Evaluating lung cancer care in the Netherlands: staging, treatment and surgical quality assurance

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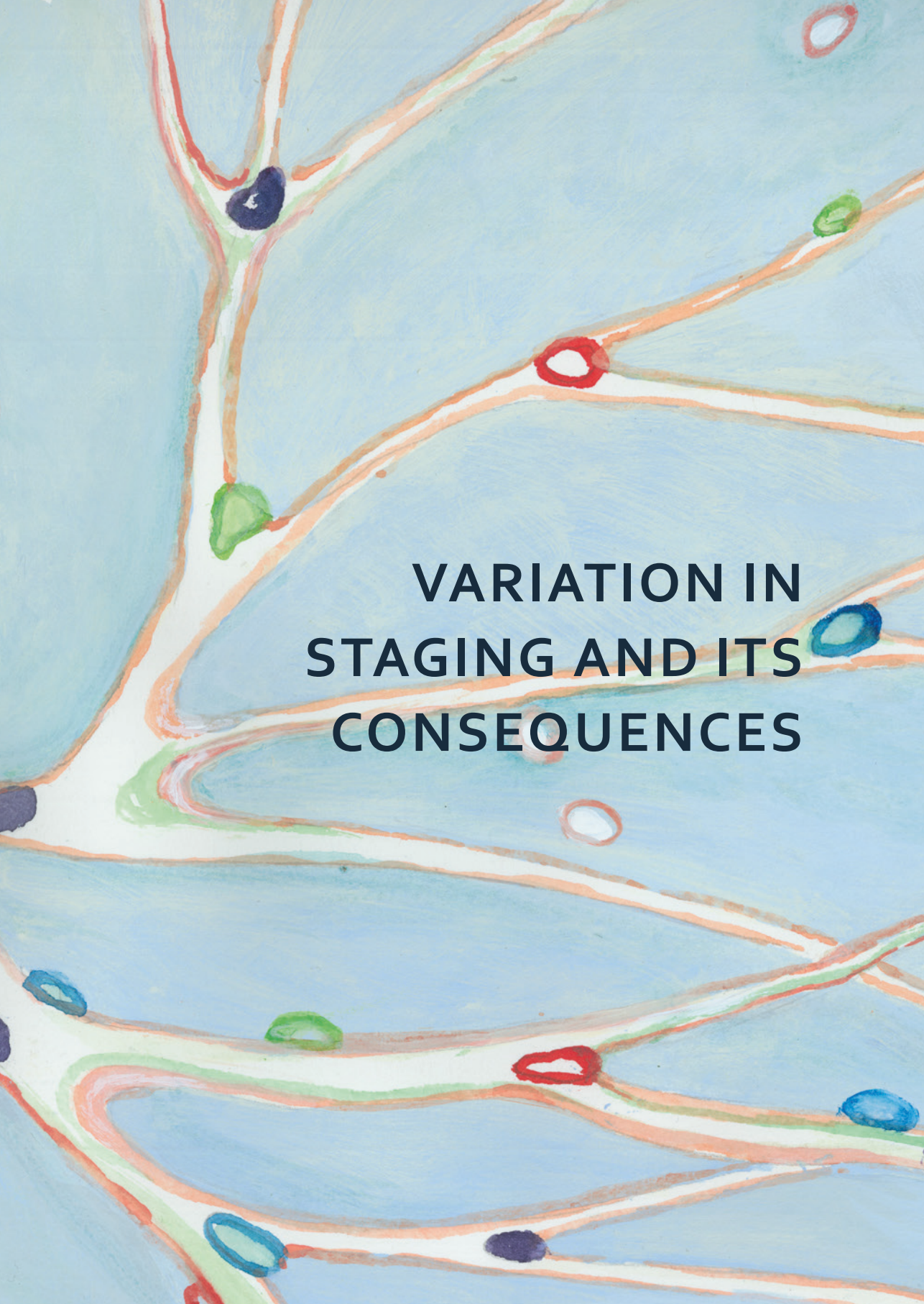
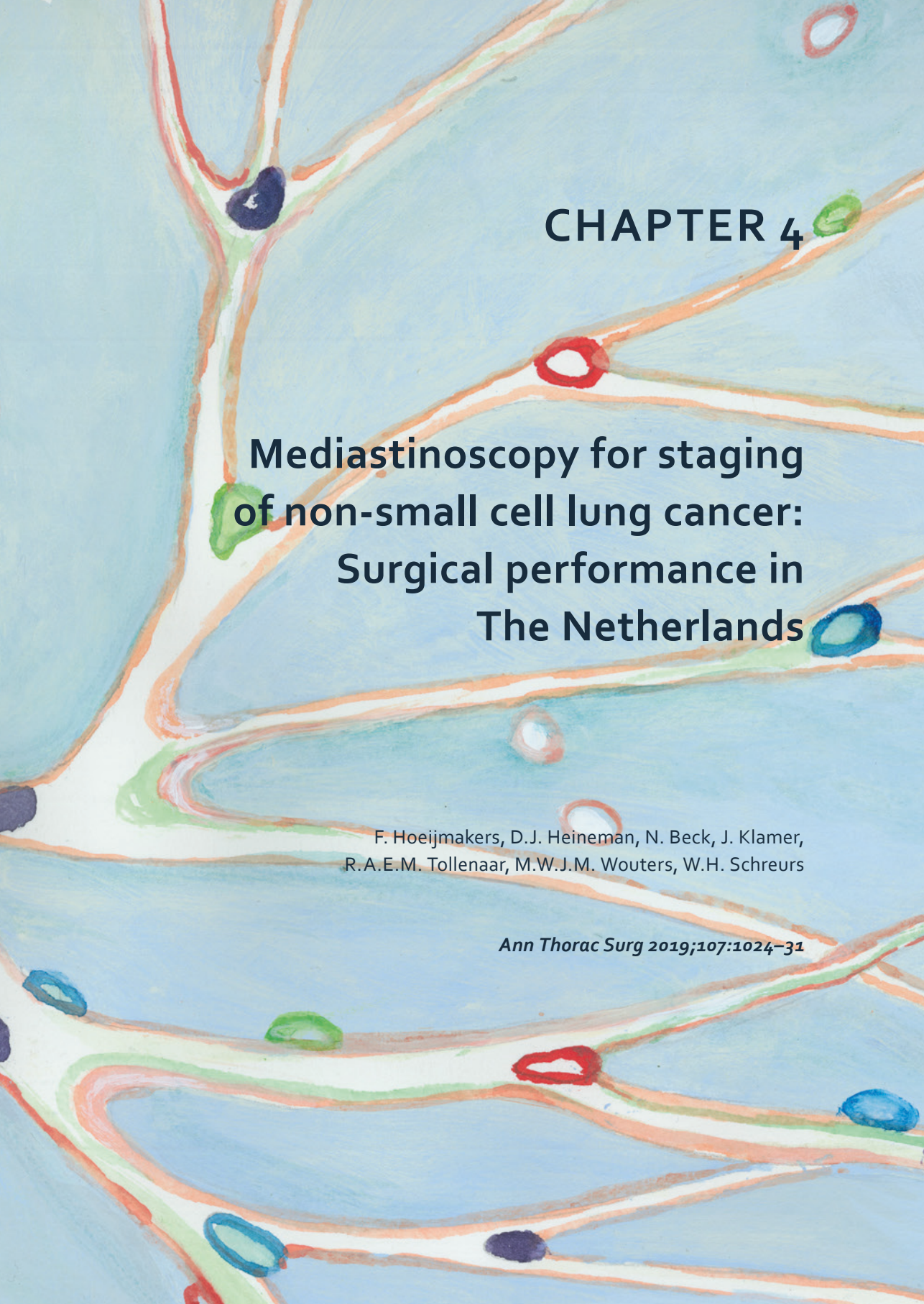
PART II



VARIATION IN STAGING AND ITS CONSEQUENCES



CHAPTER 4

Mediastinoscopy for staging of non-small cell lung cancer: Surgical performance in The Netherlands

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Ann Thorac Surg 2019;107:1024–31

ABSTRACT

Background

Accurate staging of the mediastinal lymph nodes is of great importance to determine optimal treatment options in non-small cell lung cancer (NSCLC). In case of suspected mediastinal metastases, endoscopic/endobronchial ultrasound combined with mediastinoscopy is the gold standard. The diagnostic value of these procedures stands or falls by how they are technically performed. This study used data from the Dutch Lung Cancer Audit for Surgery to evaluate surgical performance of mediastinoscopies in The Netherlands.

Methods

The study included all patients with a mediastinoscopy for staging of NSCLC and subsequent resection from 2012 to 2016. Complete case analysis was performed, excluding patients with missing data on biopsies or tumor side. Location and number of biopsied stations and adherence to guidelines for performing mediastinoscopy were analyzed. The proportion of unforeseen mediastinal lymph node metastases (unforeseen N2) was compared between mediastinoscopies that did or did not comply with the Dutch guideline.

Results

The analysis included 1,729 patients. Mediastinoscopies were performed according to the Dutch guideline (requirements: biopsies of 2 ipsilateral stations, 1 contralateral station, and N7) in 51.4% (n [888) and according to the European Society of Thoracic Surgeons guideline (N4 left, N4 right, and N7) in 75.4% (n [1,303). Overall, unforeseen N2 was present in 10.2% (n [140). In mediastinoscopies performed according to the Dutch guideline, unforeseen N2 occurred less often (8.6%) than in the nonadherence group (11.9%; p [0.043).

Conclusions

There is improvement potential in surgical performance of mediastinoscopy in The Netherlands, which is reflected by the percentage of guideline adherence and the occurrence of unforeseen N2.

INTRODUCTION

Clinical mediastinal lymph node staging in patients with non-small cell lung cancer (NSCLC) is challenging. This is reflected by 6.3% unforeseen mediastinal lymph node metastases (unforeseen N2) in all patients undergoing upfront surgery for NSCLC in the Netherlands. (1) For both prognosis and selection of the best treatment, however, adequate mediastinal staging is critical. In the presence of mediastinal metastases, upfront surgery has not demonstrated survival benefits and according to recent studies and guidelines, either definitive chemoradiotherapy or induction therapy followed by surgery should be the first treatments of choice. (2-5)

Guidelines recommend invasive mediastinal staging in patients with suspicious (mediastinal) lymph nodes on computed tomography (CT) or fluorodeoxyglucose positron emission tomography (FDG-PET). Tumors larger than 3 cm and central tumors are criteria to perform invasive mediastinal staging as well. The Dutch guideline also advises mediastinal staging in non-FDG-avid tumors. When endoscopic ultrasound (EUS) and/or endobronchial ultrasound (EBUS) with fine needle aspiration (FNA) do not provide pathological evidence of lymph node metastases, performing a cervical (video-assisted) mediastinoscopy (hereafter referred to as 'mediastinoscopy') is recommended. (6-9)

The role of mediastinoscopy in the staging process is changing. The introduction of FDG-PET allows more specific lymph node sampling and with the increased use of EUS/EBUS – with high sensitivity and specificity and benefits regarding safety and comfort for the patients – the added value of mediastinoscopy has become subject of debate. Annema et al. showed that, even when EUS/EBUS are performed by a skilled endoscopist, by additional mediastinoscopy the sensitivity of detection of mediastinal nodal disease rises to 94%. For EUS/EBUS alone sensitivity is 85%. (9) However, it is still unclear if all patients with a negative EUS/EBUS require a mediastinoscopy. Efforts are made to identify homogeneous subgroups that will likely benefit from additional mediastinoscopy. (10-12) In daily practice, the use of mediastinoscopy already seems to be progressively reserved for patients with high suspicion of N2 disease, instead of being regularly used after negative EUS/EBUS. (13)

Quality of mediastinoscopy has always been a subject of discussion because it is related to the extent of lymph node sampling and surgeons' experience. (11,14,15) Therefore, when comparing staging strategies with or without mediastinoscopy, the quality and extent of biopsies are highly relevant and should be taken into account. This study aims to evaluate the surgical performance of mediastinoscopy for mediastinal staging in daily

clinical practice in the Netherlands, by assessing guideline adherence and unforeseen N2 disease, using data from the Dutch Lung Cancer Audit for Surgery (DLCA-S). (16)

PATIENTS AND METHODS

Patient selection

Data were retrieved from the DLCA-S, a prospective, national quality registry introduced in 2012, covering all surgical procedures in the Netherlands for malignant or benign lung and mediastinal disease. (16)

All registered patients with mediastinal surgery for staging of NSCLC between January 1, 2012, and December 31, 2016, were identified. Patients with cervical mediastinoscopy and subsequent resection were included when an FDG-PET was performed and a minimum set of parameters was registered: gender, date of birth, date of surgery, type of surgery and vital status 30 days after surgery or at the time of discharge. Patients with missing data on biopsies or pathology and patients with an unknown tumor side were excluded. For the analysis on unforeseen N2 disease, patients with positive mediastinoscopy, treated with induction therapy or clinically staged as cN2 were excluded (n=353), this last group to avoid bias. It is likely that these patients had a high suspicion of N2 disease but were nevertheless operated on, because invasive staging failed to prove so.

Definitions and guideline criteria

In the DLCA-S, no distinction is made between 'biopsies', 'dissection' or 'sampling', therefore, in this study the term 'biopsied' is used for all these options. According to the Dutch guideline on the diagnosis and treatment of NSCLC, an adequate mediastinoscopy requires biopsies from at least 4 out of 6 'accessible' lymph node stations: two ipsilateral, one contralateral and station 7. Stations classified as accessible in this guideline are stations 1, 2R, 2L, 4R, 4L and 7. (6) The European Society for Thoracic Surgeons (ESTS) guideline recommends taking biopsies of at least station 4L, 4R, and 7. Additionally, station 2L and 2R can be biopsied. (8)

In the Netherlands, lung surgery is performed only by specialized surgeons who have followed a training program and have to comply to quality and quantity standards.

Outcomes

The primary outcomes assessed were overall guideline adherence according to the Dutch guideline and the proportion of postoperative unforeseen N2 disease. To assess whether

guideline adherence leads to a better outcome the proportion of unforeseen N2 disease was compared for groups based on guideline adherence.

Secondary outcomes were ESTS-guideline adherence, between-hospital variation in guideline adherence, the proportion of true false negatives and comparison of major complications (wound infection/mediastinitis, recurrent laryngeal nerve injury, tracheal injury, complications requiring reintervention or death) between groups based on guideline adherence.

Statistical analysis

The influence of patient and tumor characteristics on guideline adherence was analyzed by an univariable comparison of patients with a mediastinoscopy performed according to the Dutch guideline or not, using chi-square tests. Between-hospital variation in guideline adherence was presented in funnel plots with 95% confidence intervals (95% CI). Proportions of unforeseen N2 and true false negatives were calculated and compared for groups based on adherence to both the Dutch and ESTS guideline by chi-square test. Major complications between patients with and without guideline adherence were compared by chi-square test.

For patients with unforeseen N2 the use and results of (invasive) diagnostics were investigated – stratified by nodal station – to analyze the adherence to guidelines on mediastinal lymph node staging. SPSS 25.0 software (IBM, Armonk, NY) was used for statistical analyses, and p values of less than 0.05 were considered statistically significant.

RESULTS

Patients

Between January 1, 2012, and December 31, 2016, 1,882 eligible patients were registered. After exclusion of patients with missing data, 1,729 patients were included (*Figure 1*).

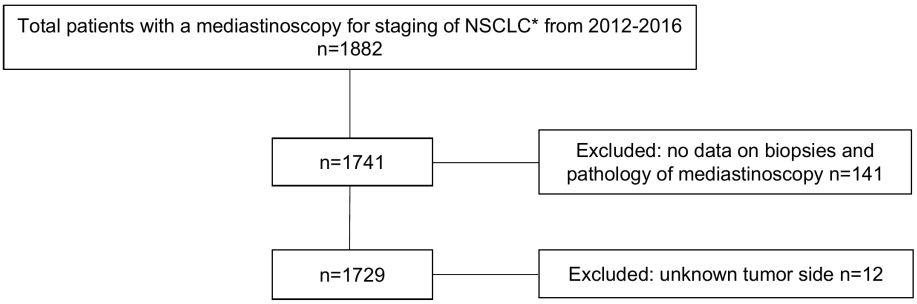

FIGURE 1. Flow chart of included and excluded patients.

Biopsied lymph node stations

The median number of lymph node stations biopsied per mediastinoscopy was 4 (*Figure 2a*). In 65.9% (n=1,140) of the patients, 4 or more stations were biopsied, which is at least needed to meet the Dutch guideline criteria. *Figure 2b* demonstrates the percentage of mediastinoscopies in which a particular station was biopsied per lymph node station, stratified for tumor side. Overall, right sided lymph node stations were relatively more frequently biopsied than left sided stations, regardless of the tumor side.

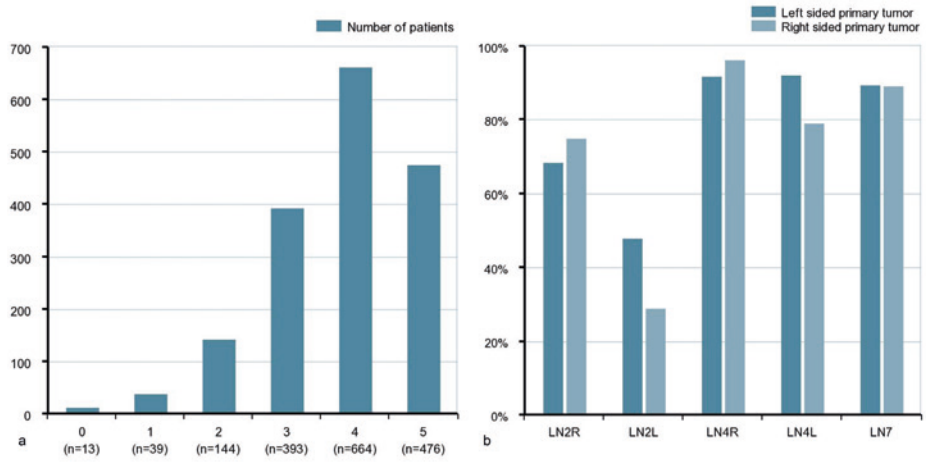

FIGURE 2. a) Number of biopsied lymph node stations at cervical mediastinoscopy (n = 1,729). b) Percentage in which each lymph node (LN) station was biopsied during mediastinoscopy (n = 1,729).

Guideline adherence and between-hospital variation

When comparing the performed mediastinoscopies to the Dutch guideline, the required lymph node stations corresponding with the primary tumor location were biopsied in 51.4% (n=888). There were no significant differences in baseline patient and tumor characteristics when comparing patients with and without a mediastinoscopy performed in accordance with the Dutch guideline (*Table 1*), except for tumor location.

Compared to the ESTS guideline, adherence was 75.4% (n=1,303). *Table 2* demonstrates that in lobe-specific guideline adherence there is more variation seen for the Dutch guideline (range, 41.3% - 72.7% vs. 68.8% - 87.9%).

Considerable between-hospital variation is seen on guideline adherence for the two guidelines (*Figure 3*). Compared to the Dutch guideline (*Figure 3a*) 4 hospitals performed significantly better than the national average, and 10 hospitals significantly worse. Among these underperforming hospitals, 4 low volume hospitals were still underperforming when comparing to the ESTS guideline (*Figure 3b*).

TABLE 1. Distribution of patient and tumor characteristics of all patients, patients staged according to the Dutch guideline and patients not staged according to the guideline.

Patient and tumor characteristicsa	All N=1,729		Guideline + (n=888)		Guideline - (n=841)		p Value
Age, mean (SD) years	66.9	(8.9)	67.2	(8.9)	66.6	(8.9)	
Sex							0.620
Male	1133	(65.5)	577	(65.0)	556	(66.1)	
Female	596	(34.5)	311	(35.0)	285	(33.9)	
ECOG score							0.308
0-I	1406	(81.3)	730	(82.2)	676	(80.4)	
II+	81	(4.7)	35	(3.9)	46	(5.5)	
Unknown/missing	242	(14.0)	123	(13.9)	119	(14.1)	
DLCO							0.263
>80%	391	(22.6)	188	(21.2)	203	(24.1)	
40-80%	960	(55.5)	494	(55.6)	466	(55.4)	
<40%	32	(1.9)	15	(1.7)	17	(2.0)	
Unknown/missing	346	(20.0)	191	(21.5)	155	(18.4)	
FEV1							0.168
>80%	630	(36.4)	327	(36.8)	303	(36.0)	
40-80%	673	(38.9)	334	(37.6)	339	(40.3)	
<40%	14	(0.8)	4	(0.5)	10	(1.2)	
Unknown/missing	412	(23.8)	233	(25.1)	189	(22.5)	
ASA score							0.306
I-II	1198	(69.3)	602	(67.8)	596	(70.9)	
III+	492	(28.5)	267	(30.1)	225	(26.8)	
Unknown/missing	39	(2.3%)	19	(2.1)	20	(2.4)	
Previous thoracic surgery							0.074
Yes	101	(5.8)	56	(6.3)	45	(5.4)	
No	1583	(91.6)	802	(90.3)	781	(92.9)	
Unknown/missing	45	(2.6)	30	(3.4)	15	(1.8)	
Charlson comorbidity index							0.799

0	579	(33.5)	292	(32.9)	287	(34.1)	
1	535	(30.9)	274	(30.9)	261	(31.0)	
2+	615	(35.6)	322	(36.3)	293	(34.8)	
Cardiac comorbidity							0.803
Yes	490	(28.3)	254	(28.6)	236	(28.1)	
No	1239	(71.7)	634	(71.4)	605	(71.9)	
Pulmonary comorbidity							0.796
Yes	632	(36.6)	322	(36.3)	310	(36.9)	
No	1097	(63.4)	566	(63.7)	531	(63.1)	
cT Stage[b]							0.275
cT1a-b (and To Tis)	388	(22.4)	205	(23.1)	183	(21.8)	
cT2a-b	740	(42.8)	371	(41.8)	369	(43.9)	
cT3	446	(25.8)	221	(24.9)	225	(26.8)	
cT4	107	(6.2)	61	(6.9)	46	(5.5)	
Unknown/Tx/Missing	48	(2.8)	30	(3.4)	18	(2.1)	
Tumor location							<0.000
Left lower lobe	189	(10.9)	78	(8.8)	111	(13.2)	
Left upper lobe	362	(20.9)	154	(17.3)	208	(24.7)	
Left, unknown lobe	215	(12.4)	94	(10.6)	121	(14.4)	
Right lower lobe	185	(10.7)	108	(12.2)	77	(9.2)	
Right middle lobe	33	(1.9)	24	(2.7)	9	(1.1)	
Right upper lobe	431	(24.9)	259	(29.2)	172	(20.5)	
Right, unknown lobe	529	(30.6)	171	(19.3)	143	(17.0)	

a Continuous data are presented as indicated and categorical data as n (%). b Staging according to TNM Classification of Malignant Tumours, 7th ed.

ASA = American Society of Anesthesiologists; DLCO = diffusing capacity of lung for carbon monoxide; ECOG = Eastern Cooperative Oncology Group; FEV1% = forced expiratory volume in 1 second, percentage of expected; Tx = primary tumor cannot be assessed.

TABLE 2. Guideline compliance per tumor location according to the Dutch and ESTS guidelines.

Tumor Location	No.	Dutch guideline (%)	ESTS guideline (%)
Right lobe			
Upper	431	60.1	71.9
Middle	33	72.7	87.9
Lower	185	58.4	72.4
Unknown	314	54.5	68.8
Left lobe			
Upper	362	42.5	80.1
Lower	189	41.3	84.1
Unknown	215	43.7	76.7
Total (	1729	51.4	75.4

ESTS = European Society of Thoracic Surgeons; No. = number.

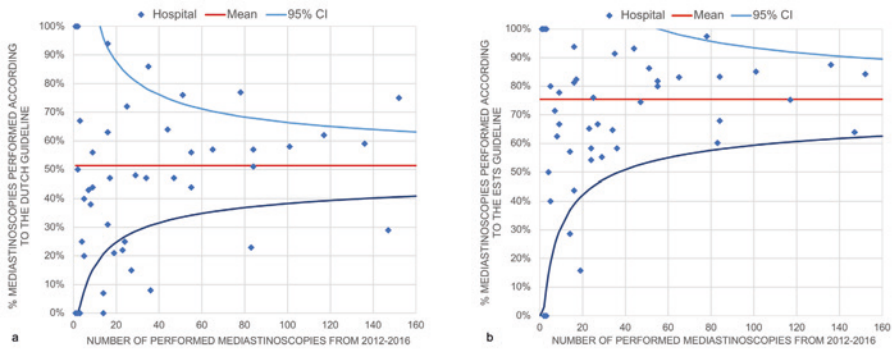

FIGURE 3. Variation between hospitals in the percentage of patients who underwent mediastinoscopy according to the criteria of a) the Dutch guideline and b) the European Society of Thoracic Surgeons (ESTS) guideline. The red lines represent the national average, and the blue lines represent the 95% confidence intervals (CI).

Unforeseen N2 disease

Postoperative histopathology showed unforeseen N2 disease in 140 of 1,376 patients (10.2%). In patients with a mediastinoscopy performed according to the Dutch guideline the unforeseen N2 rate was 8.6% (n=60). After a mediastinoscopy without Dutch guideline adherence the unforeseen N2 rate was 11.9% (n=80) (p = 0.043). For major complications, no significant difference was found between the groups (adherence 2.5%; no adherence 1.5%; p = 0.169). When comparing both groups following the ESTS

guideline, no difference in unforeseen N2 could be demonstrated: 10.1% (n=106) versus 10.3% (n=34) (p = 0.912).

In the 140 patients with unforeseen N2 disease, the primary tumor was located in the left lung in 78 patients (55.7%) and right in 62 patients (44.3%). In 61 patients, unforeseen N2 disease occurred in mediastinal lymph node stations unreachable by cervical mediastinoscopy (station 5, 6, 8 or 9). This corresponds with a true false negative rate of 5.7% (no clinically relevant or significant difference between adherence and non-adherence groups for the Dutch and ESTS guidelines). *Table 3* shows an in-depth analysis on lymph node station level of all the 140 mediastinoscopies revealing postoperative unforeseen N2. Of the 76 accessible lymph node stations (i.e. 2L/R, 4L/R and 7; highlighted in *Table 3*) with postoperative unforeseen N2 disease, 65 were biopsied during mediastinoscopy. Only in 21 of 76 cases the specific lymph node was enlarged or positive on CT/FDG-PET.

TABLE 3. Analysis of false negative mediastinoscopies (n=140).

Lymph node station	Postoperative N2 disease (false negative mediastinoscopy)	Biopsied during mediastinoscopy	EUS / EBUS performed	On CT/ FDG-PET suspect	Other mediastal lymph node on CT/ FDG-PET suspect
2L	1	0	0	0	0
2R	5	4	1	0	1
3	1	-	1	0	0
4L	5	4	2	1	3
4R	18	16	8	6	6
5/6	53	-	23	16	15
7	47	41	27	14	15
8	12	-	3	2	5
9	11	-	3	0	5

Bold indicates the station is accessible by mediastinoscopy.
CT = computed tomography; EBUS = endobronchial ultrasound; EUS = endoscopic ultrasound; FDG-PET = fluorodeoxyglucose positron emission tomography.

COMMENT

In the Netherlands, adherence to the Dutch guideline for performing mediastinoscopy in patients with NSCLC is 51% with considerable between-hospital variation. Unforeseen N2 disease is present in 10.2% of patients subsequently undergoing resection and was significantly less in patients with a mediastinoscopy performed according to the Dutch guideline. These results suggest room for improvement.

Mediastinoscopy is a technically challenging procedure. Quality of the procedure (extent of sampling and surgeons' experience) influences the quality of staging. Existing studies on surgical performance of mediastinoscopy are mostly of retrospective nature, based on data from single centers where sufficient procedures have been performed and where administration and follow-up has been adequate. (14, 17-20) The DLCA-S allows analysis on a national level, reflecting daily practice in a period where experience levels might have decreased due to the introduction of EBUS/EUS.

In this national database study, in 51% of 1,729 included patients, mediastinoscopy was performed according to the Dutch guideline. When the less strict ESTS guideline is taken as a reference, 75% of mediastinoscopies were performed accordingly. Comparisons to the ESTS guideline have been previously performed by Smulders et al. and Steunenberg et al. Their studies showed adherence of 40% (1993-1999) and 50% (2009-2014) respectively. (14, 18) This study is the first study analyzing (nationwide) adherence to the Dutch guideline.

In the distribution of the number of biopsied stations (median, 4), an increase is seen compared to Steunenberg et al. (median, 3; 2009-2014) and Van Albada et al. (median, 1; 1994-2000). (14, 19) Results are similar to those of Verhagen et al. (median=4; 2009-2012). (13) Hypotheses for the differences between these previous studies and the current study are: First, introduction of innovations such as FDG-PET, EUS/EBUS – which help direct biopsies and enable better indications for invasive staging – and video-mediastinoscopy will have contributed. (21) Second, results of previous studies probably have raised awareness on quality of surgical performance of mediastinoscopy, and (surgical) quality is a topic that has gained more attention in general, with focus on quality registries and outcome research. Third, prospective and mandatory registration of surgical characteristics of all performed mediastinoscopies will have improved reporting and documentation and will have raised focus on performance and guideline adherence, potentially resulting in improved outcomes. (22)

The ESTS guideline is less strict in its recommendations: sampling of a second ipsilateral nodal station is not required. Other explanations for the low compliance with the Dutch guideline could be: 1) the difficulty of finding level 2 – especially the upper tracheal lymph node stations (2L and 2R) were biopsied less frequently; and 2) difficulty in anatomical differentiation between level 2 and level 4 in a mediastinoscopy. The fact that for left sided tumors adherence was lower supports these arguments, because station 2L is known to be hard to reach (*Table 2*). Also, surgeons could have chosen to follow the ESTS, instead of the national guideline. The funnel plots (*Figure 3*) show wider inter-hospital variation on surgical performance and more underperforming hospitals – hospitals below the 95% CI – for the Dutch guideline, which supports this last hypothesis. The considerable between-hospital variation offers room for improvement.

The 10.2% unforeseen N2 disease in patients who underwent resection after mediastinoscopy in this study is in line with the ESTS guideline, that states that a rate of unforeseen N2 disease of 10% is acceptable. (8) Other studies show unforeseen N2 rates of 5.5%, 8.2%, 10.0% and 17.0%. (13,17,18,23) The study of Smulders (17.0%) is the oldest and was performed in a pre-FDG-PET and pre-video-mediastinoscopy era. This, and lower guideline adherence than in the current study, have probably led to a higher unforeseen N2 rate. Lemaire et al. (unforeseen N2 rate, 5.5%; 1996-2005) performed their evaluation of conventional mediastinoscopy in a single center, that performed over 200 mediastinoscopies a year. Experience (reflected by high case-volume) might play a role in their low unforeseen N2 rates. However, it is important to keep in mind that the finding of false negative results is also affected by the quality of the lymph node dissection during resection, which could account for underestimations of the unforeseen N2 rate. Therefore, drawing solid conclusions from the comparison of these results remains difficult.

For the Dutch guideline, a significant difference is seen in unforeseen N2 disease comparing patients staged according to the guideline and patients not staged according to the guideline (8.6% vs. 11.9%, $p = 0.043$). More extensive sampling and therefore better detection might be the explanation for this effect, but adequate performance of mediastinoscopy could also be an expression of a well-organized staging process, and play a role here. Also, in the non-adherence group more left sided tumors were present. Inaccessibility of station 5 and 6 by cervical mediastinoscopy will partly explain this. The difference in unforeseen N2 disease is not present when comparing groups according to the ESTS guideline or when comparing the "true" false negative rates where only nodal stations accessible by mediastinoscopy are taken into account. A possible explanation might be a more extensive mediastinal lymph node sampling when following the Dutch guideline that results in finding more (micro)metastases. Since patients with (minimal)

N2 disease are eligible for neo-adjuvant treatment this is important with regard to the optimal treatment strategy. Detection of N2 disease in station 5 and 6 can be improved, for example by performing an anterior parasternal mediastinotomy (Chamberlain procedure). (24) It is questionable, however, how necessary this is as metastases in these stations are more and more seen as 'sentinel node' for left upper lobe tumors and therefore no contraindication for surgery and not of influence for treatment choices alone.

In depth analysis of the 'false negative' cases (*Table 3*) shows that most of the postoperative positive nodal stations – that were accessible in mediastinoscopy – were actually biopsied during mediastinoscopy (for example 16/18 for 4R). Only in few patients these stations were suspected on computed tomography//PET (6/18 for 4R). This suggests that most of the unforeseen N2 cases were based on micro metastases in stations accessible with mediastinoscopy, or were present in stations not accessible with mediastinoscopy. Other studies show similar results. (17, 25) Also, station 7 was tumor positive in 41 of the 47 cases, despite biopsies by mediastinoscopy. This might be because of metastases located in the lower aspect of the subcarinal region, which is known to be hard to assess during mediastinoscopy. (26) The use of EUS might be more contributory in these cases, but was only performed in 57% of these patients.

This study has some limitations. Data in the DLCA-S are primarily collected for evaluation of surgical quality of care. To reduce registration burden, collected information is often limited and not always as detailed as desired for research purposes. For example, conventional mediastinoscopy and video-assisted mediastinoscopy (VAM) are clustered in one group, which makes distinction impossible. However, nowadays almost all Dutch hospitals use VAM, with only few exceptions. (21) Also, only for patients undergoing surgical resection of NSCLC, detailed information on patient and tumor characteristics is collected. For a substantial group of NSCLC patients with a positive mediastinoscopy or with negative mediastinoscopy but no pulmonary resection (n=1,110), insufficient data were available to include them. Especially data on tumor side (necessary to evaluate guideline adherence) and on histopathology (inclusion of NSCLC only) were essential. By not including these patients, selection bias might have been introduced. However, the distribution of the number of biopsied stations and adherence to the ESTS guideline in this group were not different compared to included patients. Next, information on *the number of biopsied single lymph nodes* and *weight of total lymph nodes procured* could have given more insights about adequate performance, but both were not registered in the DLCA-S.

Finally, data are self-reported by hospitals, by data managers, doctors and specialized nurses. This could have introduced bias. External verification of DLCA-S data showed

high levels of patient inclusion and good quality of the registered data on mortality and complications. (27) Although performance and outcomes of mediastinoscopy were not among the verified items this verification suggest adequate and reliable data collection.

In conclusion, this study on national data of 1,729 patients shows that there is still room for improvement of surgical performance of mediastinoscopy. This is reflected by the percentage of guideline adherence, between-hospital variation in guideline adherence and the occurrence of unforeseen N2. In mediastinoscopies performed according Dutch guidelines, less unforeseen N2 disease was found. Awareness on the extent of lymph node biopsies is therefore important and performance of mediastinoscopy according to guidelines will therefore be added as a quality indicator for the Dutch national audit. In the discussion on added value of mediastinoscopy it is important to consider surgical quality of the procedure and to realize that accuracy of staging procedures is subject to how a procedure is technically performed.

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