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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

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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

1. 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.

2. 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.

2.1. 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?

2.2. 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.

2.3. 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.

2.4. Assessment of endosonography procedures

According to the 2014 European guideline a systematic EBUS is defined as endosonographic examination of at least lymph node stations 4 L, 7 and 4R [2]. Lymph nodes in stations 4 L, 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 4 L, 7 and 8. Lymph nodes in stations 4 L, 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.

2.5. Assessment of cervical mediastinoscopy

Complete systematic cervical mediastinoscopy consists of assessment of mediastinal lymph node stations 2R, 4R, 7, 4 L and 2 L. 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 4 L [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 4 L were defined as 'insufficient'. One centre performed video-assisted mediastinoscopic lymphadenectomy (VAMLA), all other centres used cervical videomediastinoscopy with sampling.

2.6. 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, 7–9 need to be dissected. In left-sided resections lymph node stations 5–7 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'.

2.7. 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 2 × 2 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).

3. Results

3.1. 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 (Fig. 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).

3.2. 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) (Fig. 1).

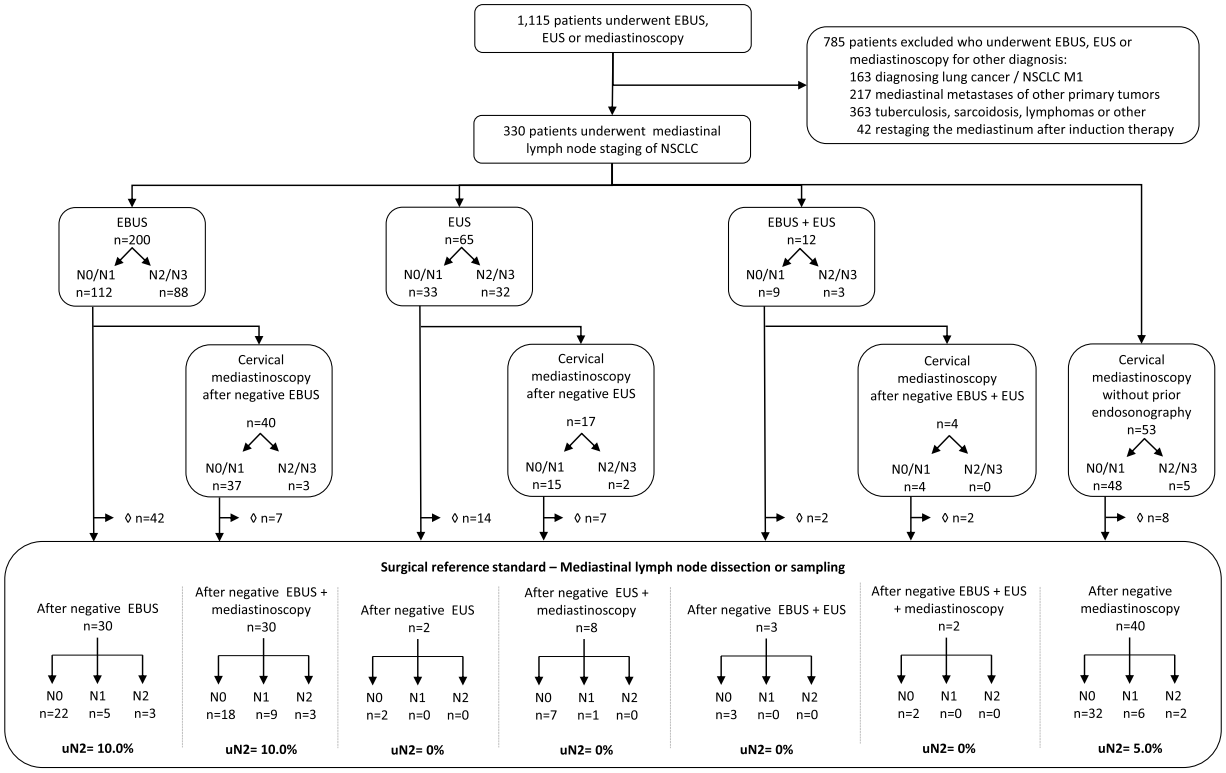

Fig. 1. Flowchart of included patients in different mediastinal lymph node staging strategies.
◊ = no surgical reference standard; EBUS = endobronchial ultrasonography; EUS = endoscopic ultrasonography; NSCLC = non-small cell lung cancer; n = number; uN2 = unforeseen N2.

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%; $p < .01$) (Fig. 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).

3.3. 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 4 L, FDG-non-avid, 4 punctures, without ROSE) and one with representative but tumour negative samples (station 7 and 4 L, 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 4 L) at mediastinoscopy.

3.4. 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.

3.5. 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%) (Fig. 1).

4. Discussion

Adherence to the 2014 European guideline regarding the initial usage of endosonography in mediastinal staging of NSCLC is good

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)	
Tumour localization, No. (%)							
Right lower lobe	5 (13)	14 (21)	16 (20)	4 (18)	6 (13)	13 (17)	.69
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)	
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	.22
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)	
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)	< .01
N1	2 (5)	9 (13)	15 (19)	0	4 (9)	4 (5)	
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)	< .01
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)	
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.

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.

(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 conscious 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.

5. 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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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

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