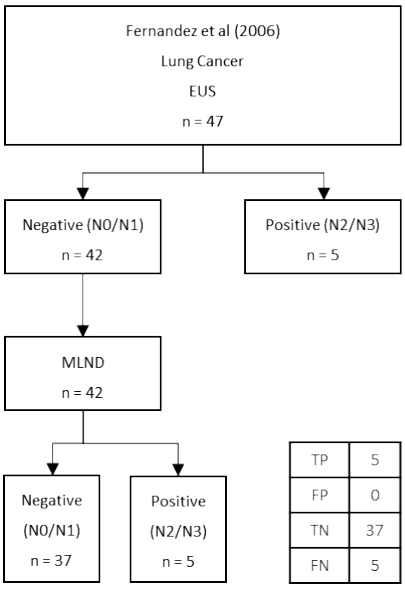

Yasufuku et al (2005)
Lung Cancer
EBUS
n = 108
Negative (N0/N1)
n = 44
Positive (N2/N3)
n = 64
MLND
n = 37
No surgical reference standard: n = 7 excluded
Negative (N0/N1)
n = 33
Positive (N2/N3)
n = 4
TP 64
FP 0
TN 33
FN 4

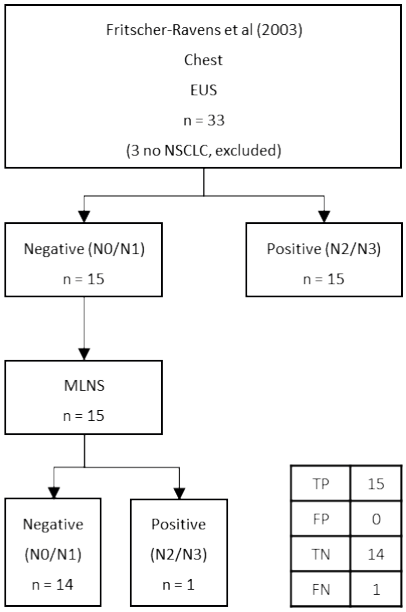

Talebian et al (3) (2015)
Lung Cancer
EUS
n = 182
Negative (N0/N1)
n = 182
Positive (N2/N3)
n = 0
MLND
n = 182
Negative
(N0/N1)
n = 155
Positive
(N2/N3)
n = 27
TP 0
FP 0
TN 155
FN 27

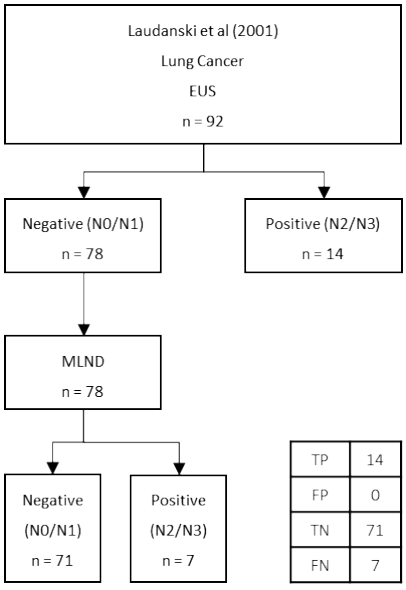

Srinivasan et al (2012)
J Gastrointestin Liver Dis
EUS
n = 79
(4 other diagnosis, 10 no FNA, excluded)
Negative (N0/N1)
n = 37
Positive (N2/N3)
n = 28
Reference N/S
n = 26
No surgical reference
standard: n = 11 excluded
Negative
(N0/N1)
n = 23
Positive
(N2/N3)
n = 3
TP 28
FP 0
TN 23
FN 3

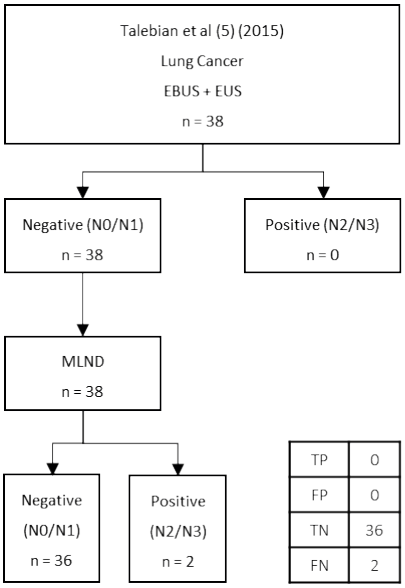

Talebian et al (1) (2010)
Lung Cancer
EUS
n = 31
Negative (N0/N1)
n = 31
Positive (N2/N3)
n = 0
MLND
n = 31
Negative
(N0/N1)
n = 25
Positive
(N2/N3)
n = 6
TP 0
FP 0
TN 25
FN 6

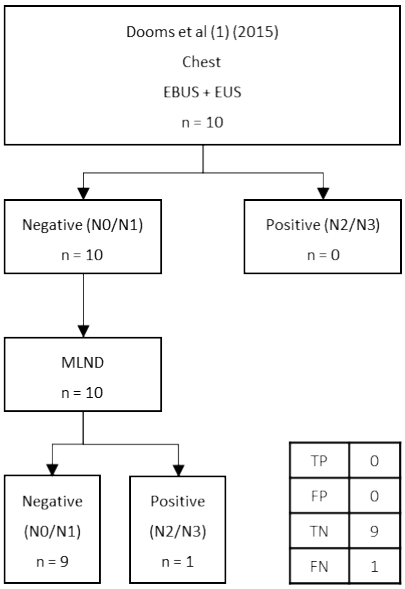

Craanen et al (2007)
Interactive CardioVascular and Thoracic Surgery
EUS
n = 20
Negative (N0/N1)
n = 14
Positive (N2/N3)
n = 6
MLND
n = 10
No surgical reference
standard: n = 4 excluded
Negative
(N0/N1)
n = 9
Positive
(N2/N3)
n = 1
TP 6
FP 0
TN 9
FN 1

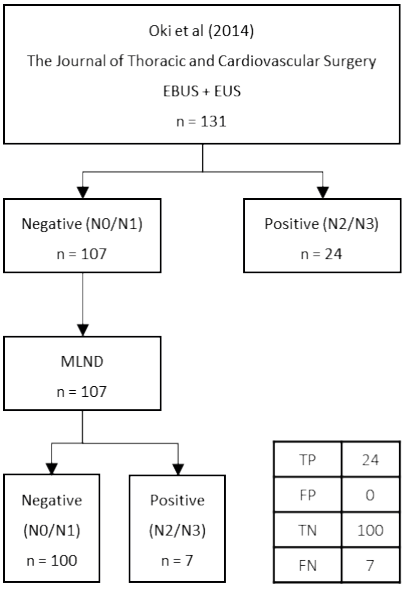

Fernandez et al (2006)
Lung Cancer
EUS
n = 47
Negative (N0/N1)
n = 42
Positive (N2/N3)
n = 5
MLND
n = 42
Negative
(N0/N1)
n = 37
Positive
(N2/N3)
n = 5
TP 5
FP 0
TN 37
FN 5

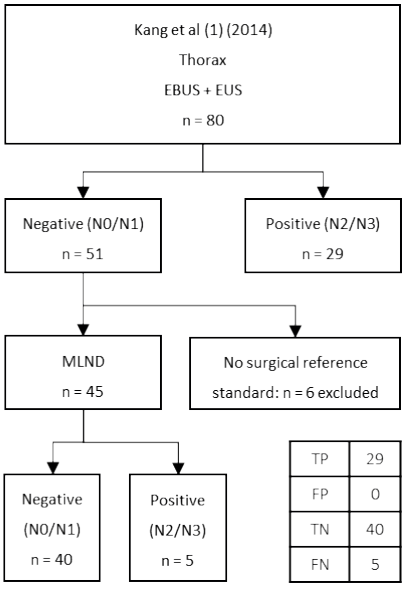

Fritscher-Ravens et al (2003)
Chest
EUS
n = 33
(3 no NSCLC, excluded)
Negative (N0/N1)
n = 15
Positive (N2/N3)
n = 15
MLNS
n = 15
Negative
(N0/N1)
n = 14
Positive
(N2/N3)
n = 1
TP 15
FP 0
TN 14
FN 1

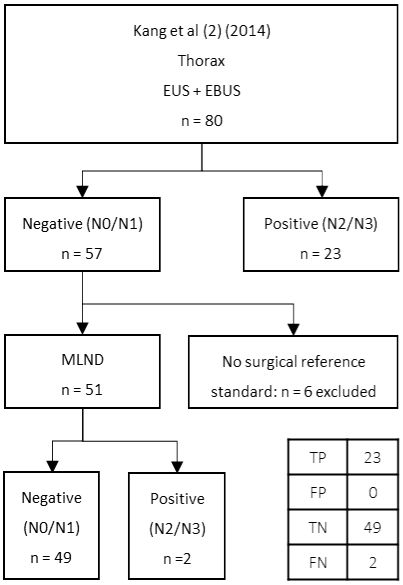

Laudanski et al (2001)
Lung Cancer
EUS
n = 92
Negative (N0/N1)
n = 78
Positive (N2/N3)
n = 14
MLND
n = 78
Negative
(N0/N1)
n = 71
Positive
(N2/N3)
n = 7
TP 14
FP 0
TN 71
FN 7

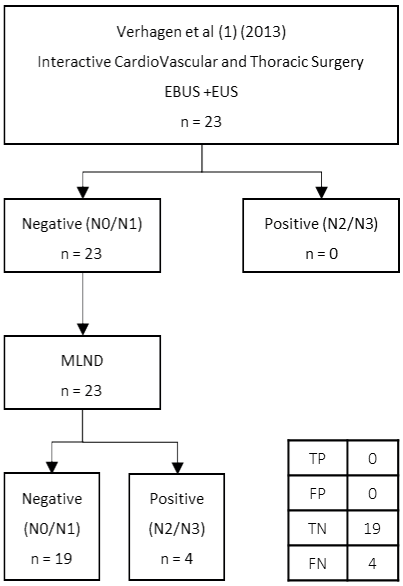

Talebian et al (5) (2015)
Lung Cancer
EBUS + EUS
n = 38
Negative (N0/N1)
n = 38
Positive (N2/N3)
n = 0
MLND
n = 38
Negative
(N0/N1)
n = 36
Positive
(N2/N3)
n = 2
TP 0
FP 0
TN 36
FN 2

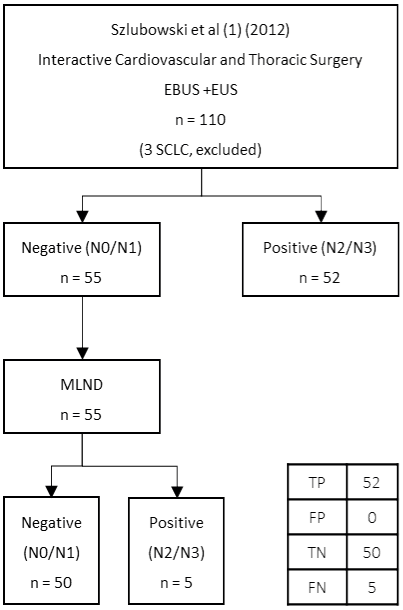

Dooms et al (1) (2015)
Chest
EBUS + EUS
n = 10
Negative (N0/N1)
n = 10
Positive (N2/N3)
n = 0
MLND
n = 10
Negative
(N0/N1)
n = 9
Positive
(N2/N3)
n = 1
TP 0
FP 0
TN 9
FN 1

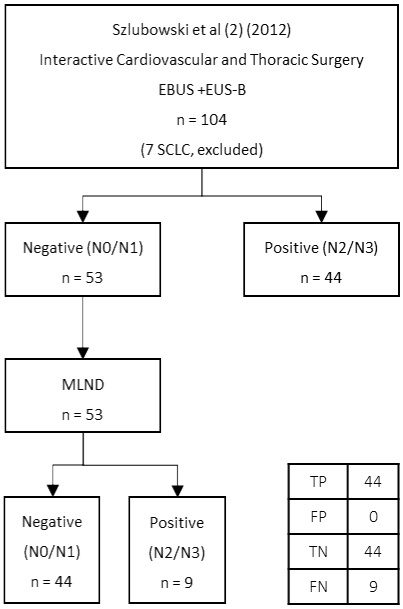

Oki et al (2014)
The Journal of Thoracic and Cardiovascular Surgery
EBUS + EUS
n = 131
Negative (N0/N1)
n = 107
Positive (N2/N3)
n = 24
MLND
n = 107
Negative
(N0/N1)
n = 100
Positive
(N2/N3)
n = 7
TP 24
FP 0
TN 100
FN 7

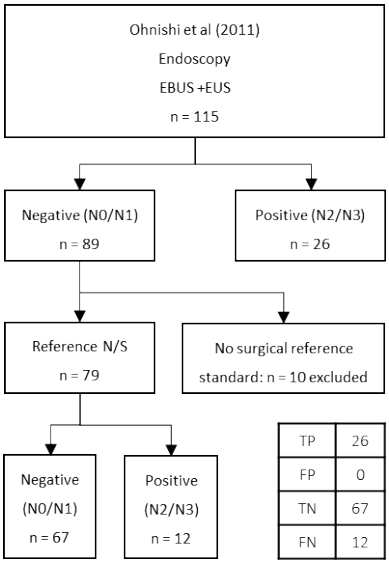

Kang et al (1) (2014)
Thorax
EBUS + EUS
n = 80
Negative (N0/N1)
n = 51
Positive (N2/N3)
n = 29
MLND
n = 45
No surgical reference
standard: n = 6 excluded
Negative
(N0/N1)
n = 40
Positive
(N2/N3)
n = 5
TP 29
FP 0
TN 40
FN 5

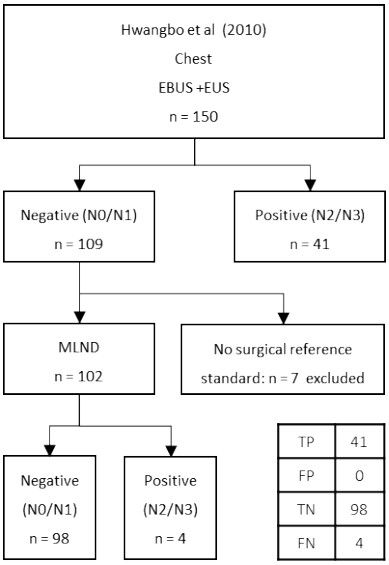

Kang et al (2) (2014)
Thorax
EUS + EBUS
n = 80
Negative (N0/N1)
n = 57
Positive (N2/N3)
n = 23
MLND
n = 51
No surgical reference standard: n = 6 excluded
Negative (N0/N1)
n = 49
Positive (N2/N3)
n =2
TP 23
FP 0
TN 49
FN 2

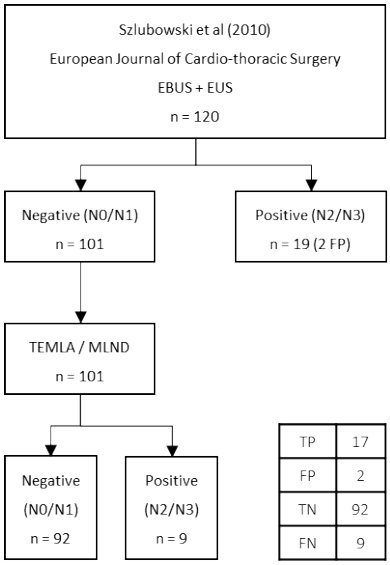

Verhagen et al (1) (2013)
Interactive CardioVascular and Thoracic Surgery
EBUS +EUS
n = 23
Negative (N0/N1)
n = 23
Positive (N2/N3)
n = 0
MLND
n = 23
Negative (N0/N1)
n = 19
Positive (N2/N3)
n = 4
TP 0
FP 0
TN 19
FN 4

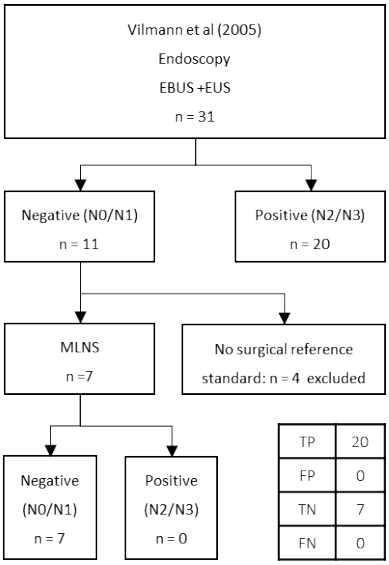

Szlubowski et al (1) (2012)
Interactive Cardiovascular and Thoracic Surgery
EBUS +EUS
n = 110
(3 SCLC, excluded)
Negative (N0/N1)
n = 55
Positive (N2/N3)
n = 52
MLND
n = 55
Negative (N0/N1)
n = 50
Positive (N2/N3)
n = 5
TP 52
FP 0
TN 50
FN 5

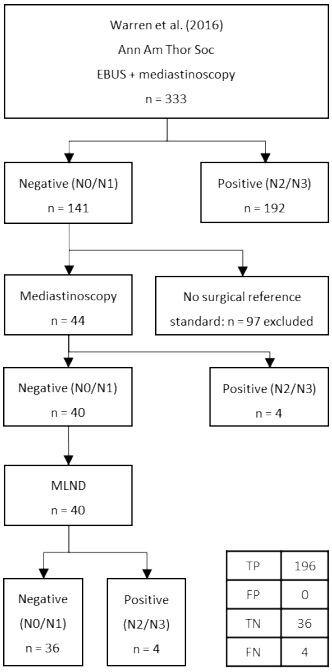

Szlubowski et al (2) (2012)
Interactive Cardiovascular and Thoracic Surgery
EBUS +EUS-B
n = 104
(7 SCLC, excluded)
Negative (N0/N1)
n = 53
Positive (N2/N3)
n = 44
MLND
n = 53
Negative (N0/N1)
n = 44
Positive (N2/N3)
n = 9
TP 44
FP 0
TN 44
FN 9

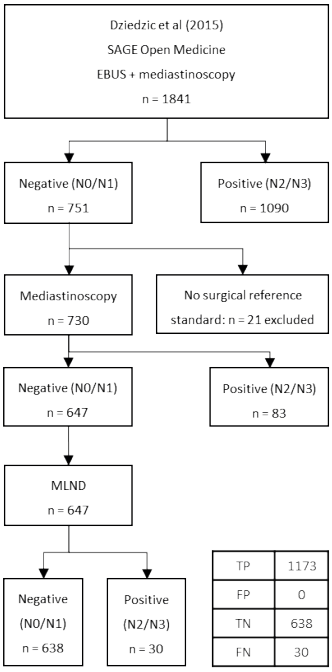

Ohnishi et al (2011)
Endoscopy
EBUS +EUS
n = 115
Negative (N0/N1)
n = 89
Positive (N2/N3)
n = 26
Reference N/S
n = 79
No surgical reference standard: n = 10 excluded
Negative (N0/N1)
n = 67
Positive (N2/N3)
n = 12
TP 26
FP 0
TN 67
FN 12

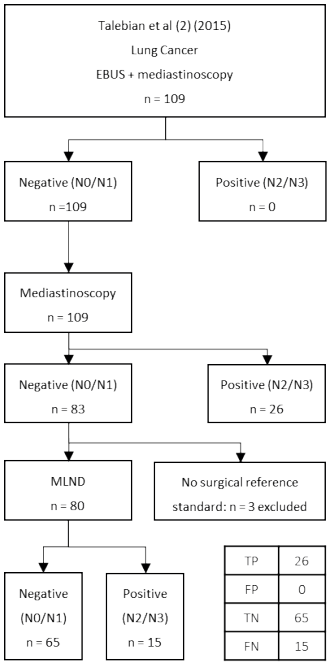

Hwangbo et al (2010)
Chest
EBUS +EUS
n = 150
Negative (N0/N1)
n = 109
Positive (N2/N3)
n = 41
MLND
n = 102
No surgical reference standard: n = 7 excluded
Negative (N0/N1)
n = 98
Positive (N2/N3)
n = 4
TP 41
FP 0
TN 98
FN 4

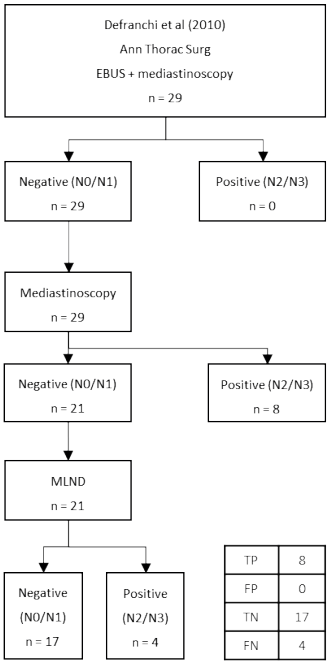

Szlubowski et al (2010)
European Journal of Cardio-thoracic Surgery
EBUS + EUS
n = 120
Negative (N0/N1)
n = 101
Positive (N2/N3)
n = 19 (2 FP)
TEMLA / MLND
n = 101
Negative (N0/N1)
n = 92
Positive (N2/N3)
n = 9
TP 17
FP 2
TN 92
FN 9

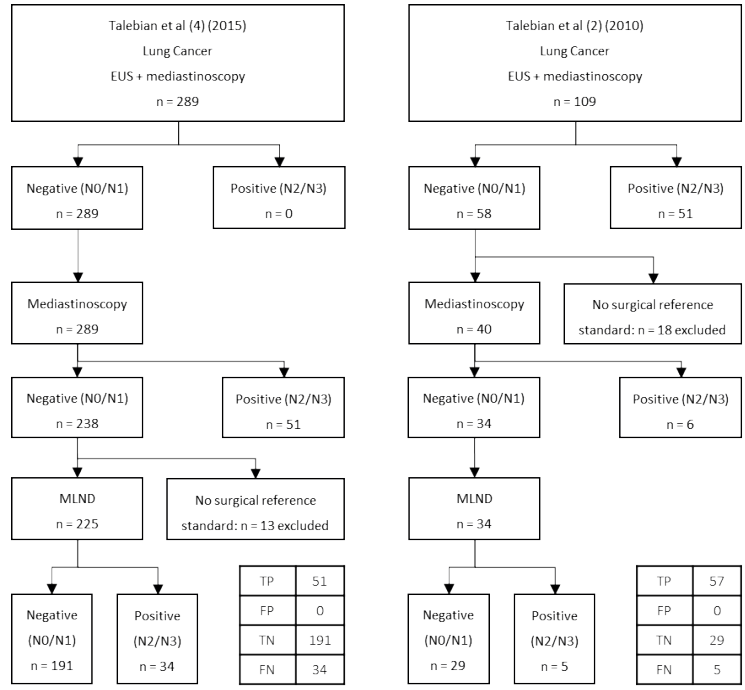

Vilmann et al (2005)
Endoscopy
EBUS +EUS
n = 31
Negative (N0/N1)
n = 11
Positive (N2/N3)
n = 20
MLNS
n =7
No surgical reference standard: n = 4 excluded
Negative (N0/N1)
n = 7
Positive (N2/N3)
n = 0
TP 20
FP 0
TN 7
FN 0

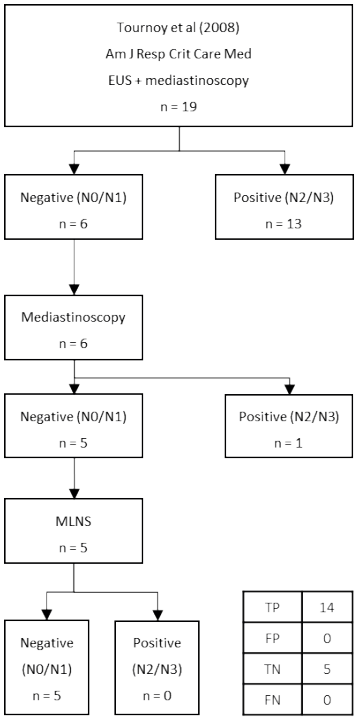

Warren et al. (2016)
Ann Am Thor Soc
EBUS + mediastinoscopy
n = 333
Negative (N0/N1)
n = 141
Positive (N2/N3)
n = 192
Mediastinoscopy
n = 44
No surgical reference standard: n = 97 excluded
Negative (N0/N1)
n = 40
Positive (N2/N3)
n = 4
MLND
n = 40
Negative (N0/N1)
n = 36
Positive (N2/N3)
n = 4
TP 196
FP 0
TN 36
FN 4

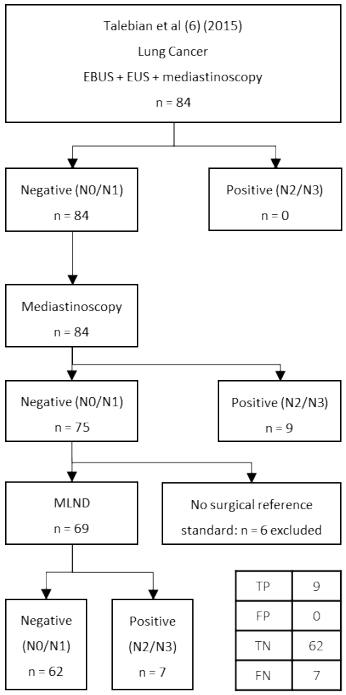

Dziedzic et al (2015)
SAGE Open Medicine
EBUS + mediastinoscopy
n = 1841
Negative (N0/N1)
n = 751
Positive (N2/N3)
n = 1090
Mediastinoscopy
n = 730
No surgical reference standard: n = 21 excluded
Negative (N0/N1)
n = 647
Positive (N2/N3)
n = 83
MLND
n = 647
Negative (N0/N1)
n = 638
Positive (N2/N3)
n = 30
TP 1173
FP 0
TN 638
FN 30

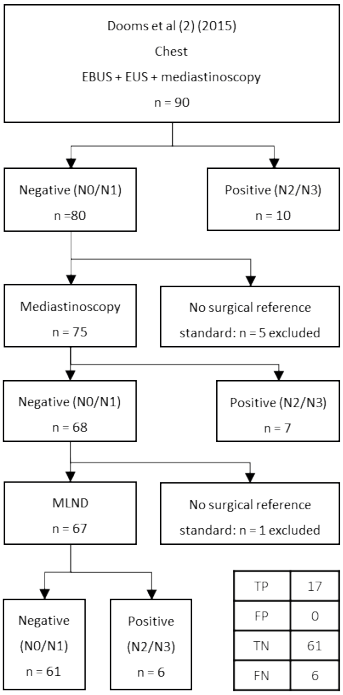

Talebian et al (2) (2015)
Lung Cancer
EBUS + mediastinoscopy
n = 109
Negative (N0/N1)
n =109
Positive (N2/N3)
n = 0
Mediastinoscopy
n = 109
Negative (N0/N1)
n = 83
Positive (N2/N3)
n = 26
MLND
n = 80
No surgical reference standard: n = 3 excluded
Negative (N0/N1)
n = 65
Positive (N2/N3)
n = 15
TP 26
FP 0
TN 65
FN 15

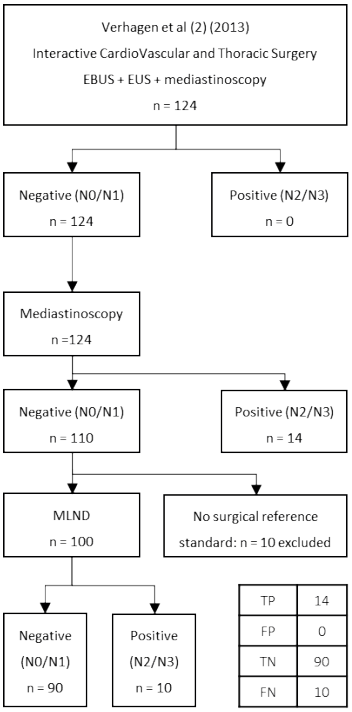

Defranchi et al (2010)
Ann Thorac Surg
EBUS + mediastinoscopy
n = 29
Negative (N0/N1)
n = 29
Positive (N2/N3)
n = 0
Mediastinoscopy
n = 29
Negative (N0/N1)
n = 21
Positive (N2/N3)
n = 8
MLND
n = 21
Negative (N0/N1)
n = 17
Positive (N2/N3)
n = 4
TP 8
FP 0
TN 17
FN 4

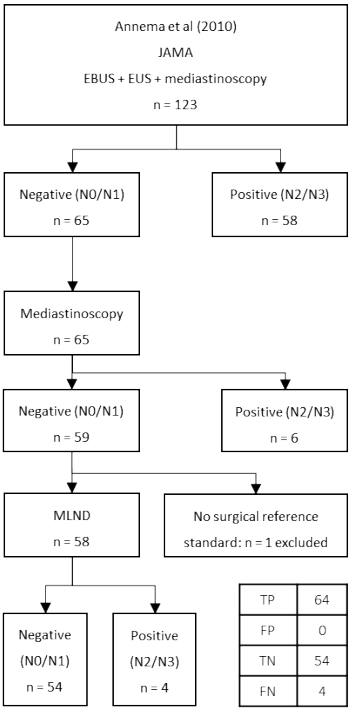

Talebian et al (4) (2015)
Lung Cancer
EUS + mediastinoscopy
n = 289
Negative (N0/N1)
n = 289
Positive (N2/N3)
n = 0
Mediastinoscopy
n = 289
Negative (N0/N1)
n = 238
Positive (N2/N3)
n = 51
MLND
n = 225
No surgical reference standard: n = 13 excluded
Negative (N0/N1)
n = 191
Positive (N2/N3)
n = 34
TP 51
FP 0
TN 191
FN 34
Talebian et al (2) (2010)
Lung Cancer
EUS + mediastinoscopy
n = 109
Negative (N0/N1)
n = 58
Positive (N2/N3)
n = 51
Mediastinoscopy
n = 40
No surgical reference standard: n = 18 excluded
Negative (N0/N1)
n = 34
Positive (N2/N3)
n = 6
MLND
n = 34
Negative (N0/N1)
n = 29
Positive (N2/N3)
n = 5
TP 57
FP 0
TN 29
FN 5


Tournoy et al (2008)
Am J Resp Crit Care Med
EUS + mediastinoscopy
n = 19
Negative (N0/N1)
n = 6
Positive (N2/N3)
n = 13
Mediastinoscopy
n = 6
Negative (N0/N1)
n = 5
Positive (N2/N3)
n = 1
MLNS
n = 5
Negative (N0/N1)
n = 5
Positive (N2/N3)
n = 0
TP 14
FP 0
TN 5
FN 0


Talebian et al (6) (2015)
Lung Cancer
EBUS + EUS + mediastinoscopy
n = 84
Negative (N0/N1)
n = 84
Positive (N2/N3)
n = 0
Mediastinoscopy
n = 84
Negative (N0/N1)
n = 75
Positive (N2/N3)
n = 9
MLND
n = 69
No surgical reference standard: n = 6 excluded
Negative (N0/N1)
n = 62
Positive (N2/N3)
n = 7
TP 9
FP 0
TN 62
FN 7

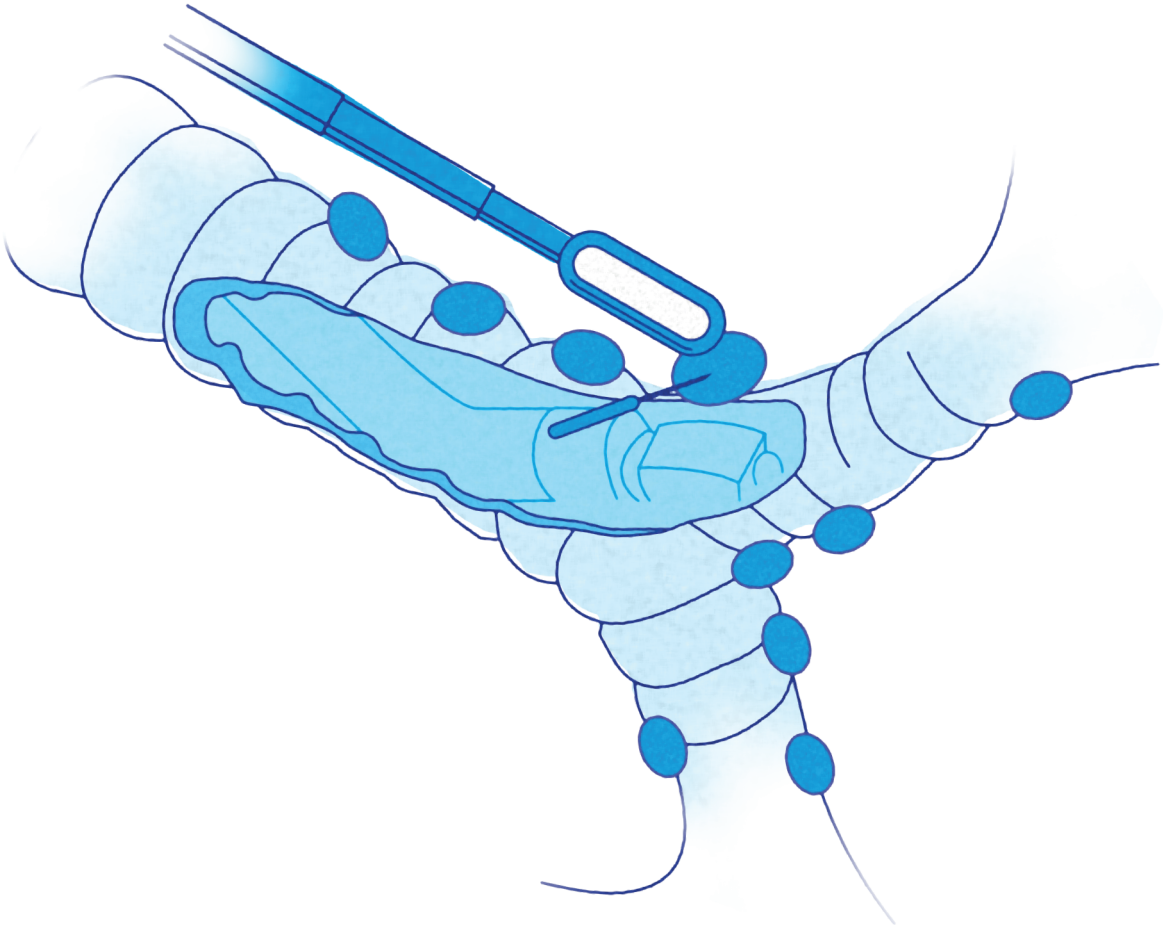

Dooms et al (2) (2015)
Chest
EBUS + EUS + mediastinoscopy
n = 90
Negative (N0/N1)
n =80
Positive (N2/N3)
n = 10
Mediastinoscopy
n = 75
No surgical reference standard: n = 5 excluded
Negative (N0/N1)
n = 68
Positive (N2/N3)
n = 7
MLND
n = 67
No surgical reference standard: n = 1 excluded
Negative (N0/N1)
n = 61
Positive (N2/N3)
n = 6
TP 17
FP 0
TN 61
FN 6


Verhagen et al (2) (2013)
Interactive CardioVascular and Thoracic Surgery
EBUS + EUS + mediastinoscopy
n = 124
Negative (N0/N1)
n = 124
Positive (N2/N3)
n = 0
Mediastinoscopy
n =124
Negative (N0/N1)
n = 110
Positive (N2/N3)
n = 14
MLND
n = 100
No surgical reference standard: n = 10 excluded
Negative (N0/N1)
n = 90
Positive (N2/N3)
n = 10
TP 14
FP 0
TN 90
FN 10


Annema et al (2010)
JAMA
EBUS + EUS + mediastinoscopy
n = 123
Negative (N0/N1)
n = 65
Positive (N2/N3)
n = 58
Mediastinoscopy
n = 65
Negative (N0/N1)
n = 59
Positive (N2/N3)
n = 6
MLND
n = 58
No surgical reference standard: n = 1 excluded
Negative (N0/N1)
n = 54
Positive (N2/N3)
n = 4
TP 64
FP 0
TN 54
FN 4

Appendix D. Details on studies divided in subgroups

Talebian et al (2015)		Multicenter retrospective analysis of patients with negative EBUS, EUS or EBUS+EUS results with or without additional mediastinoscopy	
	group **(1)**	EBUS	n = 73
	group **(2)**	EBUS + mediastinoscopy	n = 109
	group **(3)**	EUS	n = 182
	group **(4)**	EUS + mediastinoscopy	n = 289
	group **(5)**	EBUS + EUS	n = 38
	group **(6)**	EBUS + EUS + mediastinoscopy	n = 84
Dooms et al (2015)		Prospective analysis of patient with clinical N1 who underwent EBUS+EUS with or without additional mediastinoscopy	
	group **(1)**	EBUS + EUS	n = 10
	group **(2)**	EBUS + EUS + mediastinoscopy	n = 90
Kang et al (2014)		Randomised parallel controlled trial on the impact of procedure sequence and primary procedure between EBUS and EUS	
	group **(1)**	EBUS + EUS	n = 80
	group **(2)**	EUS + EBUS	n = 80
Verhagen et al (2013)		Retrospective analysis of patients with negative EBUS+EUS results with or without additional mediastinoscopy	
	group **(1)**	EBUS + EUS	n = 23
	group **(2)**	EBUS + EUS + mediastinoscopy	n = 124
Szlubowski et al (2012)		Prospective non-randomized study on EBUS + EUS versus EBUS + EUS-B	
	group **(1)**	EBUS + EUS	n = 110
	group **(2)**	EBSU + EUS-B	n = 104
Talebian et al (2010)		Retrospective analysis of patients who were initially staged with EUS with or without additional mediastinoscopy	
	group **(1)**	EUS	n = 31
	group **(2)**	EUS + mediastinoscopy	n = 109



Chapter 7

MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a multicenter randomised controlled trial

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Hermien W Schreurs
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Erik HFM van der Heijden
Willem H Steup
Jerry Braun
Valentin JJM Noyez
Fieke Hoeijmakers
Naomi Beck
Martijn van Dorp
Niels JM Claessens
Birgitta I Hiddinga
Johannes MA Daniels
David J Heineman
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Jouke T Annema
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MEDIASTrial study group

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ABSTRACT

Background In case of suspicious lymph nodes on computed tomography (CT) or fluorodeoxyglucose positron emission tomography (FDG-PET), advanced tumour size or central tumour location in patients with suspected non-small cell lung cancer (NSCLC), Dutch and European guidelines recommend mediastinal staging by endosonography (endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS)) with sampling of mediastinal lymph nodes. If biopsy results from endosonography turn out negative, additional surgical staging of the mediastinum by mediastinoscopy is advised to prevent unnecessary lung resection due to false negative endosonography findings. We hypothesize that omitting mediastinoscopy after negative endosonography in mediastinal staging of NSCLC does not result in an unacceptable percentage of unforeseen N2 disease at surgical resection. In addition, omitting mediastinoscopy comprises no extra waiting time until definite surgery, omits one extra general anaesthesia and hospital admission, and may be associated with lower morbidity and comparable survival. Therefore, this strategy may reduce health care costs and increase quality of life. The aim of this study is to compare the cost-effectiveness and cost-utility of mediastinal staging strategies including and excluding mediastinoscopy.

Methods/design This study is a multicenter parallel randomized non-inferiority trial comparing two diagnostic strategies (with or without mediastinoscopy) for mediastinal staging in 360 patients with suspected resectable NSCLC. Patients are eligible for inclusion when they underwent systematic endosonography to evaluate mediastinal lymph nodes including tissue sampling with negative endosonography results. Patients will not be eligible for inclusion when PET/CT demonstrates 'bulky N2-N3' disease or the combination of a highly suspicious as well as irresectable mediastinal lymph node. Primary outcome measure for non-inferiority is the proportion of patients with unforeseen N2 disease at surgery. Secondary outcome measures are hospitalization, morbidity, overall 2-year survival, quality of life, cost-effectiveness and cost-utility. Patients will be followed up 2 years after start of treatment.

Discussion Results of the MEDIASTrial will have immediate impact on national and international guidelines, which are accessible to public, possibly reducing mediastinoscopy as a commonly performed invasive procedure for NSCLC staging and diminishing variation in clinical practice.

Trial registration The trial is registered at the Netherlands Trial Register on July 6th, 2017 (NTR 6528).

Keywords mediastinal staging, mediastinoscopy, non-small cell lung carcinoma, endosonography, thoracic surgery.

BACKGROUND

Lung cancer is a common disease with over 12,000 new Dutch cases annually and 1.8 million worldwide. In the Netherlands 9,175 new non-small cell lung cancer (NSCLC) patients were diagnosed in 2017. [1, 2] At diagnosis about 80% of patients already have distant or regional metastases, whereas only 20% is eligible for surgical treatment with curative intent. With (the suspicion of) potential curable NSCLC, patients undergo computed tomography (CT) and fluorodeoxyglucose positron emission tomography (FDG-PET) in order to obtain information about locoregional and distant disease. In case of absence of distant metastases but presence of suspicious lymph nodes on PET/CT, Dutch and European guidelines recommend mediastinal staging by endobronchial (EBUS) and/or endoscopic esophageal ultrasonography (EUS) with sampling of suspicious mediastinal lymph nodes. [3] In patients with non-FDG-avid tumour, central tumour location or with peripheral tumours >3cm, mediastinal staging is recommended as well. In case of negative biopsy results from endosonography, surgical staging of the mediastinum by mediastinoscopy is advised to prevent possible unnecessary surgery due to false negative endosonography findings. Generally only patients without N2-3 metastases after mediastinoscopy are eligible for intended curative anatomic resection. Patients with pathologically proven N2-3 mediastinal lymph node metastases are usually recommended to undergo first line chemoradiation instead of surgery since no survival benefit has been demonstrated by additional surgery.[4] When mediastinoscopy demonstrates potentially resectable N2 metastases several treatment strategies can be followed: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery or definitive chemoradiotherapy. [5, 6]

In a randomized trial comparing endosonography (EBUS and EUS) versus surgical staging, the sensitivity for mediastinal nodal spread was 85% for endosonography and 79% for mediastinoscopy with a total cohort N2-3 prevalence of 46%. [7] Mediastinoscopy diagnosed mediastinal lymph node metastases after negative endosonography in 9.2% of patients, resulting in a combined sensitivity of 94%, which is the rationale of recommending additional mediastinoscopy after negative endosonography. However, to detect one case of single level N2 disease, 11 patients need to undergo additional surgical staging at the expense of morbidity, delay in diagnostic work-up as well as financial costs. Several more non-randomized comparative studies also demonstrated higher sensitivity for endosonography than for mediastinoscopy.[8-10] These studies have raised questions on how to identify false negative endosonography cases in order to significantly reduce or even abandon additional surgical staging.

Moreover, mediastinoscopy is associated with minor (3.2%) and major (3.5%) complications, sporadic mortality (<1%) and encompasses an additional invasive surgical procedure necessitating general anaesthesia and delaying definite curative treatment. [7, 11] Therefore, significantly reducing or even omitting the need for mediastinoscopy after negative endosonography may reduce morbidity and mortality, as well as costs.

On the other hand, if all patients with negative endosonography results would undergo an anatomic pulmonary resection without additional mediastinoscopy, at least 9.2% of patients would postoperatively turn out to have unforeseen N2 disease. In the ASTER trial, all patients with negative endosonography results and subsequent positive mediastinoscopy had single lymph node station disease and one out of three had micrometastases only.[7] Cerfolio et al. demonstrated good 5-yr survival by surgical resection and adjuvant therapy in single nodal station unforeseen N2 disease (40%) and hereby reached comparable survival as in patients with N1 disease.[12] Several others also showed favourable 5-yr survival rates in these patients.[13, 14] To strengthen these figures, recent survival data from the ASTER trial demonstrated equal 5-yr survival rates of 35% in both randomization groups, despite significantly different detection rates of upfront N2 disease.[15] Therefore, surgical treatment of minimal unforeseen N2 disease instead of definite chemoradiation is increasingly considered as treatment option as well.[5, 6] In addition, the revised European Society of Thoracic Surgery (ESTS) guideline of mediastinal staging states that there is room for trials evaluating surgical treatment instead of chemoradiation for minimal N2 disease.[16] The aim of this study is to compare the cost-effectiveness and cost-utility of mediastinal staging strategies including and excluding mediastinoscopy.

METHODS/DESIGN

Hypothesis

Omitting mediastinoscopy after negative endosonography in mediastinal staging of NSCLC does not result in an unacceptable percentage of unforeseen N2 disease at surgical resection. In addition, omitting mediastinoscopy will shorten time until definitive surgery, will prevent one general anaesthesia and hospital admission and will be associated with lower morbidity and comparable survival. Therefore, this strategy may increase quality of life and reduce health care costs.

Objective

The main objective of the proposed randomized trial is to compare the cost-effectiveness and cost-utility of mediastinal staging strategies including and excluding mediastinoscopy, provided that non-inferiority of excluding mediastinoscopy regarding unforeseen N2 disease can be demonstrated.

Study design

This will be a multicentre parallel randomized trial comparing two diagnostic strategies (with or without mediastinoscopy) for mediastinal staging in patients with suspected NSCLC, based on non-inferiority. The MEDIASTrial flowchart is shown in figure 1.

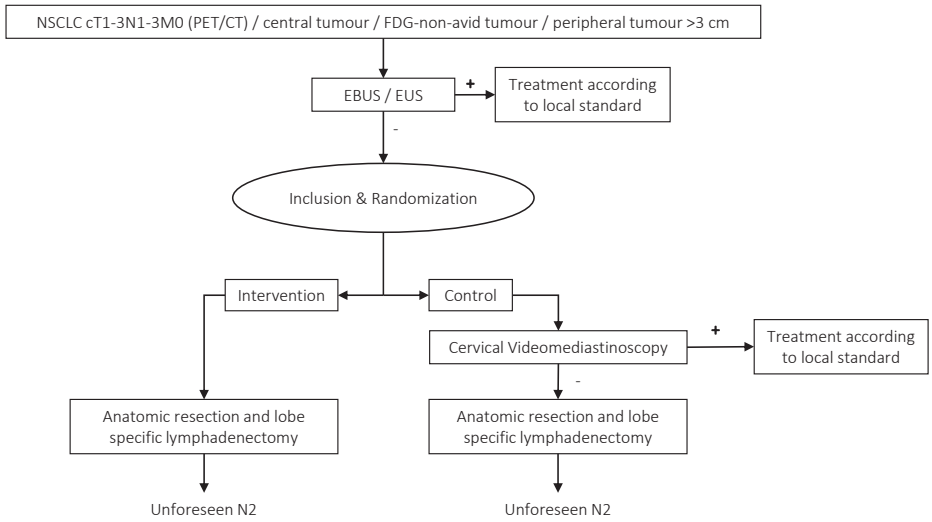

Figure 1. Flowchart

Randomization

After written informed consent, provided at the outpatient clinic, patient data are entered into a computerized database (Research Manager) and with an unchangeable computer generated number patients will be randomized (1:1) to undergo either mediastinal staging *with* or *without* additional mediastinoscopy. Randomization will be stratified by type of treatment centre and, for its potential impact on cost-effectiveness outcomes, by age below/above 66 years. Variable block size randomization will be applied.

Blinding

Blinding of patients and physicians during staging and treatment is unfeasible, since the two diagnostic strategies and dependent treatments are highly different in nature and in associated care.

Study population

Patients are eligible for inclusion in this trial when they meet the following eligibility criteria:

(1) Diagnosed (with pathological proof by bronchoscopic or transthoracic biopsy) or suspected (based on CT and FDG-PET) with NSCLC.
(2) CT and FDG-PET scan have excluded distant metastasis (stage IV disease) or an irresectable primary tumour (judged by thoracic surgeon, based on imaging).
(3) One of the criteria defining the need for mediastinal staging are met according to the European and Dutch guidelines[16, 17]:
    - PET/CT of the chest demonstrates CT-enlarged (short axis >1cm) or FDG-PET avid hilar (cN1) or mediastinal (cN2-N3) lymph nodes. PET is considered positive if the standardized uptake value (SUV) > 2.5, which is the ratio of the regional radioactivity concentration divided by the injected amount of radioactivity normalized to body weight
    - CT demonstrates a centrally located primary tumour, which is defined by visibility of the tumour on video bronchoscopy within the main stem bronchi; or tumour proximity to the mediastinum <0.5cm on CT; or location of the tumour within the inner 1/3 of the thorax. Whether the tumour fulfils these criteria will be discussed by the local multidisciplinary meetings
    - FDG-PET demonstrates a FDG non avid primary tumour.
    - Peripheral lung tumours (outer two third of the chest on CT) larger than 3cm on CT

Inclusion criteria

(1) Patients underwent systematic EBUS, preferably added by EUS, to evaluate mediastinal lymph nodes including tissue sampling with negative biopsy results. Adequate systematic EBUS / EUS is defined as evaluation of at least lymph node stations 4L, 7 and 4R by EBUS.[18] Preferably stations 4L, 7 and 8 should be evaluated by subsequent EUS as well. Lymph nodes in stations 4L, 7 and 4R larger than 8 mm as well as all CT-enlarged (>1cm) and FDG-avid (SUV>2.5) mediastinal lymph nodes should be sampled by at least 3 needle aspirations. In case of FDG-avid nodes that are smaller than 8 mm and have unsuspicious appearance on endosonography punctures are not obligatory.

(2) Patients should be fit enough to undergo resection of the primary tumour by either pneumonectomy, (bi)lobectomy or segmentectomy, judged during the local multidisciplinary meeting. Assessment of fitness includes pulmonary function testing (spirometry and diffusing capacity of the lung for carbon monoxide), followed by cardiopulmonary exercise testing (CPET) if deemed necessary by the multidisciplinary board.
(3) Patients should be able to undergo cervical mediastinoscopy (no current tracheostomy or previous mediastinoscopy)
(4) Patient age of 18 years or older and able to give informed consent and fill out questionnaires.

Exclusion criteria

(1) PET/CT demonstrates 'bulky N2-3' disease. Definition of 'bulky' N2-3 disease is copied from the definition given in the revised ESTS guideline: mediastinal infiltration of more than one mediastinal zone where the discrete lymph nodes cannot be distinguished or measured during CT or endosonography; or two or more lymph nodes with a short axis of >2.5cm in more than one mediastinal zone (according to the international association for the study of lung cancer (IASLC) node map).[16, 19]
(2) The combination of a highly suspicious as well as irresectable mediastinal lymph node. High suspicion of a lymph node is defined as FDG-PET SUV >5 and at least 3 of the following ultrasonographic malignant criteria: round shape, sharp borders, hypo- echoic texture and short axis >10mm. Whether a lymph node is irresectable is judged by the surgeon, based on extracapsular growth or growth into vital structures or due to unreachable location (for example location in lymph node station 4L in case of a right sided operation).
(3) Non-correctable coagulopathy (international normalized ratio >1.7 or platelet count $<50 \times 10^9$/l).
(4) Insufficient comprehension of the Dutch language to understand the trial information and to complete the questionnaires during follow-up period.

Participating centres

Twenty Dutch hospitals and one Belgian hospital participate in the MEDIASTrial study group, including seven academic and fourteen non-academic centres, and will enroll patients.

Intervention

Patients will undergo immediate anatomic resection of the primary tumour by either pneumonectomy, (bi)lobectomy or segmentectomy according to patient and tumour characteristics as discussed by the local multidisciplinary lung meeting in the par-

ticipating centre. If possible, patients are treated by video-assisted thoracoscopy (VATS) or robotic-assisted thoracic surgery (RATS). During the surgical procedure, at least a lobe-specific mediastinal lymph node dissection will be done according to European guidelines. [3, 20]

Usual care (comparison)

According to current national and international guidelines, patients will first undergo cervical mediastinoscopy. For this trial, only videomediastinoscopy will be used. This procedure will be done under general anaesthesia, and at least lymph node stations 2R, 4R, 4L, and 7 should be sampled for right-sided tumours, whereas at least station 4L, 4R and 7 should be sampled for left-sided tumours. Station 2L will only be removed when visualized or in case of suspicion based on PET/CT.[3, 16]

When histopathological examination of the resected lymph nodes does not demonstrate metastases, patients will undergo additional anatomic lung resection and at least, a lobe-specific lymph node dissection as described under 'intervention', which will serve as reference standard in both randomization groups.

When histopathology after mediastinoscopy demonstrates N2-3 metastases, patients are generally recommended to undergo definite chemoradiation. When mediastinoscopy demonstrates potentially resectable N2 metastases several treatment strategies can be followed: surgery and adjuvant chemotherapy, induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery or definitive chemoradiotherapy.[5, 6] Discussion within the local multidisciplinary meeting will decide exact treatment in these cases. Differences in treatment between participating centres will be adjusted by stratification per setting (academic, non-academic). These patients will be followed according to the routine follow-up scheme of this study.

Informed consent procedure

Consecutive patients will be checked for eligibility during the multidisciplinary meetings in the participating centres by the involved physicians (surgeon, pulmonologist, radiation oncologist, radiologist, nuclear medicine physician and pathologist). All patients fulfilling the inclusion criteria will subsequently be informed about the trial by their local pulmonologist or surgeon at the next outpatient clinic visit (depending on local logistics). After informed consent is given, randomization will take place by a computerized randomization program, using Research Manager Software and patients will be further staged and treated according to the study protocol. Patients unable or refusing to provide informed consent will be treated according to current clinical guidelines, which is additional surgical staging by mediastinoscopy.

Quality assurance

All participating centres should adhere to the European Association of Nuclear Medicine procedure guidelines of FDG-PET/CT for tumour imaging to guarantee high quality of performing, interpreting and reporting FDG-PET/CT-scan.[21] To assure high quality of endosonography, endoscopists have been trained in EBUS and EUS during their training as pulmonologist. Additionally, endoscopists participating in this study have performed a specific endosonography lung cancer staging training module. Also they have passed an EBUS skill and assessment tool (EBUSAT) evaluating structural EBUS anatomy and standardised mediastinal nodal sampling. The EBUSAT has demonstrated reliable and valid assessment of competence.[18] On individual basis, both EBUS simulator training and clinical EBUS-EUS training will be offered if necessary. To assure high quality of mediastinoscopy and lymphadenectomy, surgical protocols and demands have been written and will be monitored during the trial.

Outcome parameters

The following baseline characteristics will be collected; gender, age at time of randomization, height, weight, location of the primary tumour, World Health Organization (WHO) performance state, American Society of Anaesthesiologists (ASA) classification and Tumour, Node, Metastases (TNM) classification (eight edition). Schedule of events is shown in figure 2. To perform the cost-effectiveness and cost-utility analysis, the following primary and secondary outcome measures are chosen:

Primary outcome measure (for non-inferiority)

As the goal of accurate mediastinal staging is the prevention of performing lung surgery in patients with N2 disease (e.g. unforeseen N2), the proportion of patients with unforeseen N2 disease after final lung resection and mediastinal lymphadenectomy is considered as primary outcome measure for the non-inferiority design of this trial.

Secondary outcome measures

(1) The total number of days of hospital care, defined as the total number of days in hospital after randomization during a follow up period of 2 years. Every day in hospital (including outpatient clinic visits and day care treatments) related to NSCLC diagnosis, treatment or follow-up will be counted.
(2) Costs of mediastinal staging strategies (including or excluding surgical mediastinal staging) from a societal perspective, based on primary data (see also economic evaluation).
(3) Morbidity: the combination of major morbidity and 30-day mortality is chosen as composite outcome measure. Major morbidity is defined as the proportion of patients having morbidity of grade III-IV (Clavien-Dindo classification) or recurrent

laryngeal nerve injury, which is a specific serious adverse event associated with mediastinoscopy. [22]

(4) Overall 2-year survival, defined as the proportion of patients alive at 2 years follow-up, and 2-year disease-free survival, defined as the proportion of patients alive without evidence of relapse of disease at 2 years follow-up. Follow-up is done by pulmonologists at 3 monthly intervals during the first year and 6 monthly intervals during the second year. Hereafter, yearly follow-up will be done until 5 years after treatment. This follow-

(5) up scheme is in concordance with the Dutch guideline of NSCLC. Finally, 5-year overall and disease-free survival will be measured after 5 years of follow-up.

(6) Generic and disease-specific health related quality of life will be measured at baseline, 1 week after mediastinoscopy (only randomization group including mediastinoscopy), 2 weeks after start treatment (e.g. anatomic resection or chemo- and/or radiotherapy), at 4 weeks, at 3 months, at 6 months, at 1 year and at 2 year follow-up by the EQ-5D-5L, EORTC QLQ-C30 and QLQ-LC13 questionnaires.

	Enrollment	Baseline	Mediastinoscopy	1 W after mediastinoscopy	Therapy	2 W after start treatment[1]	4 W after start treatment[1]	3 M after start treatment[1]	6 M after start treatment[1]	12 M after start treatment[1]	24 M after start treatment[1]
		T0	T1	T2	T3	T4	T5	T6	T7	T8	T9
Informed consent	X										
Baseline data		X									
eCRF EBUS/EUS		X									
eCRF Mediastinoscopy			X								
eCRF PA Mediastinoscopy				X							
eCRF Therapy					X						
eCRF PA Surgery						X					
eCRF Follow-up[2]				X		X		X	X	X	X
EQ-5D-5L		+		+		+	+	+	+	+	+
EORTC QLQ-C30		+		+		+	+	+	+	+	+
EORTC QLQ-LC13		+		+		+	+	+	+	+	+
iMTA – iMCQ		+					+	+	+	+	+
iMTA – iPCQ		+					+	+	+	+	+
		Wave 1		Wave 2		Wave 3	Wave 4	Wave 5	Wave 6	Wave 7	Wave 8

Figure 2. Schedule of events

[1] Number of weeks or months after start treatment, i.e. surgical partial lung resection, chemotherapy or radiotherapy; [2] eCRF Follow-up contains information about survival, recurrence of disease and serious adverse events; [x] Digital report by local investigator; [+] Digital or written report by patient.

Sample size calculation

In the ASTER trial, surgical staging with mediastinoscopy had a sensitivity of 79% for detecting N2 disease vs. 94% for the combined use of endosonography and mediastinoscopy in a population with 75% PET/CT N2-3 disease positives.[7] Negative histology after staging was followed by surgical mediastinal lymphadenectomy, which provided the best possible reference standard. The difference in sensitivities between the two staging strategies in this trial led to unforeseen N2 rates of 14.3% after surgical staging versus 6.9% after endosonography ánd mediastinoscopy. Despite this difference in diagnostic staging, 5-year survival rates were completely equal (35% vs. 35%).[15] Therefore, for our trial we assume that the proportion of unforeseen N2 after omitting mediastinoscopy (experimental arm in our trial) may not exceed 14.3% as upper limit of its 95%-confidence interval (non-inferiority) in order to have no negative impact on survival.

We conducted a systematic review about mediastinal staging (unpublished data). Herein we found a proportion of unforeseen N2 of 6.3% after endosonography combined with mediastinoscopy (control group). We found 6.8% unforeseen N2 nodes in patients staged with endosonography alone, without mediastinoscopy. With these results, we calculated to include 171 patients in each randomization group (power 80%; alpha error 0.025). Based on an assumed 5% drop-out rate of patients after randomization, we aim to include a total of 360 patients.

Ethics

This study will be performed in accordance with the declaration of Helsinki, 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO, the Netherlands). The medical ethical committee of the Maxima Medical Center has approved the study protocol (Medical Ethical Committee (MEC) number W17.063). Important protocol modifications will be communicated as soon as possible with the local investigators and the Dutch Trialregister. Prior to randomization, written informed consent will be obtained from all patients.

Data safety

After written informed consent, patients will be assigned a study number and clinical data will be registered pseudonymous via Research Manager software. Research Manager software is certified by the 'Information Security Management System 27001'. The key to the code is safeguarded by the local principal investigator. Quality of Life and Health Economics questionnaires will be coordinated by the Netherlands Comprehensive Cancer Organisation (IKNL), having extensive experience in acquiring information on quality of life in cancer patients in general. The gathered data will be collected in the

PROFILES registry by IKNL. The PROFILES registry recently obtained the 'Data Seal of Approval'. Monitoring will be done by IKNL according to the MEDIASTrial monitoring plan.

All centers will be visited 3 months after inclusion of the third patient. In case centers have high or low inclusion rate or queries in datamanagment, additional monitor visits will be done. Monitoring will take place with specific attention to informed consent, data monitoring and completeness of case record form. Local data management will be done by IKNL, having extensive experience with management of local data collection. Collection, storage and analysis of data will be done according to the MEDIASTrial data management plan. No data safety monitoring board will be established, since this is a diagnostic trial of usual care evaluating diagnostic strategies with an expected low complication rate. Research data can be presented or published in agreement with the principal investigator (FvdB) only. No research data that can be traced to individual persons will be presented or published. The research data will be reported following the CONSORT guidelines.

Patient safety

The sponsor/coordinating investigator has an insurance which is in accordance with the legal requirements in the Netherlands (article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

The sponsor/coordinating investigator will report the concerning SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor/coordinating investigator has first knowledge of the SAEs.

In case subjects withdraw from study participation, these patients will undergo treatment and follow-up according to local treatment and follow-up protocols. These individuals will be asked for permission to just register their information on actual treatment and regular follow-up, in order to report outcome of withdrawn cases.

Data-analysis

The number of patients with pathologically proven N2 disease after final lung resection and lobe specific mediastinal lymphadenectomy divided by the total number of patients who underwent lung resection with lobe specific mediastinal lymphadenectomy is

considered the proportion of patients with unforeseen N2 (primary outcome measure). These proportions will be compared between the two randomization groups by the Chi square test, based on intention to treat (ITT). Considering that a non-inferiority hypothesis is tested a per protocol analysis (PP) will also be performed. Both, the ITT and the PP analyses should indicate non-inferiority before the diagnostic strategy without mediastinoscopy will be assessed as non-inferior to the strategy with mediastinoscopy. Incongruent results from the ITT and PP analyses will be discussed. No interim analysis is planned.

The total number of days of hospital care will be counted after randomization during a follow up period of 2 years. The mean (or median) number of days plus standard deviation (or interquartile range) will be compared between groups by the Student's t-test or Mann Whitney U test depending on the distribution (normally of skewed) of data. The number of patients with either major morbidity or death within 30 days from definite surgery divided by the total number of randomized patients is considered as the proportion of patients with either major morbidity or 30-day mortality (composite outcome measure). These proportions will be compared between the two randomization groups by Chi-square testing. The number of patients alive and the number of patients alive without evidence of relapse of disease after 2 years follow-up divided by the total number of randomized patients are considered as overall and disease-free 2 year survival rates. The log rank test will be used to compare the study arms, based on intention to treat. Generic and disease-specific health-related quality of life will be measured by EQ-5D-5L, EORTC QLQ-C30 and QLQ-LC13 questionnaires and provide continuous variables that will be compared between the randomization groups by generalized linear mixed modelling. All analyses of secondary outcomes will be carried out on an intention-to-treat basis.

Economic evaluation

The economic evaluation of both mediastinal staging strategies will be performed as a cost-effectiveness analysis as well as a cost-utility analysis from a societal perspective. The primary outcomes for the cost-effectiveness and cost-utility analyses are the costs per patient without unforeseen N2 and the costs per QALY. The costs per patient free of major complications/death and the costs per patient alive after 2 years follow-up will be considered as secondary outcome measures.

The cost-analysis will include health care costs, out-of-pocket expenses and costs of production loss. The direct medical costs will include the costs of all diagnostic procedures, therapeutic (repeat) interventions, medication, admissions, day care treatments, specialist consultations, and out-of-hospital care (like general physician, physiotherapy)

during follow-up. Out-of-pocket expenses will include the costs of health-related travel, over-the-counter medication etc. Volume data will be gathered with clinical report forms, available hospital information systems, and the iMTA Medical Consumption Questionnaire (iMCQ) and iMTA Productivity Cost Questionnaire (iPCQ) adjusted to the study setting. The Dutch costing guideline for health care research will be used to determine the relevant unit costs. In case of the mediastinal staging strategy however, micro-costing (general anaesthesia, surgical equipment, procedure duration, involved personnel, overhead) in participating centres will be done to estimate real unit costs. The friction costs method will be applied to derive the costs of lost productivity. After price-indexing all costs will be expressed in 2018 Euros. Incremental cost-effectiveness ratios will be calculated with uncertainty margins based on non-parametric bias-corrected and accelerated bootstrapping. Cost-effectiveness acceptability curves will be drawn to show the probability of a strategy being cost-effective at various levels of willingness-to-pay per QALY up to 100,000 euro. In case both mediastinal staging strategies turn out clinically equivalent, the study will be performed as a cost-minimization analysis.

DISCUSSION

The MEDIASTrial will study whether mediastinoscopy can be omitted after negative endosonography in mediastinal staging in patients with NSCLC. Since debate exists on the additional value of mediastinoscopy, this trial will provide definite evidence on this topic.[23-27] The current literature suggests that diagnostic strategies with or without mediastinoscopy may be equivalent concerning efficacy and that abandoning mediastinoscopy appears favourable concerning morbidity and speed of diagnostic process. As a result, variety in daily practice already exists in the extent of use of mediastinoscopy throughout and within countries.[7, 28, 29] A formal comparison of cost-effectiveness and cost-utility has however never been performed and no ongoing studies comparing these two strategies have been registered in trial registers so far. Results of such a trial will have immediate impact on national and international guidelines, which are accessible to public, possibly abandoning mediastinoscopy as a commonly performed invasive procedure and diminishing variation in clinical practice.

List of abbreviations

NSCLC: non-small cell lung cancer; CT: computed tomography; FDG-PET: fluorodeoxy-glucose positron emission tomography; EBUS: endobronchial ultrasound; EUS: endoscopic (esophageal) ultrasonography; ESTS: European Society of Thoracic Surgery; SUV: standardized uptake value; CPET: Cardiopulmonary Exercise Testing; IASLC: International Association for the Study of Lung Cancer; EBUSAT: EBUS skill and assessment

tool; VATS: video-assisted thoracoscopy; RATS: robotic-assisted thoracic surgery; WHO: World Health Organization; ASA: American Society of Anaesthesiologists; TNM: Tumour, Node, Metastases; WMA: World Medical Association; MEC: Medical Ethical Committee; EQ-5D-5L: Euroqol 5 Dimensions 5 Levels; EORTC: European Organization for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire; iMCQ: institute Medical Technology Assessment Medical Consumption Questionnaire; iPCQ: institute Medical Technology Assessment Productivity Cost Questionnaire; IKNL: Netherlands Comprehensive Cancer Organisation.

Declarations

Ethics approval and consent for participation

The medical ethical committee of the Maxima Medical Center has approved the study protocol and all participating centers (MEC number W17.063) on June, 15th, 2017. All participating centers signed the research contract prior to start inclusion. Before randomization, written informed consent will be obtained from all patients.

Data and version identifier

After first approval of the medical ethical committee two substantial amendments have been approved. The first amendment (approved on July, 24th, 2017) contained the inclusion of five new participating centers and the conversion of stratification strategy to stratification per type of center. The second amendment (approved on September, 25th, 2017) contained the inclusion of two new participating centers and the addition of exclusion criterion of insufficient comprehension of the Dutch language.

Consent for publication

Not applicable.

Availability of data and material

The datasets and/or analysed data will be available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

JB, FvdB, NPB, JA and MD have made substantial contributions to the conception and design of this study; have been involved in drafting the manuscript (JB, FvdB) or revising it critically for important intellectual content (JA and MD); and have given final approval of the version to be published. FvdB will act as trial principal investigator. MD drafted the economic analysis, the adjusted health care consumption questionnaire and will guide the health economic analyses. VN, WS, JB, FH, NB, WS, MvD, JM, AV, EH, NC, BH, HD, DH, HZ and PvS have made contributions to the design and organisation of this study in several meetings. The members of the MEDIASTrial study group are local investigators in participating centres and approved the final manuscript.

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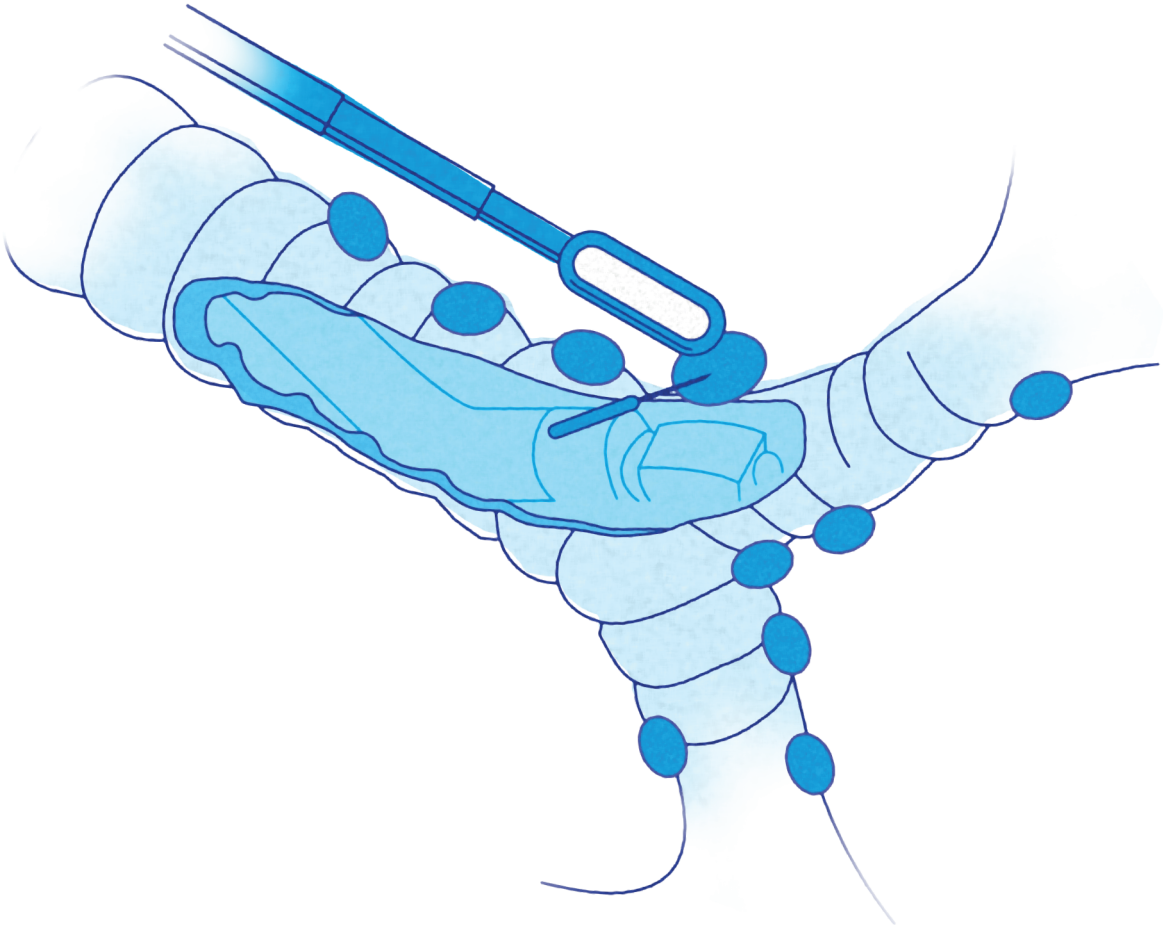
REFERENCES

1. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, Bonaventure A, Valkov M, Johnson CJ, Estève J, Ogunbiyi OJ, Azevedo e Silva G, ChenWQ, Eser S, Engholm G, Stiller CA, Monnereau A, Woods RR, Visser O, Lim GH, Aitken J, Weir HK, Coleman MP, CONCORD Working Group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet 2018, 391(10125):1023.
2. Cijfers over Kanker (Dutch Cancer Registry). Netherlands Comprehensive Cancer Organisation (IKNL), Eindhoven. 2018. http://www.cijfersoverkanker.nl. Accessed 21 Feb 2018.
3. Vilmann P, Clementsen P, Colella S, Siemsen M, De Leyn P, Dumonceau J, Herth F, Larghi A, Vazquez-Sequeiros E, Hassan C, Crombag L, Korevaar D, Konge L, Annema J: Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015, 47(6):c1.
4. Van Meerbeeck J, Kramer G, Van Schil P, Legrand C, Smit E, Schramel F, Tjan-Heijnen V, Biesma B, Debruyne C, Zandwijk N, Splinter T, Giaccone G: Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. National Cancer Institute. Journal (Print) 2007, 99(6):442-450.
5. Eberhardt WEE, De Ruysscher D, Weder W, Le Péchoux C, De Leyn P, Hoffmann H, Westeel V, Stahel R, Felip E, Peters S: 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 2015, 26(8):1573-1588.
6. Van Schil P, Lauwers P, Yogeswaran SK, Berzenji L, Hendriks JM: Surgical Management of Stage IIIA Non-Small Cell Lung Cancer. Frontiers in Oncology 2017, 7.
7. Annema JT, Van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, De Leyn P, Braun J, Carroll NR, Praet M, de Ryck F, Vansteenkiste J, Vermassen F, Versteegh MI, Veseliç M, Nicholson AG, Rabe KF, Tournoy KG: Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. JAMA 2010, 304(20):2245-2252.
8. Um S, Kim H, Jung S, Han J, Lee K, Park H, Choi Y, Shim Y, Ahn M, Park K, Ahn Y, Choi J, Lee K, Suh G, Chung M, Kwon O, Kim J, Kim H: Endobronchial Ultrasound versus Mediastinoscopy for Mediastinal Nodal Staging of Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology 2015, 10(2):331-337.
9. Yasufuku K, Pierre A, Darling G, de Perrot M, Waddell T, Johnston M, da Cunha Santos G, Geddie W, Boerner S, Le LW, Keshavjee S: A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. The Journal of Thoracic and Cardiovascular Surgery 2011, 142(6):1400.e1.
10. Tournoy KG, De Ryck F, Vanwalleghem LR, Vermassen F, Praet M, Aerts JG, Van Maele G, Van Meerbeeck JP: Endoscopic Ultrasound Reduces Surgical Mediastinal Staging in Lung Cancer: A Randomized Trial. American Journal of Respiratory and Critical Care Medicine 2008, 177(5):531-535.
11. Steunenberg B, Aerts J, Aerts B, De Groot H, Boot C, Romme P, Veen E: Quality Assessment of Video Mediastinoscopy Performed for Staging in Non-Small Cell Lung Cancer. Thorac cardiovasc Surg 2016, 64(6):520-525.

12. Cerfolio RJ, Bryant AS: Survival of Patients With Unsuspected N2 (Stage IIIA) Nonsmall-Cell Lung Cancer. The Annals of Thoracic Surgery 2008, 86(2):362-367.
13. Deok Heon Lee, Jae Bum Kim, Dong Yoon Keum, Ilseon Hwang, Chang Kwon Park: Long Term Survival of Patients with Unsuspected N2 Disease in Non-Small Cell Lung Cancer. Korean J Thorac Cardiovasc Surg 2013, 46(1):49-55.
14. Obiols C, Call S, Rami-Porta R, Trujillo-Reyes JC, Saumench R, Iglesias M, Serra-Mitjans M, Gonzalez-Pont G, Belda-Sanchís J: Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. The Annals of thoracic surgery 2014, 97(3):957-964.
15. Kuijvenhoven JC, Korevaar DA, Tournoy KG, Malfait TLA, Dooms C, Rintoul RC, Annema JT: Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer. JAMA 2016, 316(10):1110-1112.
16. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, Turna A, Van Schil P, Venuta F, Waller D, Weder W, Zielinski M: Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2014, 45(5):787-798.
17. Integraal Kanker Centrum Nederland, (IKNL): Richtlijn NSCLC (niet-kleincellig longcarcinoom). 2011, .
18. Konge L, Clementsen PF, Ringsted C, Minddal V, Larsen KR, Annema JT: Simulator training for endobronchial ultrasound: a randomised controlled trial. European respiratory journal 2015, 46(4):1140-1149.
19. Rusch V, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Postmus PE, Goldstraw P: The IASLC Lung Cancer Staging Project A Proposal for a New International Lymph Node Map in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology 2009, 4(5):568-577.
20. Rami-Porta R, Wittekind C, Goldstraw P: Complete resection in lung cancer surgery: proposed definition. Lung Cancer 2005, 49(1):25-33.
21. Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, Verzijlbergen FJ, Barrington SF, Pike LC, Weber WA, Stroobants S, Delbeke D, Donohoe KJ, Holbrook S, Graham MM, Testanera G, Hoekstra OS, Zijlstra J, Visser E, Hoekstra CJ, Pruim J, Willemsen A, Arends B, Kotzerke, J.o., ,rg, Bockisch A, Beyer T, Chiti A, Krause BJ: FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015, 42(2):328-354.
22. Dindo D, Demartines N, Clavien P: Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 2004, 240(2):205-213.
23. Rusch VW: Mediastinoscopy: An obsolete procedure? The Journal of Thoracic and Cardiovascular Surgery 2011, 142(6):1400-1402.
24. Verhagen, A F T M, Schuurbiers OCJ, Looijen-Salamon MG, Heide, S M van der, Swieten HAv, Heijden, E H M van der: Mediastinal staging in daily practice: endosonography, followed by cervical mediastinoscopy. Do we really need both? Interactive Cardiovascular and Thoracic Surgery 2013, 17(5):823-828.
25. Annema JT, de Leyn P, Clementsen P, Siemsen M, Vilmann P: Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European respiratory journal 2015, 46(6):1848-1849.
26. Li WWL, Heijden, H F M van der, Verhagen AF: Mediastinoscopy after negative endoscopic mediastinal nodal staging: can it be omitted? European Respiratory Journal 2015, 46(6):1846-1848.

27. Kim H: Reply to “Are We at the Dusk of Mediastinoscopy in Modern Clinical Practice?”. Journal of Thoracic Oncology 2015, 10(9):e92.
28. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R: Endosonography Versus Mediastinoscopy in Mediastinal Staging of Lung Cancer: Systematic Review and Meta-Analysis. The Annals of Thoracic Surgery 2016, 102(5):1747-1755.
29. Nasir B, Yasufuku K, Liberman M: When Should Negative Endobronchial Ultrasonography Findings be Confirmed by a More Invasive Procedure? Ann Surg Oncol 2018, 25(1):68-75.



Chapter 8

Mediastinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): a Statistical Analysis Plan

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ABSTRACT

Background Invasive mediastinal nodal staging is recommended by guidelines in selected patients with resectable non-small cell lung cancer (NSCLC). Endosonography is recommended as initial staging technique, followed by confirmatory mediastinoscopy in case of negative N2 or N3 cytology after endosonography. Confirmatory mediastinoscopy however is under debate owing its limited additional diagnostic value, its associated morbidity and its delay in the start of lung cancer treatment. The MEDIASTrial examines whether confirmatory mediastinoscopy can be safely omitted after negative endosonography in mediastinal nodal staging of NSCLC. The present work is the proposed statistical analysis plan of the clinical consequences of omitting mediastinoscopy, which is submitted before closure of the MEDIASTrial and before knowledge of any results was done to enhance transparency of scientific behaviour.

Methods The primary outcome measure of this non-inferiority trial will be unforeseen N2 disease resulting from lobe-specific mediastinal lymph node dissection. For non-inferiority the upper limit of the 95%-confidence interval of the unforeseen N2 rate in the group without mediastinoscopy should not exceed 14.3% in order to probably have no negative impact on survival. Since this is a non-inferiority trial both an intention to treat (ITT) and a per protocol (PP) analyses will be done. The ITT and the PP analyses should both indicate non-inferiority before the diagnostic strategy omitting mediastinoscopy will be interpreted as non-inferior to the strategy with mediastinoscopy. Secondary outcome measures include 30-day major morbidity and mortality, the total number of days of hospital care, overall and disease free 2-year survival, generic and disease-specific health related quality of life and cost-effectiveness and cost-utility of staging strategies with and without mediastinoscopy.

Discussion The MEDIASTrial will determine if confirmatory mediastinoscopy can be omitted after tumour negative systematic endosonography in invasive mediastinal staging of patients with resectable NSCLC.

BACKGROUND

Mediastinal nodal staging of non-small cell lung cancer (NSCLC) is important to determine treatment and prognosis. The European guidelines recommend invasive staging in patients with suspicious hilar or mediastinal lymph nodes on imaging (cN1-3) or centrally located, FDG-non-avid or large (>3 cm) peripherally located tumours.(1,2) Endosonography is recommended over surgical staging as initial staging technique. In case of tumour negative endosonography findings (no malignant N2 or N3 cytology) confirmatory mediastinoscopy is recommended in patients with cN1-3 and should be considered in patients with centrally located, FDG-non-avid or peripheral tumours >3 cm to rule out false negative endosonography.(1) The use of confirmatory mediastinoscopy however is under debate owing its limited additional diagnostic value (number needed to test of 11), its associated complications (6.0%) or mortality and its delay in the start of definite treatment.(3,4) The MEDIASTrial examines whether mediastinoscopy can be safely omitted after negative endosonography in invasive mediastinal nodal staging of NSCLC, based on non-inferiority.(5) The present work is the proposed statistical analysis plan (SAP) of the clinical consequences of omitting mediastinoscopy, which will be published before closure of the MEDIASTrial and before outcome measure data were available.

Summary study protocol

The MEDIASTrial (MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy) is a multicentre randomised, parallel-arm, non-inferiority study in 342 patients with proven or suspected NSCLC. The complete study protocol was already published open access.(5) The hypothesis was: *"Omitting mediastinoscopy after negative endosonography in mediastinal staging of NSCLC does not result in an unacceptable percentage of unforeseen N2 disease at surgical resection (pN2). In addition, omitting mediastinoscopy will shorten time until definitive surgery, will prevent one general anaesthesia and hospital admission and will be associated with lower morbidity and comparable survival. Therefore, this strategy may increase quality of life and reduce health care costs."*

Patients with proven or suspected, resectable (judged by the thoracic surgeon on available imaging) NSCLC without distant metastases and with an indication for invasive mediastinal staging (i.e. cN1-3 or centrally located, FDG-non-avid or large (>3 cm) peripherally located tumour) were eligible for inclusion. Prior to inclusion systematic endosonography with tissue sampling was performed (if indicated), resulting in tumour negative findings (no malignant N2 or N3 lymph nodes).

Patients with suspected metastases to lymph node stations 5 and 6 (i.e. aortopulmonary window) on imaging were eligible for inclusion. If metastatic spread to these nodal stations would lead to changes in treatment strategy according to the local multidisciplinary board extended invasive staging (i.e. parasternal mediastinotomy/scopy or VATS) should have been performed. In patients randomized in the group with mediastinoscopy, the regular cervical mediastinoscopy should have been expanded to investigate lymph node stations 5 and 6. Patients randomized in the group without confirmatory mediastinoscopy additional staging of station 5 and 6 should have been done in a separate session or by using intra-operative frozen section analysis prior to the anatomic lung resection. If metastatic spread to station 5 or 6 would not influence treatment, patients were treated as described by the study protocol with or without confirmatory mediastinoscopy depending on randomisation outcome.

Exclusion criteria were 'bulky N2-N3 disease' on FDG-PET/CT, the combination of highly suspicious as well as irresectable mediastinal lymph nodes, non-correctable coagulopathy or insufficient comprehension of the Dutch language.

After inclusion, patients were 1:1 randomised to undergo either mediastinal staging with or without confirmatory mediastinoscopy. Randomisation was stratified by type of centre (Dutch academic, Dutch non-academic, Belgian academic) and by age up to or above 66 years. Patients assigned to staging with confirmatory mediastinoscopy received usual care conform existing guidelines. When histopathology after mediastinoscopy did not demonstrate N2 or N3 lymph node metastases patients were recommended to undergo an anatomic resection of the primary tumour including lobe-specific lymph node dissection. Patients in the intervention-arm of the MEDIASTrial underwent immediate anatomic resection of the primary tumour including lobe-specific lymph node dissection without confirmatory mediastinoscopy.

The primary outcome measure for non-inferiority is the proportion unforeseen N2 disease, which is defined as pathologically proven N2 disease resulting from lobe-specific mediastinal lymph node dissection at time of tumour resection when previous invasive mediastinal nodal staging showed N0 or N1 disease. The pathological N stage results from the pathology report after pathological investigation, which was standardised by "The nationwide network and registry of histo- and cytopathology in the Netherlands". (6) Isolated cancer cell and micro-metastases were classified as positive findings when detected in lymph node dissection specimens.

Secondary endpoints include major morbidity and 30-day mortality, the total number of days of hospital care during 2-year follow up, overall 2-year survival and generic and

disease-specific health related quality of life. Additionally, a cost-effectiveness and cost-utility analysis of mediastinal staging strategies with and without mediastinoscopy will be done; this health economic perspective will be reported separately and falls beyond the scope of this analysis plan for assessing the clinical consequences.

The sample size calculation resulted in 171 patients to include in each randomisation group, or 342 patients in total (power 80%, alpha error 0.025). Based on an assumed 5% drop-out rate of patients after randomisation we aim to include a total of 360 patients. (5)

The medical ethical committee of Máxima Medical Centre approved the study protocol on June 15th, 2017. The trial was registered at the Netherlands Trial Register on July 6th, 2017 (NL6344/NTR6528). MEDIASTrial study protocol version 7.0, approved on July 1st, 2019 is the latest and currently effective study protocol. The first patient was included on July 17th, 2017 and the inclusion is expected to be complete in 2020. The full sample size calculation, study procedures and further details are available in the previously published trial protocol.(5)

Statistical analysis plan

The statistical analysis plan was conducted according to the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.(7) The checklist was provided in Appendix 1. FvdB is the clinical chief investigator and MD is the responsible senior statistician of the MEDIASTrial.

General principles

The primary analyses (for evaluation of primary outcome measure and major morbidity and 30-day mortality) will be performed when all patients have at least 30 days after the start of the treatment follow-up. The remaining secondary outcome measures will be analysed after completion of two years follow up of all evaluable patients. Before analysing, the database will be cleaned and locked. No interim analysis will be performed. Analyses will be performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, Armonk, NY). Generally, numerical outcomes will be presented as means (with standard deviation (SD) and/or range) or medians (with interquartile range (IQR and/or range)) depending on (normally or skewed) distribution of data. Numerical outcomes will be compared between groups using the unpaired t-test or Mann-Whitney U-test depending on distribution of data. Categorical data will be presented as counts and percentages and will be compared between groups using the Mantel-Haenszel chi-squared test or using Fisher's exact test in case of zero cell counts.(8,9) We will calculate 95% CI's around proportions by using the Wilson score interval for proportions.(10)

Correction for multiple testing of the secondary outcome measures will be done using the Benjamini-Hochberg method.(11) Statistical significance will be set at a p-value of less than 0.05. In case data presentation or analysis is planned to be different this will be stated in the specific outcome measure description part of this SAP. An overview of the planned statistical test per outcome measure to compare the randomisation groups is provided in Appendix 2.

Patient flow diagram

As indicated in the Consolidated Standards of Reporting Trials 2010 statement (CONSORT) the patient flow will be illustrated in a flow diagram (Figure 1).(12)

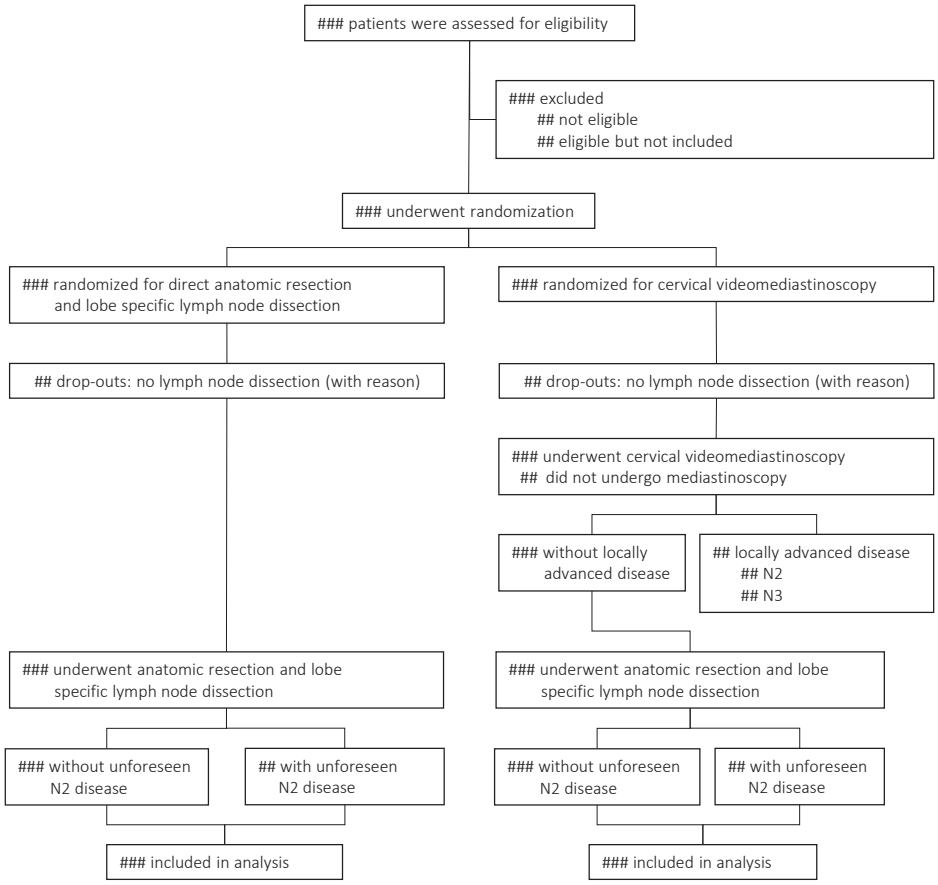

Figure 1. Enrollment, randomization and flow of study patients.
N2=ipsilateral mediastinal lymph node metastasis; N3=contralateral lymph node metastasis; Unforeseen N2 disease Pathologically proven N2 disease at lobe-specific lymph node dissection at time of tumour resection when previous mediastinal staging showed N0 or N1 disease.

Intention to treat and per protocol analysis

As this is a non-inferiority trial both intention to treat (ITT) and per protocol (PP) analyses will be done.(13) The ITT and the PP analyses should both indicate non-inferiority before the diagnostic strategy 'omitting mediastinoscopy' will be interpreted as non-inferior to the strategy with mediastinoscopy. The pathology report of the lobe-specific lymph node dissection determines the nodal state, which is the primary outcome measure of this study. All patients from the ITT population without protocol deviations or violations in eligibility and study procedures will be included in the PP analysis. All analyses of secondary outcomes will be carried out on an ITT basis.

Protocol deviation and violation

Clinical deterioration and progression of the disease between randomisation and surgery could restrain surgical options and resectability of the primary tumour and lymph nodes. Patients in whom no lobe-specific lymph dissection was performed will be considered drop-outs since the primary outcome measures are missing. This population is expected not to exceed 5% as included in the sample size calculation. Patients randomised to confirmatory mediastinoscopy in whom no mediastinoscopy was performed prior to anatomical lung resection will primarily be analysed based on intention-to-treat. In per protocol analysis these patients will be excluded for analysis.

Patient replacement and missing data

A 5% drop-out rate was included in the sample size calculation. As we assume the group of patients with missing primary outcome measures will not transcend this number, no patient replacement will be performed after inclusion of 360 patients. Clinical data management is done by professional data managers from the Dutch Comprehensive Cancer Centre. Any missing clinical data will be communicated to the study site data manager for prompt correction. Missing data in baseline characteristics (including FDG-PET/CT and endosonography results), mediastinoscopy, anatomic resection and lymph node dissection will not be imputed. For dichotomous variables the actual denominator and for continuous variables the number of patients will be stated.

Randomisation outcome and treatment results (physical condition, complications, adjuvant therapy and oncological/survival results) could affect the number of completed questionnaires. Complete case analysis will be used as primary analysis for an outcome if the proportion of missing data is below 6% or missing data can be handled with mixed models or generalised estimation equations for repeated measures. In both instances, at least 342 evaluable patients should remain.

If less than 342 evaluable patients remain, missing data patterns will be studied to assess the likelihood of data being missing (completely) at random. Logistic regression on missingness of data will be applied to identify potentially associated baseline and clinical characteristics (e.g. gender, ASA-classification, indication for mediastinal nodal staging, clinical node stage, primary tumour location) and derive propensity scores for having missing data.(14) Subsequently, multiple imputation (n=5) will be applied, including the propensity score, treatment allocation, type of centre, age at baseline, randomisation and stratification factors. Additionally, the pathological results (pN stage), use of adjuvant therapy and the results of previously conducted questionnaires will be included. Alternatively, single imputation by 'last observation carried forward' replacing missing data with the last reported value of the same patient will be performed. Finally, a complete case analysis of available cases (n<342) will be performed. Depending on the robustness of analysis results a definitive choice for the method of handling missing data will be made. The imputation method with the smallest confidence interval and point estimates closest to the results of the complete case analysis of available cases will be considered the most robust one. In case of a lack of robustness because of changes in direction of the difference between treatment groups, worst and best case scenarios of imputation will be constructed. The handling of missing data will be extensively and transparently reported in supplemental material to the final results section.

Baseline characteristics

The following baseline characteristics will be reported in the baseline characteristics table: age, gender, type of centre, World Health Organisation (WHO) performance state, American Society of Anesthesiologists (ASA) classification, primary tumour location (lobe), tumour and nodal stage according to the 8th TNM classification based on FDG-PET/CT, indication for invasive mediastinal nodal staging and the final histopathology result (Table 1). Testing for differences in baseline characteristics among groups will only be done if visual inspection of the results indicates possible significant differences.

Endosonography results

All included patients underwent systematic Endobronchial Ultrasound-guided Transbronchial Needle Aspiration (EBUS-TBNA), preferably with added Endoscopic Ultrasound-guided Fine Needle Aspiration by using the conventional endoscope (EUS-FNA) or the EBUS endoscope (EUS-B-FNA). We will report: the number of additional EUS procedures, sedation used, the proportion of procedures with rapid on site evaluation (ROSE), the number of visualized and sampled lymph nodes, the number of samples per lymph node station and the number of patients with cytologically proven N1 disease. The outcomes will be compared among the randomisation groups with subsequent presentation of outcomes for both individual groups (Table 2).

Cervical videomediastinoscopy results

We will report the number of visualized and sampled lymph node stations, the proportion of lymph node stations that were adequately sampled (i.e. at least four surgical biopsies or one entire lymph node) and the number of complete performed mediastinoscopy procedures (according to the study protocol).(5) Additionally, the pathology results whether mediastinal lymph node metastases were found including the level of the affected lymph node stations will be reported (Table 2). A calculation of the number needed to test to detect a patient with missed mediastinal lymph node metastases after endosonography by performing confirmatory cervical videomediastinoscopy will be done. Complications of mediastinoscopy will be reported in the major morbidity and mortality outcome measure. The patients randomised for mediastinoscopy who did not undergo mediastinoscopy will be reported including the reason for this protocol deviation, if applicable.

Table 1. Clinical and lung cancer characteristics of included patients

	With mediastinoscopy (n=)	Without mediastinoscopy (n=)
Age, mean (SD)/median (IQR), y		
Sex, No. (%)		
Male		
Female		
WHO performance state, No. (%)		
WHO 0		
WHO 1		
WHO 2		
WHO 3		
WHO 4		
ASA classification, No. (%)		
ASA-1		
ASA-2		
ASA-3		
ASA-4		
Tumor location, No. (%)		
Left lower lobe		
Left upper lobe		
Right lower lobe		
Right middle lobe		
Right upper lobe		

Table 1. Clinical and lung cancer characteristics of included patients (*continued*)

	With mediastinoscopy (n=)	Without mediastinoscopy (n=)
Tumour stage FDG-PET/CT, No. (%)		
T		
Nodal stage FDG-PET/CT, No. (%)		
N		
Indication for invasive mediastinal nodal staging, No. (%)		
Clinical N1-3		
Central tumour		
FDG-non-avid tumour		
Peripheral tumour >3 cm		
Final histopathology, No. (%)		
NSCLC		
Subtype		
Small cell carcinoma		
Benign		

SD=standard deviation; y=years; No.=number, WHO=World Health Organisation; ASA=American Society of Anesthesiologists; FDG-PET=fluorodeoxyglucose positron emission tomography; CT=computed tomography; TNM=tumour, node, metastasis, 8th edition; NSCLC=non-small cell lung cancer.

Table 2. Performance of diagnostic and therapeutic procedures

	With mediastinoscopy (n=)	Without mediastinoscopy (n=)
EBUS, No. (%)		
Additional EUS		
EUS, No. (%)		
EUS-B, No. (%)		
Rapid on-site evaluation, No. (%)		
Mediastinal lymph node stations		
Visualized, mean (SD)/median (IQR)		
Sampled, mean (SD)/median (IQR)		
Samples per station, mean (SD)/median (IQR)		
Cytologically proven N1 disease, No. (%)		
Confirmatory mediastinoscopy, No. (%)		0
Mediastinal lymph node stations		-
Sampled, mean (SD)/median (IQR)		
Adequate sampling*, %		-
Proven mediastinal lymph node metastases		-
N2, No (%)		
N3, No. (%)		-

Table 2. Performance of diagnostic and therapeutic procedures (*continued*)

	With mediastinoscopy (n=)	Without mediastinoscopy (n=)
Complete mediastinoscopy†, No. (%)		
Anatomical lung resection, No. (%)		
Thoracoscopic surgery, No. (%)		
Conversion to thoracotomy, No. (%)		
Duration of surgery, mean (SD)/median (IQR) minutes		
Resection type		
Segmentectomy, No. (%)		
Lobectomy, No. (%)		
Bilobectomy, No. (%)		
Pneumonectomy, No. (%)		
Mediastinal lymph node stations dissected, mean (SD)/median (IQR)		
Complete lobe-specific lymph node dissection†, No. (%)		
Unforeseen N2, No. (%)		
Foreseen N2 (station 5-6), No. (%)		

EBUS=endobronchial ultrasonography; EUS=endoscopic ultrasonography; EUS-B=endoscopic ultrasonography using the EBUS bronchoscope; No.=number; SD=standard deviation; N1=ipsilateral hilar lymph node metastasis; N2=ipsilateral mediastinal lymph node metastasis; N3=contralateral lymph node metastasis; *adequate sampling=at least 4 surgical biopsies or one entire lymph node per station. † complete according to the study protocol (5).

Surgical reference standard

We will report the used surgical technique (video-assisted thoracoscopic surgery (VATS) single- or multi-port, thoracotomy), number of converted operations, duration of surgery (minutes), used type of resection (segmentectomy, lobectomy, bilobectomy, pneumonectomy), number of sampled mediastinal lymph node stations and the number of complete lobe-specific lymph node dissections (according to the study protocol) (5). The outcomes will be compared among randomisation groups with subsequent presentation of outcomes for both individual groups (Table 2). Complications of the surgical lung tumour resection will be reported in the major morbidity and mortality outcome measure. The patients who did not undergo anatomic resection and lobe-specific lymph node dissection will be reported including the reason for not performing this procedure, if applicable.

Assessment and analysis of unforeseen N2 disease

Unforeseen N2 disease is defined as pathologically proven N2 disease resulting from lobe-specific lymph node dissection at time of tumour resection, not detected by inva-

sive clinical staging including endosonography nor by mediastinoscopy (if performed). Patients with suspected station 5 and 6 metastases on imaging who turned out to have pathologically proven station 5 or 6 metastases resulting from lymph node dissection will only be included in the unforeseen N2 calculation if pre-operative extended staging was performed (conform study protocol). In patients with suspect station 5 and 6 on imaging in whom no extended staging was performed, pathological positivity of these nodal stations will be considered foreseen N2 disease, and thus not included in unforeseen N2 calculation. Patients with unsuspicious lymph nodes in station 5 and 6 on imaging with pathologically proven metastases in these stations will be included in the unforeseen N2 calculation.

As substantiated in our study protocol, the upper limit of the two-sided 95%-confidence interval (95%-CI) of the unforeseen N2 rate in the intervention group (endosonography without mediastinoscopy) should not exceed the non-inferiority boundary of 14.3% in order to probably have no negative impact on survival.(15) A formal comparison of the unforeseen N2 rates of the randomisation groups with and without mediastinoscopy will be done based on intention-to-treat and per protocol analysis. Exploratory subgroup analysis of unforeseen N2 disease of patients with different indications for invasive staging (i.e. cN1-3 or centrally located, FDG-non-avid or large (>3 cm) peripherally located tumour) will be performed.

Finally, an overview of all patients with unforeseen N2 disease will be provided. Unforeseen N2 disease will either be classified as detection error (lymph node metastasis not detected by FDG-PET/CT, endosonography nor mediastinoscopy) or sampling error (metastasis detected by FDG-PET/CT, but missed despite lymph node sampling during endosonography and/or mediastinoscopy).

Major morbidity and 30-day mortality

Complications in the first 30 days after start of treatment are scored using the Clavien-Dindo classification.(16) Major morbidity is defined as Clavien-Dindo grade III (requiring surgical, endoscopic or radiological intervention) or IV (life-threatening complication requiring intensive care management) complications or recurrent laryngeal nerve injury. Recurrent laryngeal nerve injury is considered when postoperative hoarseness exists and should be confirmed by laryngoscopy, proving paralysis of a vocal cord. The composite outcome measure will be calculated as the number of patients with major morbidity and the number of deceased patients in the first 30 days after the start of treatment. This number divided by the total number of randomised patients will be considered the proportion of patients with major morbidity or 30-day mortality per randomisation group (Table 3).

Table 3. Morbidity and 30-day mortality

	Clavien-Dindo classification grade	With mediastinoscopy (n=)	Without mediastinoscopy (n=)
Endosonography			
Postoperative complication, No. (%)			
Postoperative complication, No. (%)			
Mediastinoscopy			
Postoperative complication, No. (%)			
Postoperative complication, No. (%)			
Anatomical lung resection			
Postoperative complication, No. (%)			
Postoperative complication, No. (%)			
30-day mortality, No. (%)			

No.=number. Clavien Dindo classification: grade 1: complication without need for interventions, grade 2: complication requiring pharmacological treatment, grade 3: complication requiring surgical, endoscopic or radiological intervention, grade 4: life-threatening complication requiring intensive care management, grade 5: death.

Assessment and analysis of secondary outcomes

Patients will be followed during two years after start of treatment. A minority of patients will have N2 or N3 disease diagnosed by mediastinoscopy and will therefore possibly be judged ineligible for surgery. In these patients the start of chemotherapy and/or radiotherapy will be considered as start of follow-up period. Follow-up will be done at 3, 6, 12 and 24 months after start treatment. The hereafter mentioned secondary outcome measures will all be compared among randomisation groups and data will be subsequently presented for the groups.

Total number of days of hospital care

The absolute number of days of hospital care in the period from randomisation until 2 years after start of treatment will be registered. Every day in hospital (including outpatient clinic visits and day care treatments) related to NSCLC diagnosis, treatment or follow-up will be included in this outcome measure. Differences between groups will be tested with Mann-Whitney U-tests.

Overall and disease-free 2-year survival

Overall 2-year survival is defined as the proportion of patients alive at 2 years after start of treatment. Disease-free 2-year survival is defined as the proportion of patients alive without evidence of relapse of NSCLC at 2 years after start of treatment. The overall and disease-free 2-year survival will be presented as Kaplan-Meier curves and compared among the randomisation groups using the log-rank test.

Generic and disease-specific health related quality of life

Generic health related quality of life will be measured using the Euroqol 5 Dimensions 5 Levels questionnaire (EQ-5D-5L) and the European organization for research and treatment of cancer (EORTC) Quality of life Questionnaire C30 (QLQ-C30). The scoring profiles on the five domains of the EQ-5D-5L (mobility, self-care, activity, pain and anxiety) will be presented in stacked histograms per follow-up moment (Figure 2). Separately the Euroqol-Visual Analog Scale representing the quality of life on a scale will be presented (0-100, 0=the worst health you can imagine, 100=the best health you can imagine). The EORTC QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting), a global health status and a number of general cancer symptoms (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea and perceived financial impact of the disease). The EORTC QLQ-C30 will provide a summary score from 0 to 100, where 100 represents best quality of life, which will be presented by using a diagram presenting the mean or median score including its standard error or interquartile range per follow-up moment (Figure 3). The lung cancer specific quality of life will be measured using the QLQ-LC13 questionnaire, which also provides a summary score from 0 to 100, with 100 representing best quality of life. The results will also be presented in a diagram presenting the scores per follow-up moment (Figure 4). All quality of life questionnaires will be filled in by the patients at baseline, 1 week after mediastinoscopy (if performed) and after 2 and 4 weeks and 3, 6, 12 and 24 months after start of treatment. Data presentation will be done using figures separately for the questionnaires per randomisation group on all follow-up moments. Comparisons between treatment groups over time will be done using generalized mixed modelling for continuous measures or generalized estimation equations for counts. Absolute values of the quality of life questionnaire results will be reported as tables in supplementary material.

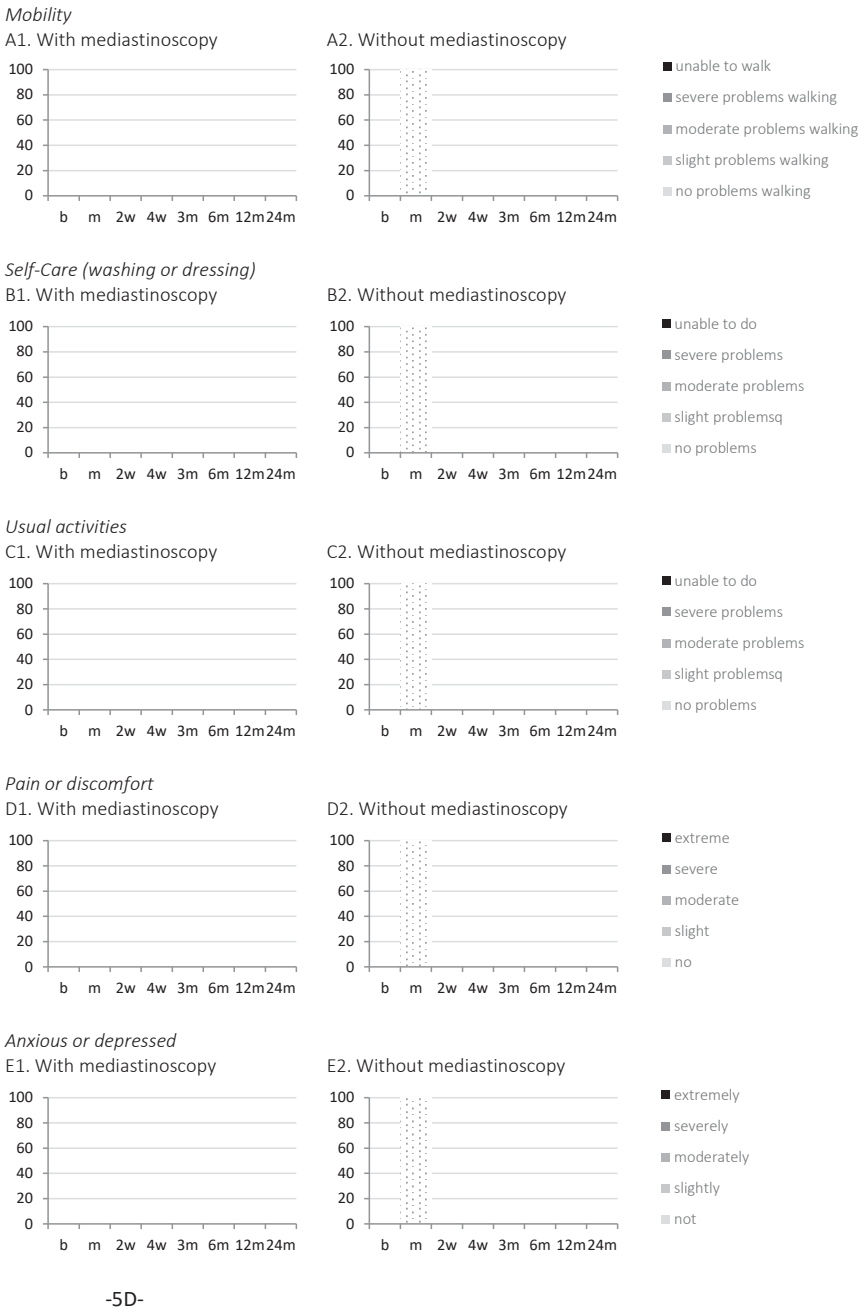

Figure 2. EQ-5D-5L results per domain.
Euroqol 5 Dimensions 5 Levels questionnaire. Vertical axis=cumulative percentage; horizontal axis=follow-up moment; b=baseline; m=1 week after mediastinoscopy; w=weeks after start of treatment; m=months after start of treatment.

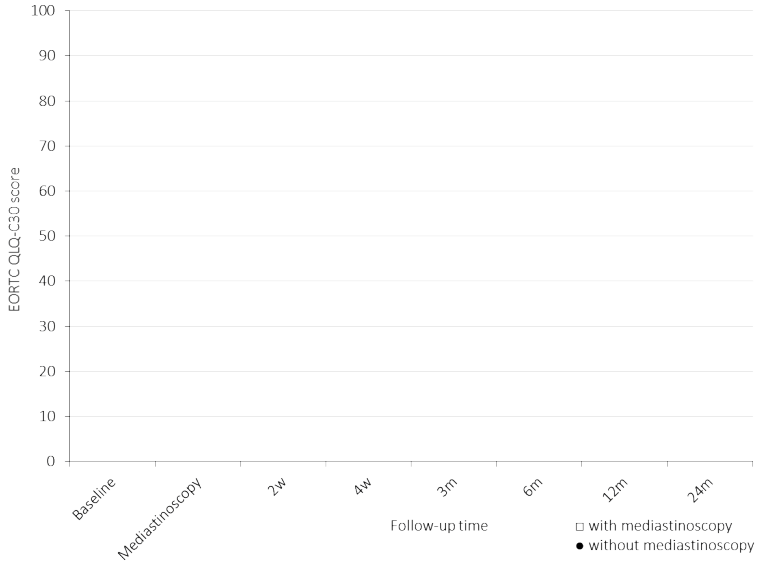

Figure 3. EORTC QLQ-C30 quality of life scores.
European Organization for Research and Treatment of Cancer Quality of life Questionnaire C30. Summary score from 0 to 100, where 100 represents best quality of life. Mean/median score with bars representing standard error/interquartile range. Mediastinoscopy=1 week after mediastinoscopy; w=weeks after start of treatment; m=months after start of treatment.

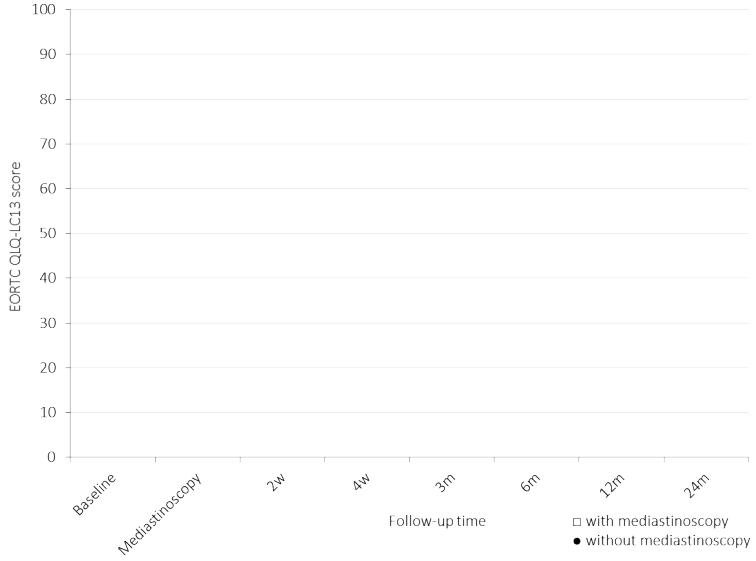

Figure 4. EORTC QLQ-LC13 lung cancer specific quality of life scores.
European Organization for Research and Treatment of Cancer Quality of life Questionnaire LC13. Score 0-100, 0=the worst health you can imagine, 100=the best health you can imagine. Mean/median score with bars representing standard error/interquartile range. Mediastinoscopy=1 week after mediastinoscopy; w=weeks after start of treatment; m=months after start of treatment.

DISCUSSION

The MEDIASTrial will determine if confirmatory mediastinoscopy can be safely omitted after tumour negative endosonography in invasive mediastinal nodal staging of patients with resectable non-small cell lung cancer. Registration of the study in the Netherlands Trial Register (NL6344/NTR6528) before start of the study, publication of the full study protocol and the present statistical analysis plan before knowledge of any results was done to enhance transparency of scientific behaviour.(5) We expect the inclusion to be complete in 2020 and we aim to publish the primary outcome measure shortly after completion of the inclusion.

Abbreviations

NSCLC=non-small cell lung cancer; SAP=statistical analysis plan; CONSORT= Consolidated Standards of Reporting Trials; ITT=intention to treat; PP=per protocol; WHO=World Health Organisation; COPD=Chronic Obstructive Pulmonary Disease; DLCO=diffusing capacity of the lung for carbon monoxide; FEV1=forced expiratory volume in the first second of expiration; EBUS-TBNA= Endobronchial Ultrasound guided-Transbronchial Needle Aspiration; EUS-FNA=Endoscopic Ultrasound guided-Fine Needle Aspiration; ROSE=rapid on-site evaluation; VATS=video-assisted thoracoscopic surgery; 95%-CI=95%-confidence interval; EQ-5D-5L= Euroqol 5 Dimensions 5 Levels questionnaire; EORTC= European organization for research and treatment of cancer; VAS=Visual Analog Scale.

Declarations

SAP history

Version 1.0 Submitted to Trials on September 24th, 2020

Sent back on October 14th, 2020 with request to change the title so that it is in the format "[title of original protocol article]: a Statistical Analysis Plan

Version 1.1 Submitted to Trials on October 16th, 2020

Sent back on January 19th, 2021 with comments for improvement: addition of the reporting guideline for SAPs checklist, identify the responsible senior statistician and the clinical chief investigator, explanation of the non-inferiority threshold and describing the planned subgroup analyses.

Version 1.2 Submitted to Trials on February 8th, 2021

Ethics approval and consent to participate

The medical ethical committee of the Maxima Medical Centre has approved the study protocol and all participating centres (MEC number W17.063) on June, 15th, 2017. All participating centres signed the research contract prior to start inclusion. Before randomisation, written informed consent was obtained from all patients.

Trial registration

The MEDIASTrial is registered at the Netherlands Trial Register on July 6th, 2017 (NL6344/NTR6528), www.trialregister.nl/trial/6344.

Consent for publication

Not applicable.

Availability of data and material

The datasets and/or analysed data will be available from the principal investigator (FvdB) on reasonable request. The Data Management plan and Trial Master File are managed by the principal investigator (FvdB).

Competing interests

Dr. Bousema and Dr. van den Broek report grants from ZonMw and the Dutch Cancer Society, during the conduct of this study. Prof. Dr. Dijkgraaf and Prof. Dr. Verhagen have nothing to disclose. Dr. van der Heijden reports research grants from Pentax Medical, Philips Medical unrelated to the content of this study. Consultancy for Philips-Volcano, Pentax Medical. Prof. Dr. Annema reports non-financial support from Hitachi Medical systems, non-financial support from Pentax, grants from Cook medical, outside the submitted work.

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Authors' contributions

All authors have made substantial contributions to the conception and design of the MEDIASTrial. JB and MD drafted the statistical analysis plan and present manuscript and EH, AV, JA and FvdB critically revised it. All authors read and approved the final version of the manuscript. MD and FvdB share the senior authorship of this manuscript.

Acknowledgements

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REFERENCES

(1) Vilmann P, Clementsen PF, Colella S, Siemsen M, de Leyn P, Dumonceau J, et al. Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline, in cooperation with the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS). Endoscopy 2015;47(6):546-560.

(2) De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 2014 May;45(5):787-798.

(3) Annema JT, van Meerbeeck JP, Rintoul RC, Dooms C, Deschepper E, Dekkers OM, et al. Mediastinoscopy vs Endosonography for Mediastinal Nodal Staging of Lung Cancer: A Randomized Trial. JAMA 2010 Nov 24,;304(20):2245-2252.

(4) Bousema JE, van Dorp M, Noyez VJJM, Dijkgraaf MGW, Annema JT, van den Broek, Frank J.C. Unforeseen N2 Disease after Negative Endosonography Findings with or without Confirmatory Mediastinoscopy in Resectable Non–Small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Journal of Thoracic Oncology 2019 Jun;14(6):979-992.

(5) Bousema JE, Dijkgraaf MGW, Papen-Botterhuis NE, Schreurs HW, Maessen JG, van der Heijden, Erik H, et al. MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a multicenter randomised controlled trial. BMC surgery 2018 May 18,;18(1):27.

(6) Stichting Palga. Landelijke PALGA Protocol: Longcarcinoom (resectie). 2019; Available at: https://www.palga.nl/assets/uploads/Protocollen/Longcarcinoom.pdf.

(7) Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA : the journal of the American Medical Association 2017 Dec 19,;318(23):2337-2343.

(8) Campbell I. Chi-squared and Fisher–Irwin tests of two-by-two tables with small sample recommendations. Statistics in Medicine 2007 Aug 30,;26(19):3661-3675.

(9) Busing, F. M. T. A, Weaver B, Dubois S. 2 × 2 Tables: a note on Campbell's recommendation. Statistics in medicine 2016 Apr 15,;35(8):1354-1358.

(10) Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Statistics in medicine 1998 Apr 30,;17(8):873.

(11) Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal Statistical Society. Series B, Methodological 1995 Jan 1,;57(1):289.

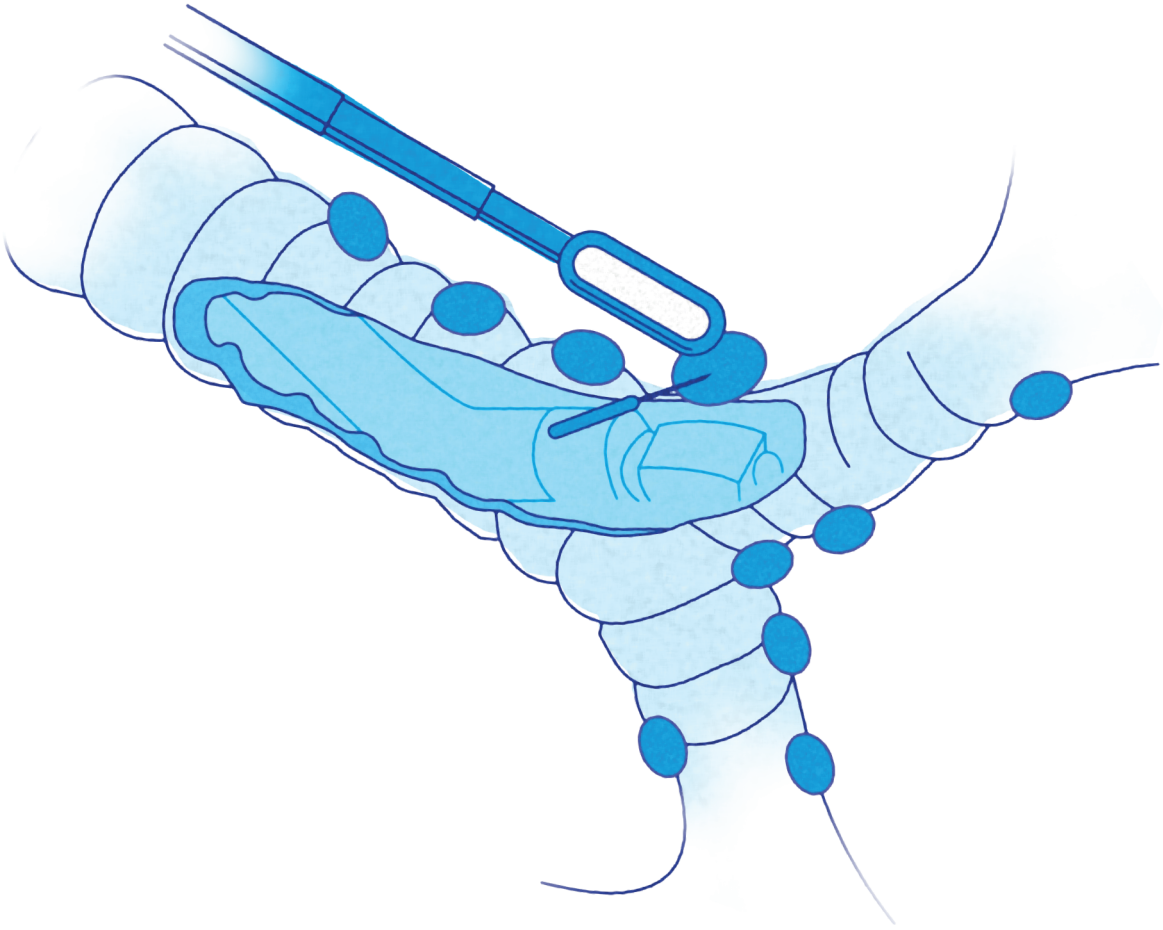
(12) Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, et al. CONSORT 2010 Explanation and Elaboration: updated guidelines for reporting parallel group randomised trials. Journal of clinical epidemiology 2010;63(8):e1-e37.

(13) Mauri L, D'Agostino RB. Challenges in the Design and Interpretation of Noninferiority Trials. The New England Journal of Medicine 2017 Oct 5,;377(14):1357-1367.

(14) Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research 2011;46(3):399-424.

(15) Kuijvenhoven JC, Korevaar DA, Tournoy KG, Malfait TLA, Dooms C, Rintoul RC, et al. Five-Year Survival After Endosonography vs Mediastinoscopy for Mediastinal Nodal Staging of Lung Cancer. JAMA 2016 Sep 13,;316(10):1110-1112.

(16) Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 2004 Aug;240(2):205-213.



Chapter 9

Endosonography with or without confirmatory mediastinoscopy for resectable lung cancer: A Randomized Clinical Trial

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ABSTRACT

PURPOSE Resectable non-small cell lung cancer (NSCLC) with a high probability of mediastinal nodal involvement requires mediastinal staging by endosonography and, in the absence of nodal metastases, confirmatory mediastinoscopy according to current guidelines. However, randomized data regarding immediate lung tumor resection following systematic endosonography versus additional confirmatory mediastinoscopy before resection are lacking.

METHODS Patients with (suspected) resectable NSCLC and an indication for mediastinal staging after negative systematic endosonography were randomly assigned to immediate lung tumor resection or confirmatory mediastinoscopy followed by tumor resection. The primary outcome in this non-inferiority trial (non-inferiority margin of 8% that previously showed to not compromise survival, $P_{non\text{-}inferior}$<0.0250) was the presence of unforeseen N2 disease following tumor resection with lymph node dissection. Secondary outcomes were 30-day major morbidity and mortality.

RESULTS Between July 17, 2017 and October 5, 2020, three-hundred-sixty patients were randomized, 178 to immediate lung tumor resection (seven drop-outs) and 182 to confirmatory mediastinoscopy first (seven drop-outs before and six after mediastinoscopy). Mediastinoscopy detected metastases in 8.0% (14/175, 95%-CI: 4.8-13.0) of patients. Unforeseen N2 rate after immediate resection (8.8%) was non-inferior compared to mediastinoscopy first (7.7%) in both ITT (Δ:1.03%, UL 95%-CIΔ: 7.2%, $P_{non\text{-}inferior}$=0.0144) and PP analyses (Δ:0.83%, UL 95%-CIΔ: 7.3%, $P_{non\text{-}inferior}$=0.0157). Major morbidity and 30-day mortality was 12.9% after immediate resection versus 15.4% after mediastinoscopy first (p=0.4940).

CONCLUSION On the basis of our chosen non-inferiority margin in the rate of unforeseen N2 confirmatory mediastinoscopy after negative systematic endosonography can be omitted in patients with resectable NSCLC and an indication for mediastinal staging.

CONTEXT SUMMARY

Key objective: Despite guideline recommendations, the value of confirmatory mediastinoscopy after tumor negative endosonography as part of mediastinal staging is under debate in patients with resectable NSCLC and a high probability of mediastinal nodal involvement. The effect of omitting confirmatory mediastinoscopy on relevant clinical outcomes has never been evaluated in a randomized setting. To our knowledge, this study is the first to report randomized data on omitting mediastinoscopy after negative systematic endosonography.

Knowledge generated: The omission of confirmatory mediastinoscopy and proceeding to immediate lung tumor resection demonstrated an unforeseen N2 rate after definite surgical lung tumor resection of 8.8%. Despite a mediastinal lymph node metastasis detection rate of 8.0% by mediastinoscopy in the control group, the unforeseen N2 rate after immediate resection did not exceed the predefined non-inferiority boundary thereby providing evidence of the redundancy of confirmatory mediastinoscopy.

Relevance: Implementation of the current findings prevents patients from morbidity of confirmatory mediastinoscopy, it reduces the lung cancer staging period and it probably saves health care costs.

List of definitions

Bulky cN2-3 disease Mediastinal infiltration of more than one mediastinal zone where the discrete lymph nodes cannot be distinguished or measured during CT or endosonography; or two or more lymph nodes with a short axis of > 2.5 cm in more than one mediastinal zone.

Central tumor Centrally located primary lung tumor defined by visibility of the tumor on videobronchoscopy within the main stem bronchi; or tumor proximity to the mediastinum <0.5cm or location of the tumor within the inner third of the thorax on computed tomography.

Clinical nodal stage (cN) Mediastinal nodal stage based on computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography and negative invasive staging procedures

EBUS(-TBNA) Endobronchial ultrasound guided transbronchial needle aspiration. Investigation of mediastinal and hilar lymph nodes with a convex ultrasound probe from the airways with the possibility of nodal sampling under real-time ultrasound control.

EUS(B)(-FNA) Endoscopic ultrasound guided fine needle aspiration, by using a conventional ultrasound endoscope (EUS) or the EBUS scope (EUSB). Investigation of mediastinal lymph nodes with a convex ultrasound probe from the esophagus with the possibility of nodal sampling under real-time ultrasound control.

Endosonography A procedure in which an endoscope is inserted into a body cavity, providing real-time endoscopic imaging as well as real-time ultrasound with the opportunity to take fine needle samples. In lung cancer staging either endobronchial (EBUS) or esophageal (EUS).

Invasive mediastinal staging mediastinal lymph node staging to determine the nodal status of lung cancer by using EBUS, EUS and/or mediastinoscopy.

Mediastinal lymph node dissection Surgical dissection of ipsilateral mediastinal lymph node stations at time of lung tumor resection to ensure the pathological nodal stage.

Mediastinoscopy Surgical procedure under general anesthesia to examine mediastinal lymph nodes, located paratracheal and subcarinal, with the possibility to take surgical biopsies.

Peripheral tumor Primary tumor located in the outer two third of the lung.

Unforeseen N2 disease (uN2) Pathologically proven N2 disease resulting from mediastinal lymph node dissection at time of lung tumor resection, not detected by clinical staging, including endosonography or mediastinoscopy (if performed).

INTRODUCTION

Lung cancer is one of the most frequently diagnosed cancers and accounts for 19% of cancer deaths worldwide.[1] Primary clinical staging includes computed tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET). Potential surgical candidates with suspicious hilar and/or mediastinal lymph nodes on imaging (cN1-3), or a centrally located, FDG-non-avid or large (>3 cm) peripherally located tumor are recommended to undergo invasive mediastinal nodal staging prior to surgical resection.[2] Of all surgically treated patients 68% has a pre-operative indication for invasive mediastinal staging.[3]

The ASTER trial demonstrated a 79% sensitivity for videomediastinoscopy to detect nodal metastases compared to 85% for endosonography. Confirmatory mediastinoscopy after negative endosonography increased the sensitivity to 94%.[4] Guidelines therefore recommends confirmatory mediastinoscopy after cN0-1 endosonography in patients with cN1-3, while it should be considered in patients with centrally located, FDG-non-avid or peripheral tumors >3 cm.[2 5, 6]

After publication of the ASTER trial the use of endosonography (either alone or combined with confirmatory mediastinoscopy) increased, whereas the use of mediastinoscopy alone decreased.[3, 7, 8] The role of confirmatory mediastinoscopy is under debate owing its limited nodal metastasis detection rate, associated morbidity and delay in start of lung cancer treatment.[3, 9, 10] Randomized data regarding immediate lung tumor resection following endosonography versus additional confirmatory mediastinoscopy are lacking.[8, 9]

Omitting confirmatory mediastinoscopy after negative endosonography will probably lower the diagnostic sensitivity and increase undesirable unforeseen N2 (uN2) after surgery. The MEDIASTrial (Netherlands Trial Register NL6344) assesses whether omitting mediastinoscopy leads to an unacceptable increase in uN2 rate, based on a clinically determined non-inferiority limit, to allow potential improvements in morbidity, quality of life and health economics.

METHODS

Trial design

The study protocol of the MEDIASTrial has previously been published and was conducted as a randomized controlled non-inferiority trial at 23 hospitals in the Netherlands and Belgium.[11] Our hypothesis was that omitting mediastinoscopy leads to a higher uN2 rate

at final surgical resection (i.e. our primary research question to test for non-inferiority), but inversely reduces morbidity, improves quality of life and reduces costs (i.e. our secondary research question).

Participants

Consecutive patients with proven or suspected, resectable NSCLC without distant metastasis, with centrally located, FDG-non-avid or large (>3 cm) peripherally located tumors or cN1-3 on imaging were enrolled. Imaging consisted of CT and FDG-PET in all patients. A systematic endosonographic assessment of nodal stations 4R-7-4L and additionally all CT-enlarged (>10 mm) and/or FDG-avid (standardized uptake value (SUV) >2.5) mediastinal nodal stations with tumor negative cytology of N2-3 stations was mandatory for inclusion. In case of nodes with unsuspicious appearance on endosonography (<8 mm, oval shape, vague borders and absence of hypo-echoic texture) samples were not obligatory since node size <8mm has shown to be a clinically feasible cut-off.[12] Patients with suspected metastases to stations 5/6 were eligible for inclusion. Extended invasive staging of station 5/6 (through parasternal mediastinotomy or video-assisted thoracoscopic surgery) should have been performed if nodal spread to these stations would change treatment strategy according to the local multidisciplinary board. Exclusion criteria were: neo-adjuvant treatment, unresectable tumor (judged by a thoracic surgeon), contraindications for mediastinoscopy or lung resection (insufficient cardiopulmonary function), non-correctable coagulopathy, age <18 years, inability to consent or bulky cN2-3 disease. Also patients with highly suspicious mediastinal lymph nodes (SUV>5 and at least three endosonographic malignant criteria (mentioned above)) but out of reach for conventional surgical resection (cervical or contralateral nodal stations) were not eligible for inclusion.[11] Written informed consent was obtained from all patients.

Randomisation

Patients were 1:1 assigned to undergo either immediate lung tumor resection and lymph node dissection (immediate lung tumor resection group) or confirmatory mediastinoscopy first followed by lung tumor resection in the absence of nodal metastases (mediastinoscopy group). Due to the invasive nature of mediastinoscopy, blinding was not possible. Stratification was performed per age group (≤ 66 years and >66 years) and type of center (academic or non-academic) to minimize bias in a planned economic evaluation.

Mediastinoscopy

Mediastinoscopy consisted of a cervical videomediastinoscopy with sampling of nodal stations 4R-7-4L in accordance with the ESTS guideline, as well as station 2R for right-sided tumors according the Dutch guideline.[13] Sampling station 2L in left-sided tumors was encouraged but not mandatory due to risks for recurrent laryngeal nerve palsy. Sampling

consisted of at least 4 surgical biopsies (biopsy forceps ≥5 mm) or an entire lymph node per station. Frozen sections were not routinely performed on mediastinoscopy biopsies.

Lung tumor resection

Lung tumor resection consisted of an anatomical resection and dissection of at least 3 mediastinal stations (including the subcarinal station) according to international guidelines.[14, 15]

Outcomes

The primary outcome was the presence of uN2 in the immediate resection group versus the mediastinoscopy group. The uN2 rate was calculated by dividing the number of patients with pathologically proven N2 resulting from lymph node dissection, not detected by endosonography nor mediastinoscopy, by the total number of patients undergoing lymph node dissection. Histopathology was performed conform international guidelines and pathologists were unaware that patients participated in a trial.[16] Exploratory subgroup analyzes were performed for the different indications for invasive staging. uN2 cases were categorized having single- or multilevel nodal station uN2 and being detection errors (not detected by imaging, endosonography nor mediastinoscopy) or sampling errors (benign lymphoid sampling results from endosonography and/or mediastinoscopy). Patients with radiologically suspect station 5/6 not undergoing extended staging in accordance with the multidisciplinary board advise, but with pathologically proven nodal spread to station 5/6 after final lymph node dissection were determined having foreseen N2. Major morbidity and 30-day mortality following mediastinoscopy and surgical resection were secondary outcomes and were scored during hospital stay and outpatient visits. Morbidity was scored according the Clavien-Dindo classification, considering grade I-II as minor and grade III-IV or laryngoscopic proven recurrent laryngeal nerve palsy as major morbidity.[17]

Trial quality

This study was performed in accordance with the Declaration of Helsinki, 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013. The medical ethical committee of Máxima MC approved the study, which was registered in the Netherlands Trial Register on July 6th, 2017 (NL6344). The study protocol and statistical analysis plan were published open-access before knowledge of any results of this trial.[11, 18] On-site monitoring and clinical data collection was performed by independent professionals. Diagnostic and therapeutic procedures were performed by trained pulmonologists and thoracic surgeons, who received feedback on protocol violations that were exposed by study monitors to ensure continuous quality.

Non-inferiority margin and sample size

A systematic review being part of the research proposal of this study showed uN2 rates of 6.3% in the mediastinoscopy group versus 6.8% after immediate resection. From the ASTER trial an uN2 rate as high as 14.3% was calculated in patients undergoing mediastinoscopy alone without compromising 5-year survival.[19] Based on these numbers we set the non-inferiority margin at 8% (difference between 6.3% - 14.3%), resulting in a sample size of 171 patients in each group to achieve a power of 80% with an alpha error of 0.0250. With an assumed drop-out rate of 5% the aimed sample size was 360 patients.

Statistical analysis

The complete statistical analysis plan was formerly published open-access.[18] Intention-to-treat (ITT) analyses of uN2 were performed, in which patients with N2 disease detected by mediastinoscopy were excluded since they did not undergo lymph node dissection that was necessary for uN2 calculation. Unforeseen N2 is usually reported in this manner. All patients with complete mediastinoscopy and lymph node dissection procedures (conform study protocol) were included for the per protocol (PP) uN2 analysis (Figure 1). We calculated 95%-confidence intervals (95%-CI) of proportions using Wilson's approximation[20], while 95%-CI for the difference in proportions (95%-CIΔ) were calculated using the slightly more conservative Miettinen-Nurminen approximation.[21] Non-inferiority was concluded if the upper limits of the 95%-CIΔ (UL 95%-CIΔ) following ITT and PP were smaller than the absolute 8% margin from the observed uN2 rates for the mediastinoscopy group. For the secondary outcomes we *did* include patients undergoing mediastinoscopy without subsequent lymph node dissection (due to proven N2 or drop-out after mediastinoscopy) to include all morbidity associated with mediastinoscopy. The respective exclusion and inclusion of patients with positive mediastinoscopy in the primary and secondary analysis resulted in different denominators. To assess its effect, we additionally performed a *modified* uN2 analysis including patients with positive mediastinoscopy in the denominator. The analyses were performed using the Statistical Package for the Social Sciences version 24.0, NCSS Statistical Software 2007[22] and WinPepi version 11.22.[23]

Role of the funding source

The funding sources had no involvement in the study design, data analysis, data interpretation and the decision to submit the article for publication.

RESULTS

Patients

Between July 17, 2017 and October 5, 2020 (mean inclusion period 26 months per center), a total of 360 patients were enrolled; 178 were assigned to immediate lung tumor

resection and 182 to mediastinoscopy. The study flow chart including 14 drop-outs is presented in Figure 1 and baseline characteristics are presented Table 1.

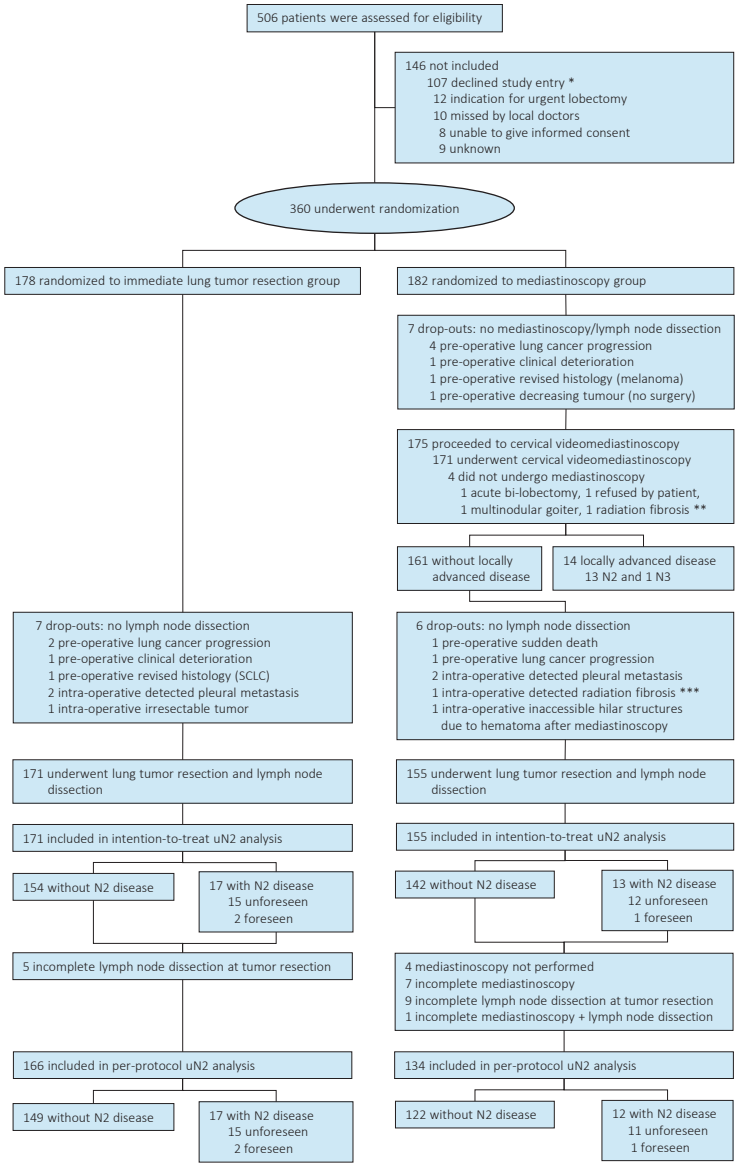

Figure 1. Enrollment, randomization and flow of study patients.
N2=ipsilateral mediastinal lymph node metastasis; N3=contralateral lymph node metastasis; Unforeseen N2 disease/uN2= Pathologically proven N2 disease at lymph node dissection at time of tumor resection when previous mediastinal staging showed N0 or N1.
*=main reasons for declining study entry were objection to clinical trials/randomization and preference for additional staging certainty with mediastinoscopy; **=cervical radiation fibrosis from a previous non-pulmonary malignancy; ***=mediastinal radiation fibrosis from a previous non-pulmonary malignancy.

Table 1. Clinical and lung cancer characteristics of included patients

	Immediate lung tumor resection group (n=171)	Mediastinoscopy group (n=175)
Age (years)	69 (62-73)	69 (63-73)
Sex		
Male	94 (55%)	105 (60%)
Female	77 (45%)	70 (40%)
WHO performance state		
WHO 0	105 (61%)	104 (59%)
WHO 1	60 (35%)	67 (38%)
WHO 2	5 (3%)	3 (2%)
WHO 3	1 (1%)	1 (1%)
ASA classification		
ASA-1	8 (5%)	4 (2%)
ASA-2	85 (50%)	91 (52%)
ASA-3	76 (44%)	74 (43%)
ASA-4	2 (1%)	6 (3%)
Tumor location		
Left lower lobe	21 (12%)	22 (13%)
Left upper lobe	36 (21%)	49 (28%)
Left central	3 (2%)	5 (3%)
Right lower lobe	29 (17%)	41 (23%)
Right middle lobe	13 (8%)	4 (2%)
Right upper lobe	67 (39%)	50 (29%)
Right central	2 (1%)	4 (2%)
Clinical tumor categories*		
cT1a	4 (2%)	1 (1%)
cT1b	18 (11%)	15 (9%)
cT1c	19 (11%)	16 (9%)
cT2a	31 (18%)	46 (26%)
cT2b	23 (14%)	25 (14%)
cT3	55 (32%)	51 (29%)
cT4	21 (12%)	21 (12%)
Clinical nodal categories*based on imaging		
cN0	58 (34%)	54 (31%)
cN1	59 (35%)	55 (32%)
cN2	38 (22%)	41 (23%)
cN3	16 (9%)	25 (14%)
Indication for invasive mediastinal nodal staging		
cN1-3	113 (66%)	121 (69%)

Table 1. Clinical and lung cancer characteristics of included patients (*continued*)

	Immediate lung tumor resection group (n=171)	Mediastinoscopy group (n=175)
Central tumor	28 (16%)	23 (13%)
FDG-non-avid tumor	2 (2%)	0
Peripheral tumor >3 cm	28 (16%)	31 (18%)
Final histopathology**		
NSCLC		
Adenocarcinoma	97 (57%)	68 (44%)
Squamous cell carcinoma	58 (34%)	66 (42%)
Other ***	9 (5%)	14 (9%)
Small cell carcinoma	3 (2%)	3 (2%)
Carcinoid	2 (1%)	2 (1%)
Synovial sarcoma	0	1 (1%)
Metastasis other malignancy	0	1 (1%)
Benign	2 (1%)	0

Data are n (%) or median (IQR). WHO=World Health Organisation; ASA=American Society of Anesthesiologists; NSCLC=non-small cell lung cancer. *TNM=tumor, node, metastasis, 8th edition based on FDG-PET and contrast enhanced chest CT imaging only; **final tumor histopathology of patients who underwent surgical resection; with mediastinoscopy n=155 and without mediastinoscopy n=171; ***other includes adenosquamous carcinoma, large cell carcinoma and NSCLC not otherwise specified.

Endosonography

All patients underwent EBUS conform protocol, added by EUS(B) in 69 patients (20%). Moderate sedation was used in 186 patients (54%), propofol in 154 (44%) and no sedation in six patients (2%). Per patient a median of five (IQR 4-7) nodal stations were visualized, two (IQR 1-3) stations were sampled, taking a median of three (IQR 2-4) samples per station. N1 metastases were cytologically proven in 20 of 346 patients (6%). Endosonography results were similar among groups (Table 2).

Mediastinoscopy

Cervical videomediastinoscopy was performed in 171 of 175 patients (98%). After randomisation, one patient refused mediastinoscopy and subsequently underwent lung tumor resection, one patient developed a thoracic empyema before undergoing mediastinoscopy and subsequently underwent emergency bi-lobectomy and in two patients mediastinoscopy was prematurely aborted; one due to severe previous radiation effects for a cervical tumor and one due to a multinodular goiter (Figure 1). Mediastinoscopy encompassed median four (IQR 4-5) stations per patient. All designated stations were assessed in 161 of 175 patients (92%, n=9 missing one station, n=1 missing two stations, n=4 no mediastinoscopy performed). Four surgical biopsies or one entire lymph node were harvested in 70% of stations (Table 2).

Lung tumor resection

The mean interval between endosonography and lung tumor resection was 28 days (95%-CI: 26-30) in the immediate resection group versus 38 days (95%-CI: 36-41) in the mediastinoscopy group. Six patients without mediastinal metastases at mediastinoscopy did not undergo resection; one suffered a sudden death 10 days after mediastinoscopy (no autopsy), one had progressive lung cancer, two had intra-operatively detected pleural metastases, one had severe mediastinal radiation fibrosis from a previous non-pulmonary malignancy and in one patient the hilar structures were inaccessible withholding lobectomy and lymph node dissection due to a severe hematoma after mediastinoscopy. This resulted in 171 operated patients with immediate resection and 155 patients after mediastinoscopy (Figure 1). Mediastinal lymph node dissection harvested a median of three (IQR 3-4) stations, resulting in complete mediastinal lymph node dissection in 311 of 326 patients (95%). In 14 incomplete procedures one station was missing and in one incomplete procedure three stations were dissected, except the subcarinal station. Lung tumor resection results were similar among groups (Table 2).

Mediastinal nodal metastases

The overall prevalence of mediastinal nodal metastases in the entire study population was 12.9% (44/340, 95%-CI: 9.8-16.9). In the immediate resection group, N2 was postoperatively established in 9.9% (17/171, 95%-CI: 6.3-15.3) including foreseen N2 in station 5/6 in 1.2% (2/171, 95%-CI: 0.3-4.2). In the mediastinoscopy group, the rate of N2-3 detected by mediastinoscopy was 8.0% (14/175, 95%-CI: 4.8-13.0; N2 n=13; single-level n=9) corresponding with a number needed to test (NNT) of 12.5 (100/8.0). After mediastinoscopy, the N2 rate among patients undergoing final resection was 8.4% (13/155, 95%-CI: 5.0-13.8) including foreseen N2 in station 5/6 in 0.7% (1/155, 95%-CI: 0.1-3.6). Herewith, the overall prevalence of N2-3 in the mediastinoscopy group was 16.0% (27/169, 95%-CI: 11.2-22.3), higher but not significantly different from the immediate resection group (p=0.0970) (Table 3).

Of the 14 patients with N2-3 detected at mediastinoscopy, nine had radiological cN1 as indication for staging, corresponding with 16.4% (9/55, 95%-CI: 8.9-28.3) positive mediastinoscopy results within this cN1 subgroup. After detection of N2-3 at mediastinoscopy nine patients underwent definite chemoradiation, one received radiotherapy, one best supportive care and two underwent neo-adjuvant chemotherapy followed by lung tumor resection. The last patient had microscopic single-level N2 detected by mediastinoscopy and underwent subsequent lung tumor resection demonstrating no further nodal metastasis.

Table 2. Performance of staging procedures

	Immediate lung tumor resection group	Mediastinoscopy Group	P value
Endosonography	n=171	n=175	
EBUS	171 (100%)	175 (100%)	-
Additional EUS			
EUS	3 (2%)	5 (3%)	0.5720
EUS-B	29 (17%)	32 (18%)	
Rapid on-site evaluation	77 (45%)	67 (38%)	0.2030
Lymph node stations			
Visualized	5 (4-7)	5 (4-7)	0.4120
Sampled	2 (1-3)	2 (1-3)	0.7840
Samples per station	3 (2-4)	3 (2-4)	0.7040
Representative samples (lymphoid)	79% (73-84)	79% (75-85)	0.8570
Cytologically proven N1 disease	7 (4%)	13 (7%)	0.1840
Cervical videomediastinoscopy		n=175	
Mediastinal lymph node stations			
Sampled		4 (4-5)	
Stations optimally sampled*		70%	
Proven mediastinal lymph node metastases			
N2		13 (7%)	
N3		1 (1%)	
Complete mediastinoscopy**		165 (94%)	
Surgical resection	n=171	n=155	
Thoracoscopic surgery	135 (79%)	111 (72%)	0.1240
Conversion to thoracotomy	22 (17%)	24 (22%)	0.2960
Surgery duration (minutes)	154 (125-198)	164 (122-205)	0.6630
Resection type			
Lobectomy	147 (86%)	128 (82%)	0.5160
Bilobectomy	12 (7%)	15 (10%)	
Pneumonectomy	12 (7%)	12 (8%)	
Mediastinal LN stations dissected	3 (3-4)	3 (3-4)	0.3590
Complete mediastinal LN dissection***	166 (97%)	145 (94%)	0.1290
Foreseen N2 (station 5-6)	2 (1%)	1 (1%)	0.6200
Unforeseen N2	15 (9%)	12 (8%)	0.7360

Data are n (%) or median (IQR) or percentage (95%-CI). EBUS=endobronchial ultrasonography; EUS=endoscopic ultrasonography; EUS-B=endoscopic ultrasonography using the EBUS bronchoscope; LN=lymph node; N1=ipsilateral hilar lymph node metastasis; N2=ipsilateral mediastinal lymph node metastasis; N3=contralateral lymph node metastasis; As none of the secondary outcome comparisons resulted in p-values below 0.05 no correction for multiple testing was necessary.

* at least 4 surgical biopsies or one entire lymph node per station;

** sampling of nodal stations 4R, 7 and 4L, as well as station 2R for right-sided tumors.

*** three mediastinal lymph node stations, including the subcarinal station.

Unforeseen N2

In the ITT analysis uN2 was found in 8.8% (15/171, 95%-CI: 5.4-14.0) in the immediate resection group versus 7.7% (12/155, 95%-CI: 4.5-13.0) in the mediastinoscopy group (Δ:1.03%, UL 95%-CIΔ: 7.2%, $P_{non\text{-}inferior}$=0.0144). In the PP analysis uN2 was found in 9.0% (15/166, 95%-CI: 5.6-14.4) after immediate resection versus 8.2% (11/134, 95%-CI: 4.7-14.1) with mediastinoscopy (Δ:0.83%, UL 95%-CIΔ: 7.3%, $P_{non\text{-}inferior}$=0.0157). uN2 rates in patients with different indications for mediastinal staging were presented in Table 3. The most remarkable difference in uN2 rate was found among patients with cN1; 13.6% in the immediate resection group versus 7.0% in the mediastinoscopy group. The modified analyses also demonstrated that the upper margin of the difference in uN2 rate felt within the chosen acceptable upper limit favoring the immediate resection strategy (Table 3).

Table 3. Analysis of primary outcome (unforeseen N2 rate) and mediastinoscopy N2-3 positives subdivided for subgroups of staging indication

	Immediate lung tumor resection group	Mediastinoscopy group
Unforeseen N2 (primary outcome)		
Intention-to-treat analysis	8.8% (15/171, 5.4-14.0)	7.7% (12/155, 4.5-13.0)
Per protocol analysis	9.0% (15/166, 5.6-14.4)	8.2% (11/134, 4.7-14.1)
cN1-3 based on imaging	10.6% (12/113, 6.2-17.7)	8.7% (9/104, 4.6-15.6)
cN1	13.6% (8/59, 7.0-24.5)	7.0% (3/43, 2.4-18.6)
cN2	10.5% (4/38, 4.2-24.1)	8.1% (3/37, 2.8-21.3)
cN3	0 (0/16)	12.5% (3/24, 4.3-31.0)
Central tumor	10.7% (3/28, 4.0-29.0)	4.6% (1/22, 0.8-21.8)
FDG-non-avid tumor	0 (0/2)	0 (0/0)
Peripheral tumor >3 cm	0 (0/28)	6.9% (2/29, 1.9-22.0)
Modified Unforeseen N2 *		
Intention-to-treat analysis	8.8% (15/171, 5.4-14.0)	7.1% (12/169, 4.1-12.0)
Per protocol analysis	9.0% (15/166, 5.6-14.4)	7.5% (11/146, 4.3-12.9)
Mediastinoscopy N2-3 positives	N/A	8.0% (14/175, 4.8-13.0)
cN1-3 based on imaging	N/A	10.7% (13/121, 6.4-17.5)
cN1	N/A	16.4% (9/55, 8.9-28.3)
cN2	N/A	7.3% (3/41, 2.5-19.4)
cN3	N/A	4.0% (1/25, 0.7-19.5)
Central tumor	N/A	0 (0/23)
FDG-non-avid tumor	N/A	0 (0/0)
Peripheral tumor >3 cm	N/A	3.2% (1/31, 0.6-16.2)

N/A=not applicable; Data are uN2% (n/N, 95%-CI). FDG =fluorodeoxyglucose; CI=confidence interval; cN: clinical nodal stage based on FDG-PET and contrast enhanced chest CT only (i.e. prior to endosonographic and/or cervical mediastinoscopy staging).

*in the modified uN2 analysis, we included the 14 patients with positive mediastinoscopy (without lymph node dissection to assess their true N-status).

Details of uN2

After immediate resection uN2 was multi-level in three patients (20%; one intranodal, two extranodal) and single-level in 12 patients (80%; seven intranodal, five extranodal). Eight uN2 cases (53%) were sampling errors (all benign lymphoid), all within reach of cervical mediastinoscopy. Seven uN2s (47%) were detection errors; two were located in the lower mediastinum (station 8 and 9, both no EUS(B)) and one was located in station 5/6.

In the mediastinoscopy group uN2 was multi-level in one patient (8%; one extranodal) and single-level in 11 patients (92%; seven intranodal, four extranodal). Six (50%) uN2 cases were sampling errors (all benign lymphoid) and six (50%) were detection errors, one in station 9 (no EUS(B)), four in station 5/6 and one in station 3.

Major morbidity and 30-day mortality

Overall, major morbidity and 30-day mortality was found in 12.9% (22/171, 95%-CI: 8.7-18.7) after immediate resection versus 15.4% (27/175, 95%-CI: 10.8-21.5) in the mediastinoscopy group (p=0.4940) (Table 4). Confirmatory mediastinoscopy resulted in minor complications in eight patients (4.6%) and major complications in three patients (1.7%): one had a surgical site infection requiring surgical drainage, one had a persistent laryngeal recurrent nerve palsy and one had a postoperative bleeding requiring re-mediastinoscopy which resulted in inaccessible hilar structures making lung tumor resection impossible. One patient (0.6%) suffered from a sudden death 10 days after mediastinoscopy, no autopsy was performed.

Table 4. Secondary outcome analysis: Morbidity and 30-day mortality

	Clavien-Dindo grade	Immediate lung tumor resection group	Mediastinoscopy group	P value
Overall		n=171	n=175	
Major morbidity	3-4	20 (12%)	22 (13%)	0.8030
30-day mortality	5	2 (1%)	5 (3%)	0.2650
Cervical videomediastinoscopy			n=175	
Minor complications	1-2		8 (5%)	-
Major complications	3-4		3 (2%)	
30-day mortality	5		1 (1%)	
Surgical resection		n=171	n=155	
Minor complications	1-2	54 (32%)	48 (31%)	
Major complications	3-4	20 (12%)	20 (13%)	0.7900
30-day mortality	5	2 (1%)	4 (3%)	

Data are n (%). Clavien-Dindo classification: grade 1: complication without need for interventions, grade 2: complication requiring pharmacological treatment, grade 3: complication requiring surgical, endoscopic or radiological intervention, grade 4: life-threatening complication requiring intensive care management, grade 5: death.

DISCUSSION

This multicenter randomized trial including patients with resectable NSCLC and a negative endosonography demonstrated non-inferiority in uN2 for the immediate resection strategy. Confirmatory mediastinoscopy reduced the uN2 rate by only 1.03%, at the expense of 10 days delay for lung tumor resection, morbidity in 6.3% (potentially impeding curative treatment), mortality in 0.6% and repeat general anesthesia in all patients involved.

A meta-analysis by Sanz-Santos showed an increase in negative predictive value from 79% to 92% by confirmatory mediastinoscopy after negative EBUS, with a NNT of 24.[24] The underlying primary research question in our trial therefore was not to assess the inevitable loss in sensitivity by omitting mediastinoscopy, but to determine whether the expected increase in uN2 was within predefined limits. Our premise hereby was that the increase in uN2 will be counterbalanced by a reduction in the drawbacks of confirmatory mediastinoscopy (secondary outcome). When designing this trial, no consensus was available to determine an acceptable loss in sensitivity nor consensus on a combined outcome measure including loss in sensitivity and gain in morbidity. Since uN2 after final lung tumor resection represents the undesirable outcome of mediastinal staging and includes both benefits (nodal spread detection among patients with N2 disease) and potential harms (demonstrating absence of nodal spread among patients without N2 at the cost of morbidity) of confirmatory mediastinoscopy, we decided uN2 to be the most clinically relevant primary outcome measure. Importantly, we were able to determine an acceptable upper non-inferiority limit for uN2 rate based on the survival data of the ASTER trial.[4,19]

Our study demonstrates that confirmatory mediastinoscopy can be omitted in cN2-3 patients, whereas the subgroup of cN1 may deserve special consideration. Most patients with positive mediastinoscopy and uN2 after immediate resection were from the cN1 subgroup. Previous research suggested cN1 patients to be at high risk of uN2 due to a potential lower diagnostic accuracy of endosonography alone.[25, 26] To overcome this potential lower diagnostic accuracy Leong demonstrated that with the addition of EUS(B) to EBUS the sensitivity increased from 49% to 71% in cN0-1 patients.[27] Albeit we demonstrated non-inferiority including those cN1 patients in our study, further research and tailored mediastinal management of cN1 patients may still be considered.

The prevalence of mediastinal nodal metastases after negative endosonography in our population was 12.9% which is in line with literature, although it was non-significantly lower in the immediate resection group (9.9%) despite randomization. This might be

explained by left-sided paratracheal metastases that are not accessible by lymph node dissection without mediastinoscopy and a random imbalance of left-sided tumors that have an increased a-priori chance of missed metastases in station 5/6 contributing to a higher N2 prevalence after negative endosonography. To test for such possible confounding factors, we performed an unplanned post-hoc analysis with a correction for significant randomization imbalances (see Supplementals). The higher rate of mediastinal nodal spread among patients receiving more diagnostic tests was also demonstrated by Sanz-Santos, demonstrating a 19.5% higher N2-3 prevalence in studies performing confirmatory mediastinoscopy.[24] Although this meta-analysis showed large heterogeneity, the randomized ASTER trial found a difference of 10% in N2-3 prevalence as well without any effect on survival.[4, 19]

Although management in patients with positive mediastinoscopy changed in 13 out of 14 patients, in 92% of patients confirmatory mediastinoscopy was negative and caused morbidity and treatment delay. In our opinion, the benefits of omitting mediastinoscopy for the entire group outweighs the potential for unnecessary surgical resection in a few, especially since the majority of false negative endosonographies includes only minimal N2 disease. Single station and microscopic metastases have better survival compared to multiple station and macroscopic uN2.[28, 29] Moreover, lacking randomised data on this topic, retrospective studies found no survival benefit of neo-adjuvant treatment compared to upfront surgery in patients with minimal N2.[30, 31] We observed that most uN2 cases in our study were single-level intranodal metastases, also after immediate resection. One of the strengths of the MEDIASTrial was the employment of independent data and monitoring specialists as well as upfront publication of protocol and statistical analysis plan. By clear instructions and quality control we achieved high-quality performance of nearly all procedures. A limitation of our study is that only 20% of patients underwent additional EUS(B). This originates from our protocol prescribing that EUS(B) should “preferably” be added to EBUS. Combined systematic EBUS and EUS(B) with routine sampling of specified as well as imaging suspect lymph nodes has demonstrated to have additional diagnostic value over only a targeted approach.[32, 33] Although we already demonstrated non-inferiority, addition of EUS(B) may further prevent patients from uN2. Moreover, despite our effort to optimize staging procedures, 13 uN2 metastases still were detection errors. Three were located in station 8/9 and may have been prevented by performing EUS(B), while six were out of reach for both endosonography and mediastinoscopy (station 3/5/6). Finally, as only 2 patients with FDG-non-avid tumors were included, conclusive statements on this subgroup were forgone.

Our population appears to be representative as two-thirds of included patients had imaging suspected lymph nodes, having the highest risk for occult nodal metastases.[2]

In contrast to the ASTER trial, we performed this multicenter trial in both tertiary and secondary centers in the Netherlands and Belgium. Therefore, our results are widely applicable and expected to be easily implemented.

In conclusion, on the basis of our chosen non-inferiority margin in the rate of unforeseen N2 confirmatory mediastinoscopy after negative systematic endosonography can be omitted in patients with resectable NSCLC and an indication for mediastinal staging.

Abbreviations

NSCLC=non-small cell lung cancer; CT=computed tomography; FDG-PET=18F-fluorodeoxyglucose positron emission tomography; SUV=standardized uptake value; uN2=unforeseen N2 disease; cN=clinical nodal stage; ITT=intention-to-treat; PP=per protocol; CI=confidence interval; NNT=number needed to test; IQR=interquartile range; EBUS=endobronchial ultrasonography; EUS(B)=endoscopic ultrasonography; ESTS=European Society of Thoracic Surgeons.

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Critical revision of the manuscript: Annema, Bousema, Van Den Broek, Dijkgraaf, Van Der Heijden, Verhagen and all members of the MEDIASTrial study group gave approval of the final version of the manuscript to be published.

Conflict of interest

Bousema and Van Den Broek report grants from ZonMw and the Dutch Cancer Society, during the conduct of this study. Van Der Heijden reports unrestricted research grants from Astra Zeneca Oncology, Pentax Medical, Philips Medical and Johnson & Johnson; consultancy for Philips Medical and Johnson & Johnson, and speakers' fees from Pentax Medical, all unrelated to the content of this study and paid to his department. Annema reports educational course support from Hitachi Medical systems, Pentax Medical, COOK

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Data sharing

The datasets and/or analyzed data will be available from the principal investigator (FvdB) on reasonable request. The Data Management plan and Trial Master File are managed by the principal investigator (FvdB).

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REFERENCES

1. Torre LA, Bray F, Siegel RL, et al: Global cancer statistics, 2012. CA: A Cancer Journal for Clinicians 65:87-108, 2015
2. Vilmann P, Clementsen PF, Colella S, et al: Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European society of gastrointestinal endoscopy (ESGE) guideline, in cooperation with the european respiratory society (ERS) and the european society of thoracic surgeons (ESTS). Endoscopy 47:546-560, 2015
3. Bousema JE, Heineman DJ, Dijkgraaf MGW, et al: Adherence to the mediastinal staging guideline and unforeseen N2 disease in patients with resectable non-small cell lung cancer: Nationwide results from the dutch lung cancer audit - surgery. Lung Cancer 142:51-58, 2020
4. Annema JT, van Meerbeeck JP, Rintoul RC, et al: Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: A randomized trial. JAMA 304:2245-2252, 2010
5. Silvestri GA, Gonzalez AV, Jantz MA, et al: Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American college of chest physicians evidence-based clinical practice guidelines. Chest 143:e211S-e250S, 2013
6. NCCN Guidelines®: NCCN clinical practice guidelines in oncology for non-small cell lung cancer V.3. 2022 J Natl Compr Canc Netw. 2022 May;20(5):497-530
7. Bousema JE, Aarts MJ, Dijkgraaf MGW, et al: Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer. The European respiratory journal 57:2001549, 2021
8. Turner SR, Seyednejad N, Nasir BS: Patterns of practice in mediastinal lymph node staging for non-small cell lung cancer in canada. The Annals of Thoracic Surgery 106:428-434, 2018
9. Krantz SB, Howington JA, Wood DE, et al: Invasive mediastinal staging for lung cancer by the society of thoracic surgeons database participants. The Annals of Thoracic Surgery 106:1055-1062, 2018
10. Bousema JE, van Dorp M, Noyez VJJM, et al: Unforeseen N2 disease after negative endosonography findings with or without confirmatory mediastinoscopy in resectable Non–Small cell lung cancer: A systematic review and meta-analysis. Journal of Thoracic Oncology 14:979-992, 2019
11. Bousema JE, Dijkgraaf MGW, Papen-Botterhuis NE, et al: MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): Study protocol of a multicenter randomised controlled trial. BMC surgery 18:27, 2018
12. Verhoeven RLJ, Leoncini F, Slotman J, et al: Accuracy and reproducibility of endoscopic ultrasound B-mode features for observer-based lymph nodal malignancy prediction. Respiration 100:1088-1096, 2021
13. Rusch V, Asamura H, Watanabe H, et al: The IASLC lung cancer staging project A proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. Journal of Thoracic Oncology 4:568-577, 2009
14. Goldstraw P: Report on the international workshop on intrathoracic staging. london, october 1996. Lung cancer (Amsterdam, Netherlands) 18:107-111, 1997
15. Lardinois D, De Leyn P, Van Schil P, et al: ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 30:787-792, 2006
16. Junker K: Histopathologic evaluation of mediastinal lymph nodes in lung cancer. Lung cancer (Amsterdam, Netherlands) 45:S79-S83, 2004

17. Dindo D, Demartines N, Clavien P: Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of surgery 240:205-213, 2004
18. Bousema JE, Annema JT, van der Heijden, Erik H F M, et al: MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): A statistical analysis plan. Trials 22:168, 2021
19. Kuijvenhoven JC, Korevaar DA, Tournoy KG, et al: Five-year survival after endosonography vs mediastinoscopy for mediastinal nodal staging of lung cancer. JAMA 316:1110-1112, 2016
20. Newcombe RG: Interval estimation for the difference between independent proportions: Comparison of eleven methods. Statistics in medicine 17:873, 1998
21. Garner W: Constructing confidence intervals for the differences of binomial proportions in SAS. Foster City, CA, USA: Gilead Sciences, 2007.
22. Hintze J: NCSS, PASS and GESS. Kaysville, Utah, USA: NCSS, 2006
23. Abramson JH: WINPEPI updated: Computer programs for epidemiologists, and their teaching potential. Epidemiologic perspectives & innovations 8:1, 2011
24. Sanz-Santos J, Almagro P, Malik K, et al: Confirmatory mediastinoscopy after negative EBUS-TBNA for mediastinal staging of lung cancer: Systematic review and meta-analysis. Annals of the American Thoracic Society, 2022
25. Dooms C, Tournoy KG, Schuurbiers O, et al: Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: A prospective multicenter study. Chest 147:209-215, 2015
26. Beyaz F, Verhoeven RLJ, Schuurbiers OCJ, et al: Occult lymph node metastases in clinical N0/N1 NSCLC; A single center in-depth analysis. Lung cancer (Amsterdam, Netherlands) 150:186-194, 2020
27. Leong TL, Loveland PM, Gorelik A, et al: Preoperative staging by EBUS in cN0/N1 lung cancer: Systematic review and meta-analysis. Journal of bronchology & interventional pulmonology 26:155-165, 2019
28. Garelli E, Renaud S, Falcoz P, et al: Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 50:322-328, 2016
29. Xu L, Su H, She Y, et al: Which N descriptor is more predictive of prognosis in resected non-small cell lung cancer. Chest 159:2458-2469, 2021
30. Thomas D, Thomas D, Arnold B, et al: The significance of upfront knowledge of N2 disease in non-small cell lung cancer. World J Surg 42:161-171, 2018
31. Keshava HB, Tan KS, Dycoco J, et al: How effective is neoadjuvant therapy followed by surgery for pathologic single-station N2 Non–Small cell lung cancer? Seminars in thoracic and cardiovascular surgery, 2020
32. Crombag LMM, Dooms C, Stigt JA, et al: Systematic and combined endosonographic staging of lung cancer (SCORE study). The European respiratory journal:1800800, 2018
33. Korevaar DA, Crombag LM, Cohen JF, et al: Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: A systematic review and meta-analysis. The Lancet Respiratory Medicine 4:960-968, 2016

SUPPLEMENTARY MATERIAL - POST-HOC ANALYSIS

As important differences in baseline characteristics may exist despite randomisation, we performed a post-hoc analysis to determine whether baseline characteristics were unevenly distributed (Chi square test or student T-test where appropriate, defined as p-value <0.05) among randomisation groups for all primary analyses; the original ITT, the original PP, the modified ITT and the modified PP. The formations of the different populations are presented in Figure 1 (original ITT and PP) and Figure 2 (modified ITT and PP).

This post-hoc analysis of baseline characteristics (Table 2-5) identified unbalanced randomisation in the ITT population (original analysis in Table 2, modified analysis in Table 3) regarding tumor location and in the PP population (original Table 4, modified Table 5) regarding tumor location and histology. For the adjusted post-hoc analysis, left and right central tumors (n≤5 per subgroup) were pooled with the left and right upper lobes (being the largest subgroups per tumor side).

Subsequently, these variables were included in the adjusted post-hoc generalized linear modeling. Unforeseen N2 was assessed as binomial response parameter with identity link to adjust for variables with significant baseline imbalances, the difference in proportions of unforeseen N2 and their upper limits of the Wald 95% two-sided confidence interval are presented in Table 1. Although the results lie within or very close to our chosen non-inferiority limit, the accepted boundary for non-inferiority cannot reliably be applied to the modified analyses with aberrant uN2 definition.

Table 1. Absolute uN2 differences between randomization groups and two-sided 95%-CI upper limits

Analysis		Absolute uN2 difference	Upper limit of two-sided Wald 95%-CI	Indicating non-inferiority
Original ITT	n=326	1.0%	7.2%	Yes
Original PP	n=300	0.8%	7.3%	Yes
Adjusted original ITT*	n=326	1.5%	7.7%	Yes
Adjusted original PP**	n=300	0.3%	7.9%	Yes
Modified ITT	n=340	1.7%	7.7%	N/A
Modified PP	n=312	1.5%	7.8%	N/A
Adjusted modified ITT*	n=340	2.1%	8.1%	N/A
Adjusted modified PP**	n=312	0.8%	8.9%	N/A

*adjusted for tumor location; **adjusted for tumor location and NSCLC histology.
N/A: not applicable since accepted upper boundary for the modified populations are unknown.
ITT=intention-to-treat analysis; PP=per-protocol analysis.

Table 2. Original Intention-To-Treat analysis

	Mediastinoscopy group (n=155)	Immediate lung tumor resection group (n=171)	p value
Age (years)	69 (63-74)	69 (62-73)	0.403
Sex			
Male	97 (63%)	94 (55%)	0.164
Female	58 (37%)	77 (45%)	
WHO performance state			
WHO 0	90 (58%)	105 (61%)	0.831
WHO 1	61 (39%)	60 (35%)	
WHO 2	3 (2%)	5 (3%)	
WHO 3	1 (1%)	1 (1%)	
ASA classification			
ASA-1	4 (2.5%)	8 (5%)	0.597
ASA-2	79 (51%)	85 (50%)	
ASA-3	68 (44%)	76 (44%)	
ASA-4	4 (2.5%)	2 (1%)	
Tumor location*			
Left lower lobe	21 (13%)	21 (12%)	**0.023**
Left upper lobe + left central	49 (32%)	39 (23%)	
Right lower lobe	35 (23%)	29 (17%)	
Right middle lobe	3 (2%)	13 (8%)	
Right upper lobe + right central	47 (30%)	69 (40%)	
Clinical tumor categories based on imaging			
cT1a	1 (1%)	4 (2%)	0.497
cT1b	13 (8%)	18 (11%)	
cT1c	14 (9%)	19 (11%)	
cT2a	42 (27%)	31 (18%)	
cT2b	21 (14%)	23 (13%)	
cT3	46 (29%)	55 (32%)	
cT4	18 (12%)	21 (12%)	

Table 2. Original Intention-To-Treat analysis (*continued*)

	Mediastinoscopy group (n=155)	Immediate lung tumor resection group (n=171)		p value
Clinical nodal categories based on imaging				
cN0	51 (33%)	58 (34%)		0.284
cN1	43 (28%)	59 (35%)		
cN2	37 (24%)	38 (22%)		
cN3	24 (15%)	16 (9%)		
Indication for invasive mediastinal nodal staging				
cN1-3	104 (67%)	113 (66%)		0.850
Central tumor	22 (14%)	28 (16%)		
FDG-non-avid tumor or pheripheral tumor >3cm	29 (19%)	30 (18%)		
Final histopathology				
NSCLC				0.210
Adenocarcinoma	68 (45%)	97 (57%)		
Squamous cell carcinoma	66 (43%)	58 (34%)	p=0.052	
Other **	14 (9%)	9 (5%)		
Small cell carcinoma	3 (2%)	3 (2%)		
Carcinoid	2 (1%)	2 (1%)		
Synovial sarcoma	1 (1%)	0		
Metastasis other malignancy	1 (1%)	0		
Benign	0	2 (1%)		

Data are numbers (%) or median (IQR). WHO=World Health Organisation; ASA=American Society of Anesthesiologists; NSCLC=non-small cell lung cancer.
* left and right central tumors (n≤5 per subgroup) were pooled with the left and right upper lobes (being the largest subgroups per tumor side); **other includes adenosquamous carcinoma, large cell carcinoma and NSCLC not otherwise specified.

Table 3. Original Per Protocol analysis

	Mediastinoscopy group (n=134)	Immediate lung tumor resection group (n=166)	p value
Age (years)	69 (63-73)	69 (63-73)	0.381
Sex			
Male	83 (62%)	91 (55%)	0.214
Female	51 (38%)	75 (45%)	
WHO performance state			
WHO 0	78 (58%)	102 (61%)	0.676
WHO 1	53 (40%)	58 (35%)	
WHO 2	3 (2%)	5 (3%)	
WHO 3	0	1 (1%)	
ASA classification			
ASA-1	4 (3%)	7 (4%)	0.852
ASA-2	67 (50%)	82 (50%)	
ASA-3	60 (45%)	75 (45%)	
ASA-4	3 (2%)	2 (1%)	
Tumor location*			
Left lower lobe	18 (13%)	20 (12%)	**0.035**
Left upper lobe + left central	45 (34%)	39 (24%)	
Right lower lobe	28 (21%)	27 (16%)	
Right middle lobe	3 (2%)	13 (8%)	
Right upper lobe + right central	40 (30%)	67 (40%)	
Clinical tumor categories based on imaging			
cT1a	1 (1%)	4 (2%)	0.659
cT1b	12 (9%)	17 (10%)	
cT1c	12 (9%)	17 (10%)	
cT2a	35 (26%)	30 (18%)	
cT2b	19 (14%)	23 (14%)	
cT3	38 (28%)	54 (33%)	
cT4	17 (13%)	21 (13%)	

Table 3. Original Per Protocol analysis (*continued*)

	Mediastinoscopy group (n=134)	Immediate lung tumor resection group (n=166)		p value
Clinical nodal categories based on imaging				
cN0	44 (33%)	56 (34%)		0.378
cN1	38 (28%)	57 (34%)		
cN2	32 (24%)	38 (23%)		
cN3	20 (15%)	15 (9%)		
Indication for invasive mediastinal nodal staging				
cN1-3	90 (67%)	110 (66%)		0.870
Central tumor	19 (14%)	27 (16%)		
FDG-non-avid tumor or peripheral tumor >3cm	25 (19%)	29 (18%)		
Final histopathology				
NSCLC				0.112
Adenocarcinoma	57 (43%)	94 (57%)		
Squamous cell carcinoma	57 (43%)	57 (34%)	**0.034**	
Other **	13 (8%)	8 (5%)		
Small cell carcinoma	3 (2%)	3 (2%)		
Carcinoid	2 (2%)	2 (1%)		
Synovial sarcoma	0	2 (1%)		
Metastasis other malignancy	1 (1%)	0		
Benign	1 (1%)	0		

Data are numbers (%) or median (IQR). WHO=World Health Organisation; ASA=American Society of Anesthesiologists; NSCLC=non-small cell lung cancer.

* left and right central tumors (n≤5 per subgroup) were pooled with the left and right upper lobes (being the largest subgroups per tumor side); **other includes adenosquamous carcinoma, large cell carcinoma and NSCLC not otherwise specified.

Table 4. Modified Intention-To-Treat analysis [#]

	Mediastinoscopy group (n=169)	Immediate lung tumor resection group (n=171)	p value
Age (years)	69 (63-73)	69 (62-73)	0.524
Sex			
Male	102 (60%)	94 (55%)	0.315
Female	67 (40%	77 (45%)	
WHO performance state			
WHO 0	99 (59%)	105 (61%)	0.813
WHO 1	66 (39%)	60 (35%)	
WHO 2	3 (2%)	5 (3%)	
WHO 3	1 (1%)	1 (1%)	
ASA classification			
ASA-1	4 (2%)	8 (5%)	0.565
ASA-2	87 (52%)	85 (50%)	
ASA-3	74 (44%)	76 (44%)	
ASA-4	4 (2%)	2 (1%)	
Tumor location*			
Left lower lobe	22 (13%)	21 (12%)	**0.020**
Left upper lobe + left central	53 (31%)	39 (23%)	
Right lower lobe	40 (24%)	29 (17%)	
Right middle lobe	4 (2%)	13 (8%)	
Right upper lobe + right central	50 (30%)	69 (40%)	
Clinical tumor categories based on imaging			
cT1a	1 (1%)	4 (2%)	0.549
cT1b	15 (9%)	18 (11%)	
cT1c	16 (9%)	19 (11%)	
cT2a	44 (26%)	31 (18%)	
cT2b	24 (14%)	23 (13%)	
cT3	49 (29%)	55 (32%)	
cT4	20 (12%)	21 (12%)	

Table 4. Modified Intention-To-Treat analysis # (*continued*)

	Mediastinoscopy group (n=169)	Immediate lung tumor resection group (n=171)		p value
Clinical nodal categories based on imaging				
cN0	52 (31%)	58 (34%)		0.426
cN1	52 (31%)	59 (35%)		
cN2	40 (23%)	38 (22%)		
cN3	25 (15%)	16 (9%)		
Indication for invasive mediastinal nodal staging				
cN1-3	117 (69%)	113 (66%)		0.678
Central tumor	22 (13%)	28 (16%)		
FDG-non-avid tumor or peripheral tumor >3cm	30 (18%)	30 (18%)		
Final histopathology**				
NSCLC				0.210
Adenocarcinoma	68 (45%)	97 (57%)	0.052	
Squamous cell carcinoma	66 (43%)	58 (34%)		
Other ***	14 (9%)	9 (5%)		
Small cell carcinoma	3 (2%)	3 (2%)		
Carcinoid	2 (1%)	2 (1%)		
Synovial sarcoma	1 (1%)	0		
Metastasis other malignancy	1 (1%)	0		
Benign	0	2 (1%)		

Data are numbers (%) or median (IQR). WHO=World Health Organisation; ASA=American Society of Anesthesiologists; NSCLC=non-small cell lung cancer.

'Modified' refers to the analysis including patients who did not undergo mediastinal lymph node dissection as reference standard (e.g. patients with positive mediastinoscopy

* left and right central tumors (n≤5 per subgroup) were pooled with the left and right upper lobes (being the largest subgroups per tumor side); **final tumor histopathology of patients who underwent surgical resection; with mediastinoscopy n=155 and without mediastinoscopy n=171; ***other includes adenosquamous carcinoma, large cell carcinoma and NSCLC not otherwise specified.

Table 5. Modified Per Protocol analysis [#]

	Mediastinoscopy group (n=146)	Immediate lung tumor resection group (n=166)	p value
Age (years)	69 (64-73)	69 (63-73)	0.431
Sex			
Male	88 (60%)	91 (55%)	0.331
Female	58 (40%)	75 (45%)	
WHO performance state			
WHO 0	86 (59%)	102 (61%)	0.661
WHO 1	57 (39%)	58 (35%)	
WHO 2	3 (2%)	5 (3%)	
WHO 3	0	1 (1%)	
ASA classification			
ASA-1	4 (3%)	7 (4%)	0.841
ASA-2	73 (50%)	82 (50%)	
ASA-3	66 (45%)	75 (45%)	
ASA-4	3 (2%)	2 (1%)	
Tumor location*			
Left lower lobe	19 (13%)	20 (12%)	**0.028**
Left upper lobe + left central	49 (33%)	39 (24%)	
Right lower lobe	32 (22%)	27 (16%)	
Right middle lobe	4 (3%)	13 (8%)	
Right upper lobe + right central	42 (29%)	67 (40%)	
Clinical tumor categories based on imaging			
cT1a	1 (1%)	4 (2%)	0.652
cT1b	14 (10%)	17 (10%)	
cT1c	14 (10%)	17 (10%)	
cT2a	37 (25%)	30 (18%)	
cT2b	22 (15%)	23 (14%)	
cT3	40 (27%)	54 (33%)	
cT4	18 (12%)	21 (13%)	

Table 5. Modified Per Protocol analysis # (*continued*)

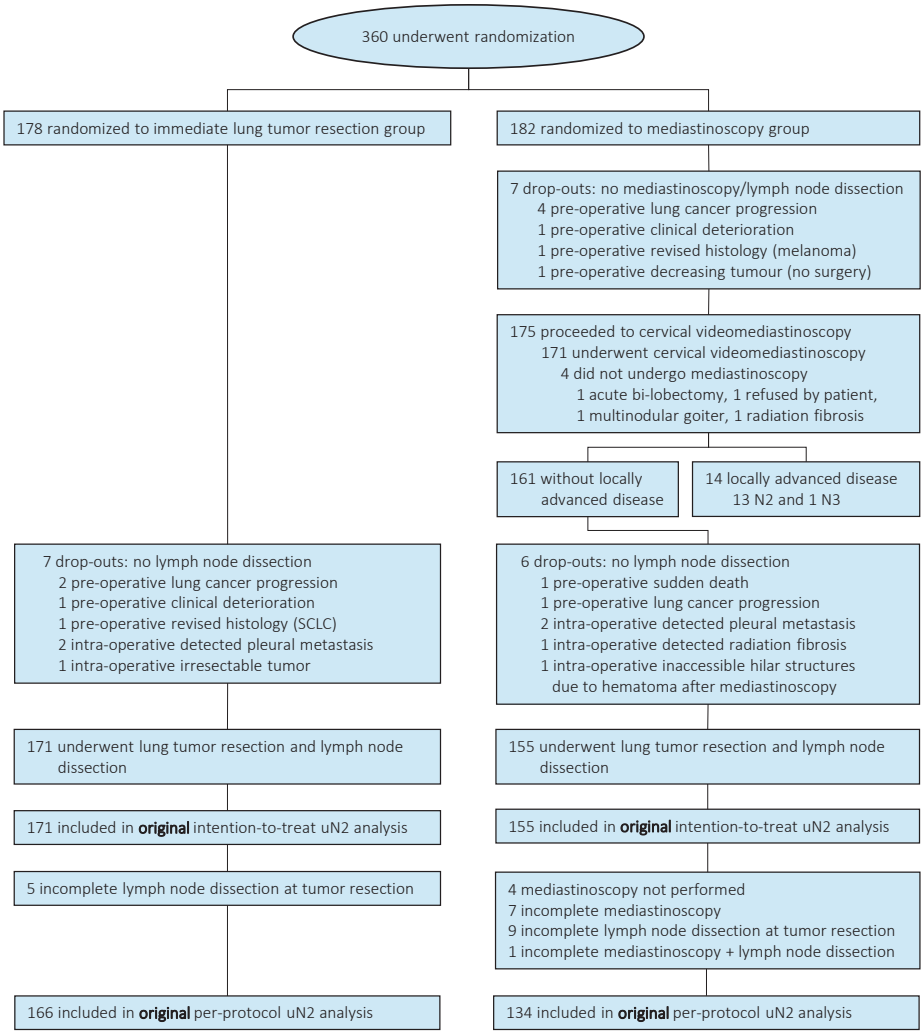
	Mediastinoscopy group (n=146)	Immediate lung tumor resection group (n=166)		p value
Clinical nodal categories based on imaging				
cN0	45 (31%)	56 (34%)		0.482
cN1	45 (31%)	57 (34%)		
cN2	35 (24%)	38 (23%)		
cN3	21 (14%)	15 (9%)		
Indication for invasive mediastinal nodal staging				
cN1-3	101 (69%)	110 (66%)		0.719
Central tumor	19 (13%)	27 (16%)		
FDG-non-avid tumor or peripheral tumor >3cm	26 (18%)	29 (18%)		
Final histopathology**				
NSCLC				0.112
Adenocarcinoma	57 (43%)	94 (57%)		
Squamous cell carcinoma	57 (43%)	57 (34%)	**0.034**	
Other ***	13 (8%)	8 (5%)		
Small cell carcinoma	3 (2%)	3 (2%)		
Carcinoid	2 (2%)	2 (1%)		
Synovial sarcoma	0	2 (1%)		
Metastasis other malignancy	1 (1%)	0		
Benign	1 (1%)	0		

Data are numbers (%) or median (IQR). WHO=World Health Organisation; ASA=American Society of Anesthesiologists; NSCLC=non-small cell lung cancer.

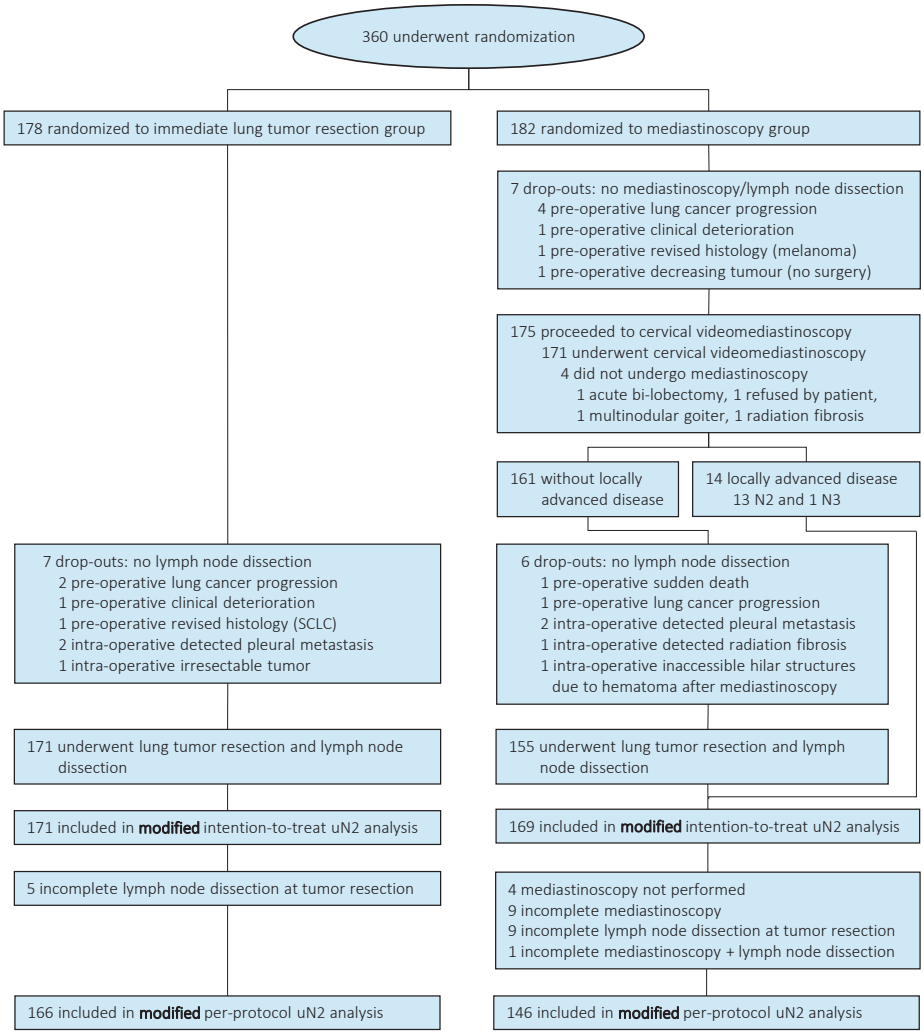
'Modified' refers to the analysis including patients who did not undergo mediastinal lymph node dissection as reference standard (e.g. patients with positive mediastinoscopy;

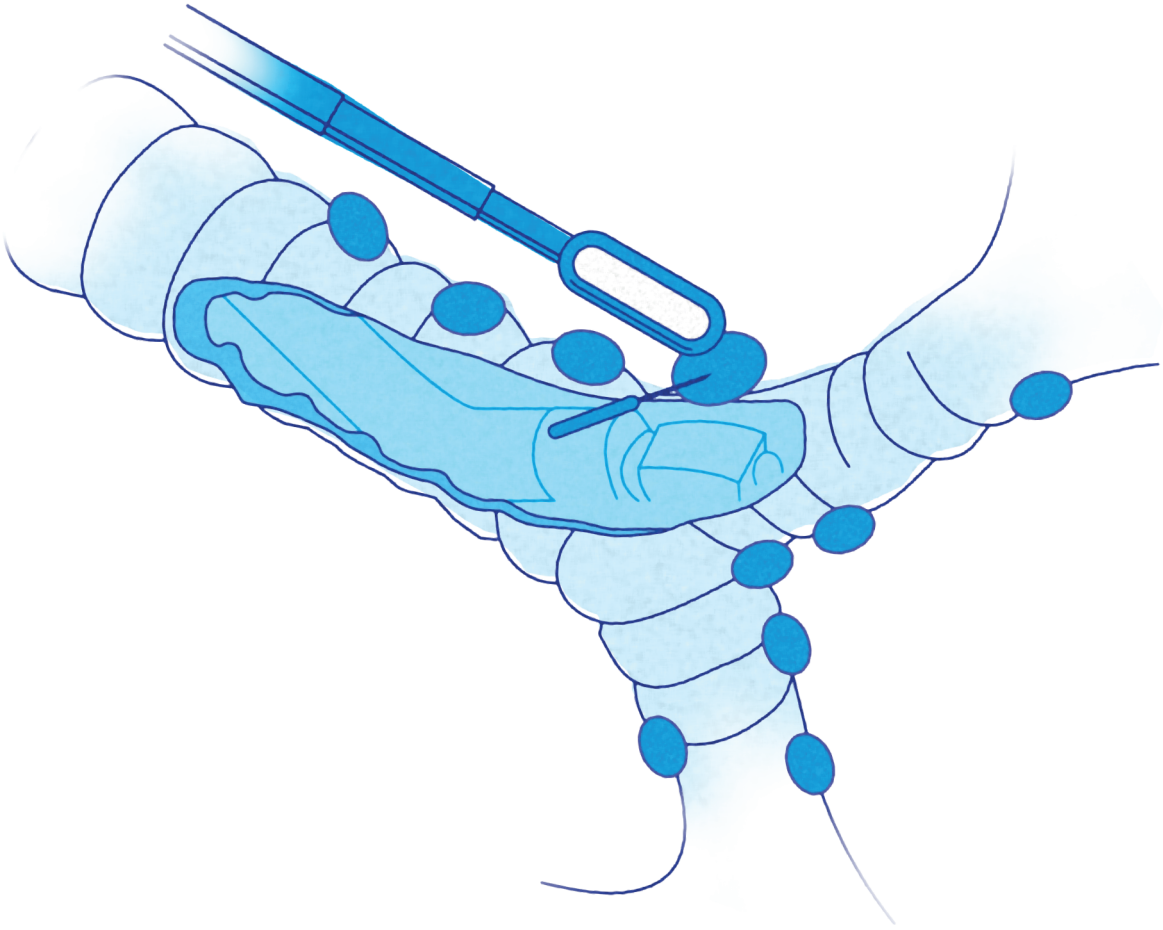
* left and right central tumors (n≤5 per subgroup) were pooled with the left and right upper lobes (being the largest subgroups per tumor side); **final tumor histopathology of patients who underwent surgical resection; with mediastinoscopy n=134 and without mediastinoscopy n=166; ***other includes adenosquamous carcinoma, large cell carcinoma and NSCLC not otherwise specified.

Appendix figure 1. Flowchart **original** intention-to-treat and per protocol populations



Appendix figure 2. Flowchart **modified** intention-to-treat and per protocol populations





Chapter 10

General discussion and future perspectives

GENERAL DISCUSSION

This thesis describes the role of confirmatory mediastinoscopy as part of invasive mediastinal nodal staging of patients with resectable non-small cell lung cancer (NSCLC). The current invasive staging strategy has been induced by historical standards, clinical trials and subsequent evolving guidelines. After publication of the 2007 European Society for Thoracic Surgeons (ESTS) guideline (recommending mediastinoscopy as single invasive staging procedure) the availability of and experience with endoscopic techniques (endobronchial ultrasonography (EBUS) and endoscopic ultrasonography (EUS(B))) for mediastinal nodal staging has tremendously increased in Europe.[1] In the ASTER trial (published in 2010) endosonography had a higher sensitivity for mediastinal nodal metastases detection than mediastinoscopy alone (85% versus 79%). When adding confirmatory mediastinoscopy to endosonography the sensitivity increased to 94%.[2] The higher the sensitivity of the staging process, the lower the rate of unforeseen N2 (uN2), which is defined as N2 detected at definite surgery and missed by endosonography and/or mediastinoscopy. Largely based on these results, the 2015 conjoint European Society of Gastrointestinal Endoscopy (ESGE), European Respiratory Society (ERS) and European Society of Thoracic Surgeons (ESTS) guideline recommended to perform EBUS preferably added by EUS(B) as initial staging technique followed by confirmatory mediastinoscopy in case no N2 or N3 metastases were detected at endosonography.[3]

The recommendations in the conjoint guideline were subsequently questioned as confirmatory mediastinoscopy comes with morbidity and has a rather low additional diagnostic value by itself. Goal of this thesis and specifically the MEDIASTrial was to evaluate the effect of omitting mediastinoscopy as part of the staging strategy. After publication of the conjoint ERS, ESGE and ESTS guideline and while including patients for the MEDIASTrial additional evidence on performance of endosonographic staging was published. A meta-analysis by Korevaar et al. showed a significant increase in sensitivity for detection of mediastinal nodal metastases by using both EBUS and EUS(B) in a combined approach, compared with either test alone.[4] Moreover, the prospective multicenter SCORE-study by Crombag et al. showed a 9% higher sensitivity for mediastinal nodal metastases detection by using a systematic endosonographic approach with combined EBUS and EUS(B), with samples of station 4R, 4L and 7 (if short axis $\geqslant$8 mm or endosonographic suspect) and all PET-CT suspect stations compared to a targeted EBUS approach (EBUS with samples of PET-CT suspect stations only).[5]

The MEDIASTrial ultimately showed that on the basis of non-inferiority in the rate of uN2 (as surrogate marker of clinically relevant diagnostic accuracy) confirmatory mediastinoscopy after negative systematic endosonography can be omitted in patients with

resectable NSCLC and an indication for mediastinal staging. Although non-inferiority in uN2 was already proven, in the immediate resection group only 31 of 171 patients (18%) underwent additional EUS(B) and only a median of 2 mediastinal station were sampled by endosonography. Ultimately 12 of 15 uN2's in the immediate resection group appeared to be located in station 4R, 4L and 7 and 9 out of 15 uN2's were within reach of EUS(B). Therefore, standard addition of EUS(B) and routine samples of station 4R, 4L and 7 (if short axis $\geqslant$8 mm, conform the SCORE study) may potentially further prevent patients from uN2 and subsequently further strengthen the conclusions drawn from the MEDIASTrial.[5,6]

For patients with insufficient endosonography, bulky cN2-3 disease or highly suspicious mediastinal lymph nodes out of reach for conventional surgical resection confirmatory mediastinoscopy should still be strongly considered since this were exclusion criteria for the MEDIASTrial. Another potential high risk subgroup for false negative endosonography results were clinical N1 patients (cN1, based on imaging) which are known to have an occult N2 disease prevalence of approximately 25%.[7,8] Prospective non-randomized studies from the Leuven Lung Cancer Group showed an unsatisfactory sensitivity for mediastinal metastases detection of 38% of endosonography in cN1 patients, while primary mediastinoscopy in this cN1 subgroup resulted in a sensitivity of 73%.[7,8] However, endosonography in the Leuven Lung Cancer Group study consisted of lobe-specific EBUS examination of mediastinal lymph nodes only and just one out of fourteen patients with false negative endosonography results underwent both EBUS and EUS(B). In ten of these fourteen patients, the addition of EUS(B) might have prevented these patients from false negative results since the missed metastases where within reach of EUS(B) (lymph node station 4L, 5, 7 and 8).[9] A meta-analysis by Leong et al. demonstrated that the addition of EUS(B) to EBUS the sensitivity increased from 49% to 71% in a meta-analysis including cN0-1 patients.[10] This is however still lower than the 85% sensitivity of endosonography achieved in the entire group in the ASTER-trial.[2]

The MEDIASTrial results emphasized the potential high risk of cN1 as most patients with metastases detected by mediastinoscopy (9/14) and with uN2 after immediate resection (8/15) were from this cN1 subgroup. The uN2 percentage of cN1 patients after immediate resection in the MEDIASTrial (13.6%) was however still lower than 14.3% uN2 in the surgical staging group in the ASTER-trial, which had similar 5-year overall survival as the combined staging group with 6.9% uN2 in the same trial.[6,11] Additional in-depth analysis of the cN1 subgroup in the MEDIASTrial showed that patients with tumor positive cytology of N1 nodes after endosonography may be the sub-subgroup at highest risk. Figure 1 displays a flowchart of endosonography, mediastinoscopy (if performed) and lung tumor resection with lymph node dissection of the cN1 MEDIASTrial patients. The most

remarkable findings in this subgroup are 40% (2/5) uN2 in patients with prior N1 positive endosonography versus 11% (6/54) uN2 in endosonography negatives and immediate resection. Moreover, when performing mediastinoscopy in patients with proven N1 metastases at endosonography, 55% (6/11) of them turned out to have N2 disease at mediastinoscopy, while we found only 6.8% (3/44) N2 mediastinoscopy positives in cN1 patients with negative endosonography. Additional analyses of our Dutch Lung Cancer Audit – Surgery (DLCA-S) dataset including all patients who underwent a primary lung resection with lymph node dissection for NSCLC in 2017-2018 showed similar results. Unforeseen N2 was found in 46% (11/24) after immediate resection in patients with proven N1 metastases at endosonography. These uN2 metastases were single-level in 81% of patients. The database included no mediastinoscopy N2 positives withholding conclusions on mediastinoscopy results after N1 positive endosonography.[12]

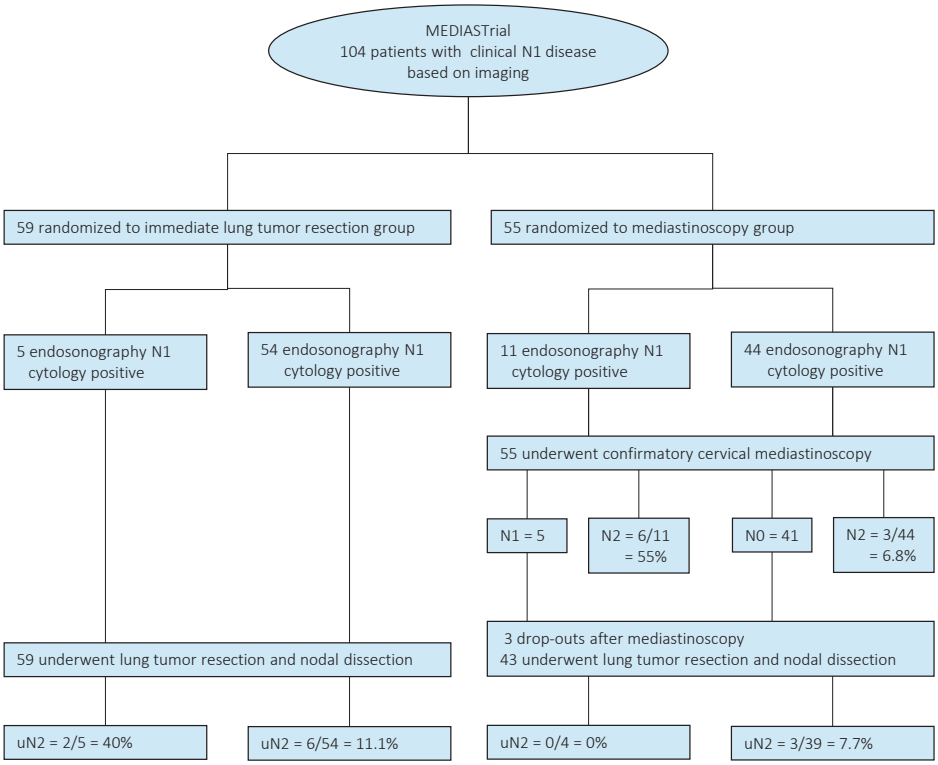


Figure 1. Flowchart of clinical N1 patients in the MEDIASTrial.

These subgroups should however be interpreted with care as they are small and potentially biased populations. Sampling of N1 stations was not mandatory in the MEDIASTrial endosonography protocol, resulting in only two third of cN1 patients who underwent

sampling of N1 stations at endosonography. Although we do not have this detailed data on endosonography procedures, this may be a selection of patients with high risk endosonographic characteristics or high risk tumor characteristics only. Therefore, albeit we demonstrated non-inferiority including cN1 patients in the MEDIASTrial and the subgroups were underpowered for firm conclusions, further research and tailored mediastinal management of cN1 patients, especially those with proven N1 metastases at endosonography, should be strongly considered.

Regarding invasive mediastinal staging as part of optimal lung cancer treatment uN2 is a commonly used outcome measure. In all studies included in this thesis uN2 was calculated by dividing the number of patients with pathologically proven N2 resulting from lymph node dissection, not detected by endosonography or mediastinoscopy, by the total number of patients undergoing lymph node dissection. Although this definition of uN2 is generally used, one may argue that patients with malignant mediastinoscopy results should also be included in the denominator of this calculation. One of the reviewers in the assessment of our MEDIASTrial publication questioned this specific definition, which resulted in our modified uN2 calculation in the MEDIASTrial, also including mediastinoscopy positives in the uN2 calculation. The modified analysis demonstrated upper margins of the difference in uN2 rate within the chosen acceptable upper limit favoring the immediate resection strategy.[6]

Another point of discussion is whether to include nodal spread to station 5/6 in the uN2 calculation. Although limited data exists from expert centres on transaortic EUS-guided fine needle aspiration of station 5/6, these nodes cannot be reached by conventional EBUS, EUS or mediastinoscopy.[13] Malignant spread to station 5/6 usually results from left upper lobe tumors. In these patients a significantly better 3-year survival was found in patients with station 5/6 metastases compared to patients with N2 disease in station 7.[14] Therefore, station 5/6 are sometimes considered N1 nodes in left upper lobe tumors, which makes pre-operative tissue confirmation less necessary in these cases and subsequent inclusion in uN2 calculation gets debatable. We recognized this debate when designing the MEDIASTrial and included in the study protocol that if metastatic spread to these nodal stations would lead to changes in treatment strategy according to the local multidisciplinary board extended invasive staging (i.e. parasternal mediastinotomy/scopy or VATS) should have been performed. In patients with suspect station 5/6 on imaging in whom no extended staging was performed, pathological positivity of these nodal stations will be considered foreseen N2 disease, and thus not included in unforeseen N2 calculation. The MEDIASTrial included a random imbalance of left-sided tumors which have an increased a-priori chance of missed metastases in station 5/6 contributing to a higher N2 prevalence after negative endosonography. Post-hoc

analysis with a correction for significant randomization imbalances however showed no significant differences among the groups.[6]

Taking into account the applied definition of uN2 when comparing studies, the most pivotal question is to what extent uN2 disease is acceptable before long-term survival is compromised. For the MEDIASTrial we set the non-inferiority margin in uN2 difference at 8%, being the difference between a minimum of 6.3% uN2 after endosonography and mediastinoscopy resulting from a systematic review during the research proposal and an upper limit of 14.3% uN2 in the ASTER trial among patients undergoing mediastinoscopy alone without compromising 5-year survival (i.e. 35%).[2] Several other studies showed 5-year survival rates of 34-48% in surgical patients with uN2 disease undergoing adjuvant therapy with similar survival rates compared to primary surgically treated patients with N1 or minimal N2 disease.[15-21] This emphasizes that load of missed mediastinal metastases is important, which was evinced in differences in overall survival rates between patients with single and multiple station N2 disease and between patients with microscopic (0.2 to 2 mm) and macroscopic N2 disease.[22-24] In the MEDIASTrial 85% of uN2 cases had single-level metastases only.[6] Moreover, the positive effect of invasive mediastinal staging on overall survival benefit is suggested in both our nationwide Dutch and a large American cohort. This probably results from detecting patients with extensive mediastinal nodal disease, since these likely benefit more from multimodality therapy than from primary surgery.[25, 26]

When discussing the role of uN2 rates, the quality of mediastinal lymph node dissection is of utmost importance. Being the gold standard for N-status in surgical NSCLC patients, the nodal stage determines adjuvant treatment choice and prognosis and it reflects the accuracy of mediastinal lymph node staging. The ESTS guideline recommends lobe-specific lymph node dissection with dissection of at least three mediastinal lymph node stations per lobe.[1, 27] Van Der Woude et al. presented nationwide Dutch Lung Cancer Audit – Surgery data indicating that only 59% of mediastinal lymph node dissections were complete, with a wide variation among hospitals in completeness levels.[28] Although this database contains less detailed information than is desired for research purposes, it may indicate a problem with guideline compliance for the gold standard of surgical lung cancer treatment. On the other hand, under research circumstances in the MEDIASTrial a complete mediastinal lymph node dissection conform ESTS guidelines was achieved in 95% (311/326) of patients.[6]

Besides the completeness in terms of assessed nodal stations there is debate whether lymph node sampling is enough or lymph node stations should be dissected completely. The only available randomized trial on this topic was published in 2011. Darling et al.

included patients with T1-2N0-1 resectable NSCLC and showed no survival benefit of a mediastinal lymph node dissection after a frozen section negative mediastinal lymph node sampling, either by mediastinoscopy or VATS.[29] However, several more recent published observational and retrospective studies showed there is increasing evidence indicating that a radical lymph node dissection has a positive influence on survival.[30-33] We addressed this debate when designing the MEDIASTrial and considered several ways to measure the extensiveness of the prescribed lymph node dissection (i.e. video assessment, specimen weight, lymph node count). However, lacking standard values for these measurements and potentially compromising the feasibility of the study by increasing the data collection load we decided to only register which lymph node stations were assessed.

Future perspectives

The results of the MEDIASTrial are expected to be implemented in national and international guidelines. However, the former studies in this thesis indicate the challenges in daily practice.

In our nationwide Dutch Lung Cancer Audit – Surgery database study we showed that 43% underwent initial endosonography followed by a confirmatory mediastinoscopy in 44% of them, resulting in a 19% properly staged patients according to the guidelines.[12] Moreover, in our multicenter retrospective study we found that only the minority of patients underwent systematic performed combined EBUS and EUS(B) procedures, while in the MEDIASTrial only 20% of patients underwent additional EUS(B).[6, 34] While the evidence for omitting mediastinoscopy relieves patients and physicians from one additional staging procedure, systematic performance endosonography is mandatory. Although the MEDIASTrial showed non-inferiority in uN2 based on EBUS alone in most patients, the routine addition of EUS(B) may even further prevents patients from uN2.

The ESTS, ERS and ESGE meanwhile composed a multidisciplinary project group to update the 2015 conjoint guideline on the Staging of Lung Cancer, which is expected to be published in autumn 2024. In my opinion, the most interesting but challenging recommendation will be the staging pattern of cN1 patients, especially those with endosonography proven N1 metastases. Another point of discussion should be the recommendation grade for routinely performing additional EUS(B) in combination with EBUS. Alongside updating current guidelines, the International Association for the Study of Lung Cancer Lung Cancer Staging Project is currently working on the ninth edition of the TNM staging system. The current eight version includes a straightforward N0 tot N3 nodal classification system. These categories however leave no room for subtyping based on extensiveness and location of lymph node involvement. The ninth edition TNM

staging system for lung cancer is expected in 2024, probably including an elaborated nodal classification system based on criteria that define treatment options for the different categories, including minimal N2.

The long-term results of the MEDIASTrial including overall and disease-free 2-year survival, quality of life and health economics are expected in 2024. When omitting a surgical staging procedure under general anesthesia a direct cost reduction is obviously expected. Based on the uN2 results the strategy without mediastinoscopy appears to be oncological safe, and therefore a large rebound in costs of adjuvant therapy of uN2 patients is not expected. Beside the expected health economic benefits, omitting mediastinoscopy spares the environment in the current Dutch nitrogen and worldwide non-recycle plastic surgical equipment crisis. After publication of these secondary outcomes, the follow-up will be continued for survival, with the first evaluation at 5-year after surgery.

The results and available data of the MEDIASTrial are available for further research. The first side-study including MEDIASTrial data is currently being performed by pathologists from the Leiden University Medical Center. In the DANDELION study the prognostic significance of micrometastasis and isolated tumor cells in lymph nodes in patients with early stage non-small cell lung cancer is investigated by additional histopathological examination with immunohistochemistry. This study will provide us with information on the prognostic features of micrometastasis as well as information among the most optimal technique of histopathologic examination of lymph node samples.

As result of the MEDIASTrial the absolute number of mediastinoscopies is expected to decrease significantly which may potentially compromise the experience of current thoracic surgeons and the learning curve of residents with this procedure. At the same time, the upcoming centralization of lung surgery in the Netherlands will contrary increase the number of mediastinoscopy procedures per hospital or thoracic surgeon who retains lung surgery. Though, the indication for surgical tissue sampling by mediastinoscopy will persist for a category of lung cancer patients excluded for the MEDIASTrial (i.e. bulky cN2-3 disease, highly suspicious but irresectable lymph nodes) as well as for diagnosing other mediastinal masses or mediastinal nodal involvement (i.e. lymphoma, sarcoidosis or metastasis of other malignancy). In the upcoming era of molecular cancer diagnostics and personalized medicine the need for surgical/histological samples will probably persist. However, for this indication mediastinoscopy potentially gets competition of EBUS cryobiopsy which has recently been introduced with promising results in lymphoma and sarcoidosis diagnostics. EBUS cryobiopsy has shown to be safe and has the theoretical advantage of larger samples (comparable to surgical biopsies) allowing histology

and molecular testing.[35] A recent randomized trial by Herth et al. showed that adequate samples for molecular lung cancer testing were obtained using EBUS-transbronchial needle aspiration (TBNA) and cryobiopsy in 97% versus 79% after EBUS-TBNA alone. However, in the same study the higher rate of adequate large samples did not lead to diagnostic benefit of EBUS-cryobiopsy over EBUS-TBNA alone in lung cancer diagnosis and nodal metastases detection.[35, 36]

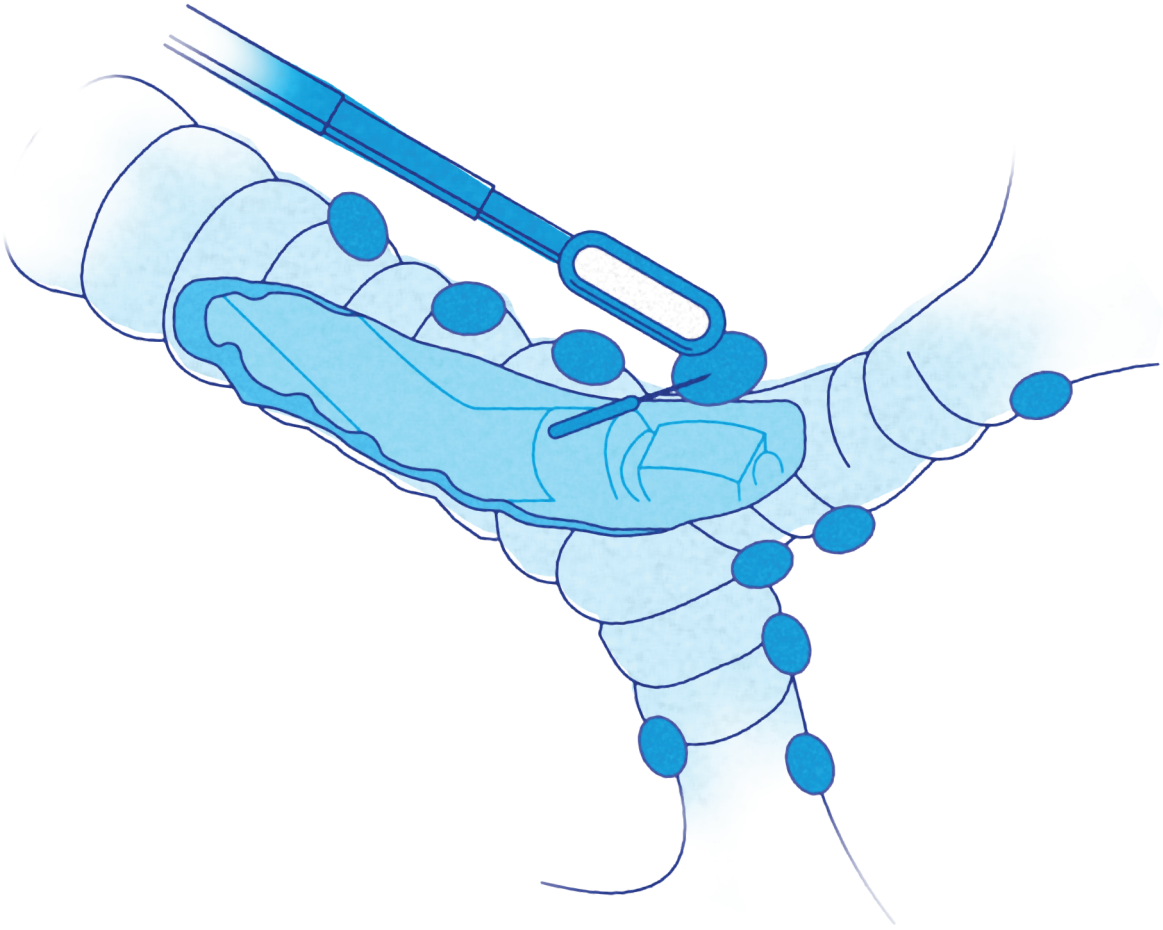
Finally, outside the scope of this thesis, the first papers on immunotherapy as neoadjuvant or adjuvant treatment in patients with resectabele lung cancer have yet been published.[37-39] The selection of patients who benefit from neoadjuvant treatment however is controversial. The currently available data suggests higher event-free-survival benefit in stage III lung cancer compared to stage I/II disease, however none of the studies had adequate power for firm subgroup conclusions.[39] To optimally identify patients benefitting from neoadjuvant treatment one could suggest to maximize sensitivity of invasive staging (i.e. EBUS, EUS and mediastinoscopy) which may again argue against the conclusions of MEDIASTrial. However, we have shown that by performing systematic endosonography we create a population with 12.9% false negative endosonography results, of which the great majority had single-level N2 (i.e. minimal N2 disease).[6] One should recognize that these minimal N2 disease patients are different stage III lung cancers compared to patients with extended N2 disease (i.e. multi-level or bulky N2) or even N3 disease already diagnosed by endosonography. This may be a potential part of the nodal and overall lung cancer staging system to be adapted for the divergent treatment options in the feature. Awaiting further evidence on neoadjuvant treatment, the little increase in minimal uN2 disease with good adjuvant treatment options, weighs up to the invasiveness of confirmatory mediastinoscopy for the entire group involved. Further research on the effectiveness and indication and immunotherapy will follow, which can potentially also influence the mediastinal nodal staging pattern and the demand for larger endobronchial or endoscopic samples.

REFERENCES

1. De Leyn P, Dooms C, Kuzdzal J, et al: Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 45:787-798, 2014
2. Annema JT, van Meerbeeck JP, Rintoul RC, et al: Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: A randomized trial. JAMA 304:2245-2252, 2010
3. Vilmann P, Clementsen PF, Colella S, et al: Combined endobronchial and esophageal endosonography for the diagnosis and staging of lung cancer: European society of gastrointestinal endoscopy (ESGE) guideline, in cooperation with the european respiratory society (ERS) and the european society of thoracic surgeons (ESTS). Endoscopy 47:546-560, 2015
4. Korevaar DA, Crombag LM, Cohen JF, et al: Added value of combined endobronchial and oesophageal endosonography for mediastinal nodal staging in lung cancer: A systematic review and meta-analysis. The Lancet Respiratory Medicine 4:960-968, 2016
5. Crombag LMM, Dooms C, Stigt JA, et al: Systematic and combined endosonographic staging of lung cancer (SCORE study). The European respiratory journal:1800800, 2018
6. Bousema JE, Dijkgraaf MGW, van der Heijden, Erik H F M, et al: Endosonography with or without confirmatory mediastinoscopy for resectable lung cancer: A randomized clinical trial. Journal of clinical oncology 41:3805-3815, 2023
7. Dooms C, Tournoy KG, Schuurbiers O, et al: Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: A prospective multicenter study. Chest 147:209-215, 2015
8. Decaluwé Herbert, Dooms Christophe, D'Journo Xavier Benoit, et al: Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: A prospective multicentre study. The European Respiratory Journal 50:1701493, 2017
9. Annema, Jouke T., MD, PhD: Endosonographic staging for N1 disease. Chest 147:e122, 2015
10. Leong TL, Loveland PM, Gorelik A, et al: Preoperative staging by EBUS in cN0/N1 lung cancer: Systematic review and meta-analysis. Journal of bronchology & interventional pulmonology 26:155-165, 2019
11. Kuijvenhoven JC, Korevaar DA, Tournoy KG, et al: Five-year survival after endosonography vs mediastinoscopy for mediastinal nodal staging of lung cancer. JAMA 316:1110-1112, 2016
12. Bousema JE, Heineman DJ, Dijkgraaf MGW, et al: Adherence to the mediastinal staging guideline and unforeseen N2 disease in patients with resectable non-small cell lung cancer: Nationwide results from the dutch lung cancer audit - surgery. Lung Cancer 142:51-58, 2020
13. von Bartheld, Martin B., BSc, Rabe, Klaus F., MD, PhD, Annema, Jouke T., MD, PhD: Transaortic EUS-guided FNA in the diagnosis of lung tumors and lymph nodes. Gastrointestinal Endoscopy 69:345-349, 2009
14. Citak N, Sayar A, Metin M, et al: The prognostic significance of metastasis to lymph nodes in aortopulmonary zone (stations 5 and 6) in completely resected left upper lobe tumors. The Thoracic and Cardiovascular Surgeon 63:568-576, 2015
15. Cerfolio RJ, Bryant AS: Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. The Annals of Thoracic Surgery 86:362-367, 2008
16. Obiols C, Call S, Rami-Porta R, et al: Survival of patients with unsuspected pN2 non-small cell lung cancer after an accurate preoperative mediastinal staging. The Annals of thoracic surgery 97:957-964, 2014
17. Deok Heon Lee, Jae Bum Kim, Dong Yoon Keum, et al: Long term survival of patients with unsuspected N2 disease in non-small cell lung cancer. Korean J Thorac Cardiovasc Surg 46:49-55, 2013

18. Kim MP, Correa AM, Hofstetter WL, et al: Occult stage IIIA-N2 patients have excellent overall survival with initial surgery. Journal of thoracic disease 10:6670-6676, 2018
19. Thomas D, Thomas D, Arnold B, et al: The significance of upfront knowledge of N2 disease in non-small cell lung cancer. World J Surg 42:161-171, 2018
20. Keshava HB, Tan KS, Dycoco J, et al: How effective is neoadjuvant therapy followed by surgery for pathologic single-station N2 Non–Small cell lung cancer? Seminars in thoracic and cardiovascular surgery, 2020
21. Hui WK, Charaf Z, Hendriks JMH, et al: True prevalence of unforeseen N2 disease in NSCLC: A systematic review + meta-analysis. Cancers 15:3475, 2023
22. Yoo, Changhoon|Yoon, Shinkyo|Lee, Dae Ho|Park, Seung-Il|Kim, Dong Kwan|Kim, Yong-Hee|Kim, Hyeong Ryul|Choi, Se Hoon|Kim, Woo Sung|Choi, Chang-Min|Jang, Se Jin|Song, Si Yeol|Kim, Su Ssan|Choi, Eun Kyung|Lee, Jae Cheol|Suh, Cheolwon|Lee, Jung-Shin|Kim, Sang-We: Prognostic significance of the number of metastatic pN2 lymph nodes in stage IIIA-N2 Non–Small-cell lung cancer after curative resection. Clinical Lung Cancer 16:e203-e212, 2015
23. Garelli E, Renaud S, Falcoz P, et al: Microscopic N2 disease exhibits a better prognosis in resected non-small-cell lung cancer. European Journal of Cardio-Thoracic Surgery 50:322-328, 2016
24. Xu L, Su H, She Y, et al: Which N descriptor is more predictive of prognosis in resected non-small cell lung cancer. Chest 159:2458-2469, 2021
25. Meadows-Taylor MB, Faris NR, Smeltzer MP, et al: The relative survival impact of guideline-concordant clinical staging and stage-appropriate treatment of potentially curable non-small cell lung cancer. Chest 162:242-255, 2022
26. Bousema JE, Aarts MJ, Dijkgraaf MGW, et al: Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer. The European respiratory journal 57:2001549, 2021
27. Rami-Porta R, Wittekind C, Goldstraw P: Complete resection in lung cancer surgery: Proposed definition. Lung Cancer 49:25-33, 2005
28. van der Woude L, Wouters MWJM, Hartemink KJ, et al: Completeness of lymph node dissection in patients undergoing minimally invasive- or open surgery for non-small cell lung cancer: A nationwide study. European journal of surgical oncology 47:1784-1790, 2021
29. Darling GE, Maziak DE, Inculet RI, et al: Positron emission tomography-computed tomography compared with invasive mediastinal staging in non-small cell lung cancer: Results of mediastinal staging in the early lung positron emission tomography trial. Journal of Thoracic Oncology 6:1367-1372, 2011
30. Smeltzer MP, Faris NR, Ray MA, et al: Association of pathologic nodal staging quality with survival among patients with Non–Small cell lung cancer after resection with curative intent. JAMA Oncology 4:80-87, 2018
31. Heiden BT, Eaton DB, Chang S, et al: Assessment of updated commission on cancer guidelines for intraoperative lymph node sampling in early stage NSCLC. Journal of thoracic oncology 17:1287-1296, 2022
32. Handa Y, Tsutani Y, Mimae T, et al: Systematic versus lobe-specific mediastinal lymphadenectomy for hypermetabolic lung cancer. Ann Surg Oncol 28:7162-7171, 2021
33. Yao A, Liu Z, Rao H, et al: Exploration of the optimal number of regional lymph nodes removed for resected N0 NSCLC patients: A population-based study. Frontiers in oncology 12:1011091, 2022
34. Bousema JE, van Dorp M, Hoeijmakers F, et al: Guideline adherence of mediastinal staging of non-small cell lung cancer: A multicentre retrospective analysis. Lung Cancer 134:52-58, 2019

35. Fan Y, Zhang A, Wu X, et al: Transbronchial needle aspiration combined with cryobiopsy in the diagnosis of mediastinal diseases: A multicentre, open-label, randomised trial. The lancet respiratory medicine 11:256-264, 2023
36. Botana-Rial M, Lojo-Rodríguez I, Leiro-Fernández V, et al: Is the diagnostic yield of mediastinal lymph node cryobiopsy (cryoEBUS) better for diagnosing mediastinal node involvement compared to endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA)? A systematic review. Respiratory medicine 218:107389, 2023
37. Forde PM, Spicer J, Lu S, et al: Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. The New England journal of medicine 386:1973-1985, 2022
38. Felip E, Altorki N, Zhou C, et al: Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): A randomised, multicentre, open-label, phase 3 trial. The Lancet (British edition) 398:1344-1357, 2021
39. Chen LN, Wei AZ, Shu CA: Neoadjuvant Immunotherapy in Resectable Non-Small-Cell Lung Cancer. London, England, SAGE Publications, 2023



Chapter 11

English summary
Nederlandse samenvatting
PhD portfolio
About the author
Dankwoord

ENGLISH SUMMARY

Chapter 1 introduces mediastinal nodal staging of patients with resectabele non-small cell lung cancer (NSCLC) as main topic of this thesis. The current international guidelines recommend endosonography (preferably endobronchial ultrasonography (EBUS) combined with endoscopic ultrasonography (EUS(B)) as initial staging procedure followed by confirmatory mediastinoscopy in case of absence of N2-3 metastases detected by endosonography. The role of confirmatory mediastinoscopy is however under debate due to its limited additional diagnostic value and its associated morbidity, hospital admission, general anaesthesia and delay in definite lung cancer treatment.

The first part of the thesis focusses on the daily practice of invasive mediastinal nodal staging and adherence to the (inter)national guidelines. **Chapter 2** describes a multicenter (n=6) retrospective analysis of 330 patients on guideline adherence for mediastinal nodal staging. Although initial staging by endosonography was performed in 84% of patients, the quality of endosonography procedures was insufficient in 30%. Confirmatory mediastinoscopy was omitted in 60% of patients with negative endosonography. Significant variability was found among participating centres regarding staging strategy and systematic performance of procedures. However, unforeseen N2 (uN2) rates after mediastinal staging by endosonography with and without confirmatory mediastinoscopy were comparable.

In **Chapter 3** a nationwide analysis of adherence to the mediastinal staging guidelines using data from the Dutch Lung Cancer Audit – Surgery was described. We analysed all patients who underwent a primary lung resection with lymph node dissection for NSCLC in 2017-2018 and assessed the use of initial endosonography, confirmatory mediastinoscopy and uN2 rates. A total of 2,238 patients were included of which 43% underwent initial endosonography followed by a confirmatory mediastinoscopy in 44% of them, resulting in 19% properly staged patients according to the guidelines. In the entire group no differences in uN2 were found among patients staged conform guidelines or not. However, in the subgroup of patients with clinical N1-3 based on imaging a significant difference in uN2 was found of 23% in patients who were not staged versus 13% uN2 after endosonography and mediastinoscopy.

Chapter 4 consists of a nationwide Dutch cohort study including all clinical stage IA-IIIB NSCLC patients primarily treated by surgical resection in 2005-2017, registered in the Netherlands Cancer Registry. A total of 22,555 patients were included and a significant increase in the use of invasive nodal staging (i.e. endosonography and/or mediastinoscopy) from 26% in 2005 to 40% in 2017 was found. The use of endosonography increased

from 19% in 2011 to 32% in 2017 (p<.01), while mediastinoscopy decreased from 24% in 2011 to 21% in 2017 (p=.08). Despite these changes, uN2 was stable over the years at 8.7%. Performance of invasive staging indicated a possible overall survival benefit in patients with cN1-3 disease, with five-year overall survival of 44% in patients with staging versus 39% in patients without invasive staging (p=.12).

In the second part of this thesis we focussed on the value of confirmatory mediastinoscopy after tumor negative endosonography in mediastinal nodal staging of resectable non-small cell lung cancer. In **Chapter 5** we investigated patients' preferences regarding invasive mediastinal nodal staging of resectable lung cancer. An internet-based questionnaire was distributed among MEDIASTrial participants and was completed by 97 patients (57%). An adaptive-conjoint-analysis and Hierarchical Bayes estimation to determine the most important attribute was designed based on literature, expert opinion and patient interviews. The length of the staging period was significantly the most important attribute followed by the risk of a futile surgical lung resection and resection of the primary tumor. A treatment-trade-off showed that avoidance of 7% futile lung resections would cover the burden of confirmatory mediastinoscopy, with a dichotomy among patients always (39%) or never (38%) willing to undergo confirmatory mediastinoscopy after N2 and N3 negative endosonography.

Chapter 6 is a systematic review and meta-analysis assessing uN2 disease following negative endosonography with or without confirmatory mediastinoscopy in resectable NSCLC as well as the complications of mediastinoscopy. The MEDLINE, EMBASE and Cochrane databases were searched till September 19, 2018 and a total of 5,073 articles were found of which 42 studies or subgroups (covering 3,248 patients undergoing the surgical reference standard of treatment) were considered in the analysis. Random effects meta-analysis showed 9.6% uN2 after endosonography and mediastinoscopy versus 9.9% uN2 after endosonography alone. Random effects meta-analysis of mediastinoscopy (eight studies; 1,245 patients in total) showed an overall complication rate of 6.0%, including 1.9% Clavien-Dindo grade III-IV complications and 2.8% laryngeal recurrent nerve palsy.

Chapter 7 is the study protocol of the multicenter randomized MEDIASTrial. Patients with (suspected) resectable NSCLC and an indication for mediastinal staging after negative systematic endosonography were randomly assigned to immediate lung tumor resection or confirmatory mediastinoscopy followed by tumor resection. The primary outcome in this non-inferiority trial was the presence of uN2 disease following tumor resection with lymph node dissection. Secondary outcomes are 30-day major morbidity and mortality.

In **Chapter 8** the statistical analysis plan of the MEDIASTrial is described. A systematic review being part of the research proposal of the MEDIASTrial showed an uN2 rate of 6.3% after endosonography and mediastinoscopy. From the ASTER-trial an uN2 rate as high as 14.3% was calculated in patients undergoing mediastinoscopy alone without compromising 5-year survival. Based on these numbers we set the non-inferiority margin at 8% (difference between 6.3% - 14.3%), resulting in a sample size of 171 patients in each group to achieve a power of 80% with an alpha error of 0.0250. With an assumed drop-out rate of 5% the aimed sample size was 360 patients. Intention-to-treat (ITT) analyses of uN2 were performed, in which patients with N2 disease detected by mediastinoscopy were excluded since they did not undergo lymph node dissection that was necessary for uN2 calculation. All patients with complete mediastinoscopy and lymph node dissection procedures (conform study protocol) were included for the per protocol (PP) uN2 analysis. Non-inferiority was concluded if the upper limits of the 95%-CIΔ (UL 95%-CIΔ) following ITT and PP were smaller than the absolute 8% margin from the observed uN2 rates for the mediastinoscopy group.

In **Chapter 9** we describe the primary outcomes of the MEDIASTrial in which between July 17, 2017 and October 5, 2020, three-hundred-sixty patients were randomized. One-hundred-seventy-eight to immediate lung tumor resection (seven drop-outs) and 182 to confirmatory mediastinoscopy first (seven drop-outs before and six after mediastinoscopy). Mediastinoscopy detected metastases in 8.0% (14/175) of patients. The uN2 rate after immediate resection (8.8%) was non-inferior compared to mediastinoscopy first (7.7%) in both ITT (Δ:1.03%, UL 95%-CIΔ: 7.2%, $P_{non\text{-}inferior}$=.0144) and PP analyses (Δ:0.83%, UL 95%-CIΔ: 7.3%, $P_{non\text{-}inferior}$=.0157). Major morbidity and 30-day mortality was 12.9% after immediate resection versus 15.4% after mediastinoscopy first (p=.4940).

The general discussion of this thesis (**Chapter 10**) considers current literature and the additional value of the MEDIASTrial results. The MEDIASTrial ultimately showed that on the basis of non-inferiority in the rate of uN2 (as surrogate marker of clinically relevant diagnostic accuracy) confirmatory mediastinoscopy after negative systematic endosonography can be omitted in patients with resectable NSCLC and an indication for mediastinal staging. For patients with insufficient endosonography, bulky cN2-3 disease or highly suspicious mediastinal lymph nodes but out of reach for conventional surgical resection confirmatory mediastinoscopy should still be strongly considered since this were exclusion criteria for the MEDIASTrial. Another potential high risk subgroup for false negative endosonography results were clinical N1 patients based on imaging. Albeit the MEDIASTrial demonstrated non-inferiority including cN1 patients in the MEDIASTrial and the subgroups were underpowered for firm conclusions, further research and tailored

mediastinal management of cN1 patients, especially those with proven N1 metastases at endosonography, should be strongly considered.

In the future the MEDIASTrial results are expected to be implemented in national and international guidelines. The long-term results of the MEDIASTrial including overall and disease-free 2-year survival, quality of life and health economics are expected in 2024. Afterwards, long time survival will be continued until 5 years. Outside the scope of this thesis, the first papers on immunotherapy as neoadjuvant or adjuvant treatment in patients with resectabele lung cancer have yet been published.

Further research on its the effectiveness and indication will follow, which can potentially also influence the mediastinal nodal staging pattern and the demand for larger endobronchial or endoscopic samples.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 introduceert mediastinale lymfeklier stadiëring bij patiënten met een resectabel niet-kleincellig longcarcinoom (NSCLC) als onderwerp van dit proefschrift. De huidige internationale richtlijnen adviseren endosonografie (bij voorkeur endobronchiale echografie (EBUS) gecombineerd met endoscopische echografie (EUS(B)) als primaire stadiëringsonderzoek, gevolgd door een bevestigende cervicale mediastinoscopie indien er geen N2-3 metastasen zijn aangetoond bij endosonografie. De rol van de bevestigende mediastinoscopie staat echter ter discussie als gevolg van zijn beperkte additionele diagnostische waarde en de bijkomende morbiditeit, ziekenhuis opname, algehele anesthesie en de vertraging tot de start van de longkanker behandeling.

Het eerste deel van dit proefschrift focust zich op de klinische praktijk van invasieve mediastinale stadiëring en de naleving van de (inter)nationale richtlijnen in Nederland. **Hoofdstuk 2** beschrijft een multicenter (n=6) retrospectieve analyse van 300 patiënten naar de naleving van de richtlijn voor mediastinale lymfeklier stadiëring. Endosonografie was het primaire stadiëringsonderzoek in 84% van de patiënten, echter werd 30% van deze procedures onvolledig uitgevoerd. Een bevestigende mediastinoscopie werd achterwege gelaten bij 60% met negatieve endosonografie resultaten. Er is significante variatie tussen de deelnemende ziekenhuizen wat betreft naleving van de richtlijn en de compleetheid van de uitgevoerde procedures. Ondanks de beperkte naleving van de richtlijnen was er geen verschil in onvoorziene N2 ziekte na endosonografie met of zonder bevestigende mediastinoscopie.

In **Hoofdstuk 3** beschrijven we een landelijke analyse van de naleving van de richtlijn voor mediastinale lymfeklier stadiëring met behulp van data van de Dutch Lung Cancer Audit - Surgery. Alle patiënten die een anatomische long resectie als primaire longkanker behandeling ondergingen in 2017-2018 werden geïncludeerd. We onderzochten het gebruik van endosonografie als primaire onderzoek, het uitvoeren van een bevestigende mediastinoscopie en de onvoorziene N2 getallen. Er werden 2.238 patiënten geïncludeerd waarvan 43% endosonografie als primaire onderzoek onderging, gevolgd door een bevestigende mediastinoscopie in 43% van hen, resulterend in 19% van de patiënten gestadieerd conform de richtlijn. In de hele groep werden geen verschillen in onvoorziene N2 gezien tussen de verschillende strategieën van stadiëring. Echter in de subgroep van patiënten met N1-3 gebaseerd op radiologische beeldvorming werd een significant verschil gevonden van 23% onvoorziene N2 zonder voorgaande mediastinale stadiëring versus 13% na endosonografie en mediastinoscopie.

Hoofdstuk 4 is een landelijke Nederlandse cohortstudie met data van de Nederlandse Kanker Registratie van alle klinische stadium IA-IIIB NSCLC patiënten die die een anatomische long resectie als primaire longkanker behandeling ondergingen van 2005 tot 2017. Er werden 22.555 patiënten geïncludeerd en er werd een significante toename gezien in het gebruik van invasieve mediastinale stadiëring (endosonografie en/of mediastinoscopie) van 26% in 2005 tot 40% in 2017. Meer specifiek nam het gebruik van endosonografie toe van 19% in 2011 tot 32% in 2017 (p<.01), terwijl het gebruik van mediastinoscopie afnam van 24% in 2011 tot 21% in 2017 (p=.08). Ondanks deze verschuiving in strategie van stadiëring was het aantal patiënten met onvoorziene N2 ziekte stabiel gedurende die periode (rond 8.7%). Het gebruik van invasieve stadiëring suggereerde een overleving winst bij patiënten met klinisch N1-3 ziekte, met een 5-jaars overleving van 44% bij patiënten met stadiëring versus 39% bij patiënten zonder invasieve stadiëring (p=.12).

In het tweede deel van dit proefschrift ligt de focus op de waarde en noodzaak van bevestigende mediastinoscopie na een negatieve endosonografie bij patiënten met resectabel NSCLC.

In **Hoofstuk 5** onderzochten we de voorkeuren van patiënten met resectabel NSCLC omtrent invasieve mediastinale stadiëring. Een digitale vragenlijst werd verspreid onder MEDIASTrial proefpersonen en werd compleet ingevuld door 97 van hen (57%). Om te onderzoeken wat het belangrijkste aspect van mediastinale stadiëring was werden een Adaptive-Conjoint-Analysis en Hierarchical Bayes Estimation ontworpen op basis van literatuur, expert opinie en patiënten interviews. De duur van de stadiëringsperiode bleek significant het belangrijkste te zijn, gevolgd door het risico op een oncologisch niet zinvolle longresectie. Een Treatment-Trade-Off toonde aan dat het voorkomen van 7% oncologisch niet zinvolle longresecties de trade-off zou zijn om de nadelen van een bevestigende mediastinoscopie te compenseren. Er werd echter wel een dichotomie gevonden tussen patiënten die altijd (39%) en nooit (38%) een mediastinoscopie zouden willen ondergaan na een negatieve endosonografie.

Hoofdstuk 6 is een systematische literatuur review en meta-analyse van onvoorziene N2 na endosonografie met of zonder bevestigende mediastinoscopie bij resectabel NSCLC alsmede een analyse van de complicaties van mediastinoscopie. De databases van MEDLINE, EMBASE en Cochrane werden doorzocht tot 19 September 2018, waarbij 5.073 artikelen worden gevonden, waarvan 42 studies of subgroepen (totaal 3.248 patiënten die de chirurgische referentie standaard ondergingen) werden geïncludeerd in de analyse. De random effects meta-analyse toonde 9.6% onvoorziene N2 na endosonografie en mediastinoscopy versus 9.9% na endosonografie alleen. Random effect

meta-analyse van mediastinoscopy (8 studies; 1.245 patiënten totaal) toonde 6.0% complicaties, waarvan 1.9% Clavien-Dindo graad III-IV complicaties en 2.8% nervus laryngeus recurrens letsel.

Hoofdstuk 7 is de publicatie van het studieprotocol van de multicenter gerandomiseerde MEDIASTrial. Patiënten met (de verdenking op) resectabel NSCLC en een indicatie voor mediastinale stadiëring die reeds een negatieve systematische endosonografie hebben ondergaan worden gerandomiseerd voor directe longtumor resectie of eerst een bevestigende mediastinoscopie gevolgd door longtumor resectie. De primaire uitkomstmaat voor deze non-inferioriteitstudie was detectie van onvoorziene N2 ziekte tijdens de longtumor resectie met mediastinale lymfeklier dissectie. Secundaire uitkomsten zijn 30-dagen morbiditeit en mortaliteit.

In **Hoofdstuk 8** wordt het statistische analyse plan van de MEDIASTrial beschreven. Een systematische literatuur review verricht tijdens het schrijven van het onderzoekprotocol toonde een onvoorzien N2 van 6.3% na endosonografie en mediastinoscopy. Van de ASTER-trial wisten we reeds dat een onvoorzien N2 getal van 14.3% geen negatieve impact heeft op de 5-jaars overleving. Derhalve hebben we gebaseerd op deze getallen de non-inferioriteitsmarge gesteld op 8% (verschil tussen 6.3% en 14.3%), wat resulteert in een sample size van 171 patiënten in elke groep bij een power van 80% met aan alpha error van 0.00250. Met een te verwachten drop-out percentage van 5% komt de totale sample size uit 360 patiënten. De analyse van onvoorziene N2 wordt verricht volgens intention-to-treat (ITT), waarbij patiënten met N2 gedetecteerd tijdens mediastinoscopie worden geëxcludeerd aangezien zij geen mediastinale lymfeklierdissectie als gouden standaard ondergingen. Alle patiënten met een complete mediastinoscopie en lymfeklierdissectie (conform studieprotocol) werden aansluitend geïncludeerd in de per protocol (PP) onvoorziene N2 analyse. Non-inferioriteit werd aangenomen als, zowel in de ITT als de PP analyse, het verschil in de bovengrenzen (BG) van het 95% betrouwbaarheidsinterval van het onvoorziene N2 percentage in de directe resectie groep kleiner was dan 8% in vergelijking met de mediastinoscopie groep (BG 95%-BIΔ).

In **Hoofdstuk 9** beschrijven we de primaire uitkomsten van de MEDIASTrial waarin tussen 17 juli 2017 en 5 oktober 2020 driehonderdzestig patiënten werden gerandomiseerd. Daarvan werden 178 gerandomiseerd voor directe longtumor resectie (zeven drop-outs) en 182 voor bevestigende mediastinoscopie eerste (zeven drop-outs voor en zes na mediastinoscopie). Mediastinoscopie toonde metastasen in 8.0% (14/174) van de patiënten. Onvoorziene N2 na directe resectie (8.8%) was non-inferieur aan de strategie met bevestigende mediastinoscopie (7.7%), in zowel ITT(Δ:1.03%, BG 95%-BIΔ: 7.2%, $P_{non\text{-}inferieurr}$=.0144) als de PP analyse (Δ:0.83%, BG 95%-BIΔ: 7.3%, $P_{non\text{-}inferieurr}$=.0157).

Ernstige morbiditeit en 30-dagen mortaliteit werd gezien bij 12.9% na directe resectie versus 15.4% na bevestigende mediastinoscopie gevold door resectie (p=.4940).

De algemene discussie van dit proefschrift **(Hoofdstuk 10)** beschouwt de huidige literatuur en de additionele waarde van de MEDIASTrial en andere artikelen in dit proefschrift. De MEDIASTrial heeft aangetoond dat op basis van non-inferioriteit in onvoorziene N2 ziekte (als surrogaat uitkomst van klinisch relevante diagnostische nauwkeurigheid) een bevestigende mediastinoscopie na een negatieve systematisch uitgevoerde endosonografie achterwege gelaten kan worden bij patiënten met resectabel NSCLC en een indicatie voor mediastinale lymfeklier stadiëring. Voor patiënten met onvolledig uitgevoerde endosonografie, bulky N2-3 ziekte of hoog-verdachte irresectabele lymfeklieren zal een bevestigende mediastinoscopie echter overwogen moeten blijven worden, aangezien deze patiënten geëxcludeerd werden voor de MEDIASTrial. Een andere potentiele risicogroep om een vals negatieve endosonografie te hebben zijn klinische N1 patiënten. Ondanks dat de MEDIASTrial non-inferioriteit aantoonde voor de hele groep, lijkt de klinische N1 groep het meest in gevaar echter was er onvoldoende power voor sterke conclusies binnen deze subgroep. Binnen de klinische N1 subgroep moet verder onderzoek en een gepersonaliseerd mediastinum management sterk overwogen worden, specifiek voor patiënten met endosonografie bewezen N1 metastasen.

Naar verwachting zullen de resultaten van de MEDIASTrial geïmplementeerd worden in nationale en internationale richtlijnen. De eerste lange termijn resultaten van de MEDIASTrial zijn de totale en ziektevrije 2-jaars overleving, kwaliteit van leven en zorgkosten en worden verwacht in 2024. Daarna zal de follow-up van overleving gecontinueerd worden. Buiten het onderwerp van dit proefschrift zijn de eerste artikelen over immunotherapie als (neo-)adjuvante behandeling bij patiënten met resectabel NSCLC inmiddels gepubliceerd. Verder onderzoek naar de effectiviteit en met name de indicatiestelling hiervan zullen volgen en dit kan potentieel ook de strategie van mediastinale lymfeklierstadiëring beïnvloeden.

AMC GRADUATE SCHOOL FOR MEDICAL SCIENCES

PHD PORTFOLIO

Name PhD student:	J.E. Bousema
PhD period:	April 2017 – April 2024
Name PhD supervisor:	prof. dr. J.T. Annema
	prof. dr. M.G.W. Dijkgraaf
	dr. F.J.C. van den Broek

1. PhD training

General courses	**Year**
- BROK (Basiscursus regelgeving klinisch onderzoek)	2017
- Practical biostatistics	2018
- Didactical skills	2018
- Scientific writing in English	2018
- Oral presentation in English	2018
- Searching for a systematic review	2018
- Clinical epidemiology 1: Randomized clinical trials	2018
- Clinical epidemiology 2: Observational epidemiology	2019
- Clinical epidemiology 3: Evaluation of medical tests	2018
- Clinical epidemiology 4: Systematic reviews	2019
- The AMC World of Science	2019
- WMO-GCP refresher	2021

Specific courses	**Year**
- EPGS-ERS EBUS cursus Amsterdam	2017
- EPGS-ERS EBUS cursus Amsterdam	2018

Seminars, workshops and master classes	**Year**
- Workshop Research Manager	2018
- ESTS Webinar: Paul de Leyn	2018

Presentations	**Year**
- Kring longchirurgie Noord-Holland Oral presentation: MEDIASTinal staging of non-small cell lung cancer By endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol	2017

- Lung Surgical Rounds regio zuid 2018
  Oral presentation: Mediastinal nodal staging of non-small cell lung cancer in the Netherlands
- European Society of Thoracic Surgeons International Congress Ljubljana 2018
  Poster discussion: Unforeseen N2 disease after (minimal) invasive mediastinal staging of non-small cell lung cancer: a systematic review and meta-analysis
- Europen Respiratory Society International Congress Paris 2018
  Poster discussion: Guideline adherence and quality of (minimal) invasive staging of non-small cell lung cancer
- Refereeravond Chirurgie/Anesthesiologie Maastricht 2018
  Oral presentation: Local infiltration catheter for postoperative analgesia after laparoscopic liver surgery and thoracoscopic lung surgery
- T-score onderwijs regio VIII (Maastricht) 2018
  Oral presentation: Mediastinal nodal staging of NSCLC: guideline, literature and MEDIASTrial
- Nederlandse Vereniging voor Heelkunde Najaarsdag 2018
  Oral presentation: Subpleural multilevel intercostal continuous analgesia after thoracoscopic pulmonary resection
- Werkgroep Longtumoren Leiden 2019
  Oral presentation: Quality control in the MEDIASTrial and adherence to the guideline of mediastinal nodal staging in the Netherlands
- Lung Surgical Rounds regio zuid 2018
  Oral presentation: Guideline adherence of mediastinal staging of non-small cell lung cancer in the Netherlands: a multicentre retrospective analysis
- Expert meeting Johnson&Johnson 2019
  Oral presentation: Mediastinal nodal staging: current literature and national results
- Refereeravond Heelkunde regio VIII (Maastricht) 2019
  Oral presentation: Mediastinal nodal staging of resectable non-small cell lung cancer
- Nederlandse Vereniging voor Heelkunde Chirurgendagen 2020
  Oral presentation: Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer (cancelled due to COVID-19)
- Nederlandse Vereniging voor Heelkunde Chirurgendagen 2020
  Oral presentation: Patients' preferences regarding invasive mediastinal lymph node staging of resectable non-small cell lung cancer (cancelled due to COVID-19)
- Werkgroep Longtumoren Arnhem/Nijmegen 2020

Oral presentation: Invasive mediastinal staging of resectable non-small cell lung cancer in the Netherlands

- Refereermiddag Longchirurgie Spaarne Gasthuis 2021
  Oral presentation: Invasieve mediastinal staging of resectable non-small cell lung cancer in the Netherlands
- Nederlandse Vereniging voor Longchirurgie lustrumcongres 2022
  Oral presentation: Invasieve mediastinal staging of resectable non-small cell lung cancer in the Netherlands
- Belgian Surgical Week 2022
  Oral presentation: Invasive mediastinal staging of resectable non-small cell lung cancer
- Thoracic Oncology Winter Symposium 2023
  Oral presentation: Invasive mediastinal nodal staging of resectable non-small cell lung cancer
- Nationaal Longkanker Symposium 2023
  Oral presentation: Invasive mediastinal nodal staging of resectable non-small cell lung cancer
- Maxima MC wetenschapsdag 2023
  Oral presentation: Endosonografie met of zonder bevestigende mediastinoscopie voor mediastinale lymfeklier stadiëring bij resectabel niet-kleincellig longcarcinoom (MEDIASTrial)
- Nederlandse Vereniging voor Heelkunde Chirurgendagen 2023
  Oral presentation: Endosonografie met of zonder bevestigende mediastinoscopie voor mediastinale lymfeklier stadiëring bij resectabel niet-kleincellig longcarcinoom (MEDIASTrial)

(Inter)national conferences	**Year**
- Nederlandse Vereniging voor Heelkunde Chirurgendagen	2017
- Nederlandse Vereniging voor Heelkunde Chirurgendagen	2018
- Europen Respiratory Society International Congress Paris	2018
- European Society of Thoracic Surgeons International Congress Ljubljana	2018
- Nederlandse Vereniging voor Heelkunde Najaarsdag	2019
- Nederlandse Vereniging voor Heelkunde Chirurgendagen	2019
- Expert meeting Johnson&Johnson	2019
- Nederlandse Vereniging voor Heelkunde Najaarsdag (cancelled due to COVID-19)	2019
- Nederlandse Vereniging voor Heelkunde Chirurgendagen (cancelled due to COVID-19)	2020
- Nederlandse Vereniging voor Heelkunde Najaarsdag	2020

(cancelled due to COVID-19)

- Nederlandse Vereniging voor Heelkunde Voorjaarsdag 2021
- Nederlandse Vereniging voor Longchirurgie Jaarsymposium 2021
- Nederlandse Vereniging voor Longchirurgie Lustrumcongres 2022
- Belgian Surgical Week 2022
- Nederlandse Vereniging voor Heelkunde Chirurgendagen 2023
- Nederlandse Vereniging voor Heelkunde Najaarsdag 2023

2. Teaching

Lecturing	**Year**
- IKNL datamanagers scholingsdag, Topic: Surgical lung cancer staging	2022
- Erasmus MC, Medicine master, Topic: Acute abdominal pain	2023

Mentoring

- I. Huijbregts, medicine master thesis 2017

3. Parameters of Esteem

Grants	**Year**
- ZonMw Research Grant (€299.696,- project number 843004109)	2017
- KWF Research Project (€231.283,- project number 11313)	2017

4. Publications

Peer reviewed

- **Bousema J.E.**, Dijkgraaf M.G.W., Papen-Botterhuis N.E., Schreurs W.H., Maessen J.G., Van Der Heijden E.H., Steup W.H., Braun J., Noyez V.J.J.M., Hoeijmakers F., Beck N., Van Dorp M., Claessens N.J.M., Hiddinga B.I., Daniels J.M.A., Heineman D.J., Zandbergen H.R., Verhagen A.F.T.M., Van Schil P.E., Annema J.T., Van Den Broek F.J.C. on behalf of the MEDIASTrial study group. MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): study protocol of a randomised controlled trial. BMC Surg. 2018 May:18(1):27.
- **Bousema J.E.**, Struik G.M., Van Der Ham A.C. Een infectieuze oorzaak van acute verergering van chronische liespijn bij een jonge sporter. Sport & Geneeskunde. 2019 Apr:1:16-20.
- **Bousema J.E.**, Van Dorp M., Noyez V.J.J.M., Dijkgraaf M.W.G., Annema J.T., Van Den Broek F.J.C. Unforeseen N2 disease following negative endosonography with or

without confirmatory mediastinoscopy in resectable non-small cell lung cancer: a systematic review and meta-analysis. J Thorac Oncol. 2019 Jun;14(6):979-992.

- **Bousema J.E.**, van de Luijtgaarden K.M., Wilhelmus S., Poelman M.M. Acute severe abdominal pain in a young woman caused by a well-differentiated papillary mesothelioma of the peritoneum. BMJ Case Rep. 2019 Aug:1(8).
- **Bousema J.E.**, Van Dorp M., Hoeijmakers F., Huijbregts E.A., Barlo N.P., Bootsma G.P., Van Boven W.J.P., Claessens N.J.M., Dingemans A.M.C., Hanselaar W.E., Kortekaas R.Th.J., Lardenoije J.H.P., Maessen J.G., Schreurs W.H., Vissers Y., Youssef-El Soud M., Dijkgraaf M.G.W., Annema J.T., Van Den Broek F.J.C. Guideline adherence of mediastinal staging of non-small cell lung cancer: a multicentre retrospective analysis. Lung Cancer. 2019 Aug;134:52-58.
- **Bousema J.E.**, Dias E.M., Hagen S.M., Govaert B., Meijer P., Van Den Broek F.J.C. Subpleural multilevel intercostal continuous analgesia after thoracoscopic pulmonary resection: a pilot study. J Cardiothorac Surg. 2019 Oct:14(1):179.
- **Bousema J.E.**, Heineman D.J., Dijkgraaf M.G.W., Annema J.T., Van Den Broek F.J.C. Adherence to the mediastinal staging guideline and unforeseen N2 disease in patients with resectable non-small cell lung cancer: Nationwide results from the Dutch Lung Cancer Audit - Surgery. Lung Cancer. 2020 Apr;142:51-58.
- **Bousema J.E.**, Dijkgraaf M.G.W., Van Der Heijden E.H.F.M., Verhagen A.F.T.M., Annema J.T., Van Den Broek F.J.C. on behalf of the MEDIASTrial study group. MEDIASTinal staging of non-small cell lung cancer by endobronchial and endoscopic ultrasonography with or without additional surgical mediastinoscopy (MEDIASTrial): a statistical analysis plan. BMC Trials. 2021 Feb:22:168.
- **Bousema J.E.**, Aarts M.J., Dijkgraaf M.G.W., Annema J.T., Van Den Broek F.J.C. Trends in mediastinal nodal staging and its impact on unforeseen N2 and survival in lung cancer. Eur Respir J. 2021 Apr:57:2001549.
- **Bousema J.E.**, Hoeijmakers F., Dijkgraaf M.G.W., Annema J.T., Van Den Broek F.J.C., Van Den Akker-Van Marle M.E. Patients' preferences regarding invasive mediastinal lymph node staging of resectable non-small cell lung cancer. Patient Prefer Adherence. 2021 Sep:15:2185-2196.
- Van Dorp M., **Bousema J.E**., Torensma B., Dickhoff C. Van Den Broek F.J.C., Schreurs W.H., Gonzalez M. Kazemier G., Heineman D.J. Pulmonary metastasectomy with lymphadenectomy for colorectal pulmonary metastases: A systematic review. Eur J Surg Oncol. 2022 Jan;48(1):253-260.
- Spaans L.N., **Bousema J.E.**, Van Den Broek F.J.C. Variation in postoperative pain management after lung surgery in the Netherlands: a survey of Dutch thoracic surgeons. Br J Anaesth. 2022 Mar;128(3):e222-e225.
- Spaans L.N., Dijkgraaf M.G.W., Meijer P., Mourisse J., Bouwman R.A., Verhagen A.F.T.M., Van Den Broek F.J.C., **OPtriAL study group**.

Optimal postoperative pain management after VATS lung resection by thoracic epidural analgesia, continuous paravertebral block or single-shot intercostal nerve block (OPtriAL): study protocol of a three-arm multicentre randomised controlled trial. BMC Surg. 2022 Sep 4;22(1):330.

- Spaans L.N., **Bousema J.E.**, Meijer P., Bouwman R.A.A., Van Den Broek R., Mourisse J., Dijkgraaf M.G.W., Verhagen A.F.T.M., Van Den Broek F.J.C. Acute pain management after thoracoscopic lung resection: a systematic review and explorative meta-analysis. Interdiscip Cardiovasc Thorac Surg. 2023 Jan 4;36(1).
- **Bousema J.E.**, Dijkgraaf M.G.W., Van Der Heijden E.H.F.M., Verhagen A.F.T.M., Annema J.T., Van Den Broek F.J.C. on behalf of the MEDIASTrial study group. Endosonography With or Without Confirmatory Mediastinoscopy for Resectable Lung Cancer: A Randomized Clinical Trial. J Clin Oncol. 2023 Aug 1;41(22):3805-3815.

Other

- **Bousema J.E.**, Lavrijssen B, Van Der Linde D. Preventive aortic root replacement in Marfan syndrome. Erasmus Journal of Medicine, 2010 (2); 1.
- **Bousema J.E.**, Dijkgraaf M.G.W., Annema J.T., Van Den Broek F.J.C., MEDIASTrial tudiegroep. Mediastinale stadiëring van niet-kleincellig longcarcinoom door middel van endobronchiale en endoscopische echografie met of zonder toegevoegde mediastinoscopie: de MEDIASTrial. Ned Tijdschr Oncol. 2018 Aug:15:194-7.

ABOUT THE AUTHOR

Jelle Egbert Bousema was born on January 5th 1989 in Breda, the Netherlands. He was raised as the eldest of three children and graduated from pre-university education at the Newman College Breda in 2008. After being drawn from numerus fixus in 2008, he started studying Medicine at the Erasmus University Rotterdam in 2009. In December 2015 Jelle obtained his medical degree and started working at the surgical department of the Sint Franciscus Gasthuis (Rotterdam, the Netherlands, dr. T.M.A.L. Klem) in January 2016. During this period, he obtained a ZonMw research grant together with Frank van den Broek, which resulted in the start as PhD candidate at the Máxima MC (Veldhoven/Eindhoven, the Netherlands) and University of Amsterdam in April 2017 (prof. dr. J.T. Annema, prof. dr. M.G.W. Dijkgraaf and dr. F.J.C. van den Broek). His research focused on invasive mediastinal nodal staging of resectable non-small cell lung cancer with the international, multidisciplinary and multicenter randomized MEDIASTrial as most important task. In January 2020 Jelle returned to the clinic and started working at the surgical department in the Ikazia hospital (Rotterdam, the Netherlands, dr. P.T. den Hoed). In January 2021 he subsequently started with his general surgery training at the Ikazia hospital (dr. P.T. den Hoed), which continued in 2023 at the Erasmus Medical Center (Rotterdam, the Netherlands, dr. S.M. Lagarde) and in January 2024 he returned back to the Ikazia hospital for the continuation of his surgical training (dr. W.J. Vles).

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