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Keywords

Non-small cell lung cancer; Mediastinal lymph node staging; Endosonography; Mediastinoscopy; Thoracic surgery; Overall survival.

Summary of take home message for social media purposes

Invasive mediastinal nodal staging of patients with resectable NSCLC significantly increased over the years in the Netherlands. Performance of invasive staging led to a possible overall survival benefit in patients with clinical N1-3 disease.

Abstract

Introduction Guidelines for invasive mediastinal nodal staging in resectable 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 (OS).

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 OS and compared outcomes in the entire group and in cN1-3 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 OS 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 OS 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 substituting) 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 (OS).[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 OS 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'.

OS was assessed using Kaplan Meier estimates assessing differences by the log-rank test. The effect of invasive mediastinal staging on OS 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.

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)	
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, a total of 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).

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).

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.

Overall survival

Five-year OS rate of patients with pN0 was 61% versus 43% and 31% in patients with pN1 and unforeseen pN2, respectively. Five-year OS 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 OS rate of 39% compared to 28% in patients with more than one malignant uN2 lymph node (p<.01). OS was comparable among patients with pN1 and single node uN2 (43% vs 39%, p=.32).

Five-year OS 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 OS 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).

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.

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 OS, 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 OS 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 OS 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 OS 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 OS of 39% in patients primarily treated by surgical lung tumour resection, while 4-year OS was 51% in patients receiving neo-adjuvant therapy and subsequent surgical lung tumour resection.[24] The ESPATUE trial showed 5-year-OS 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 OS 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 OS.

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. 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 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

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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.

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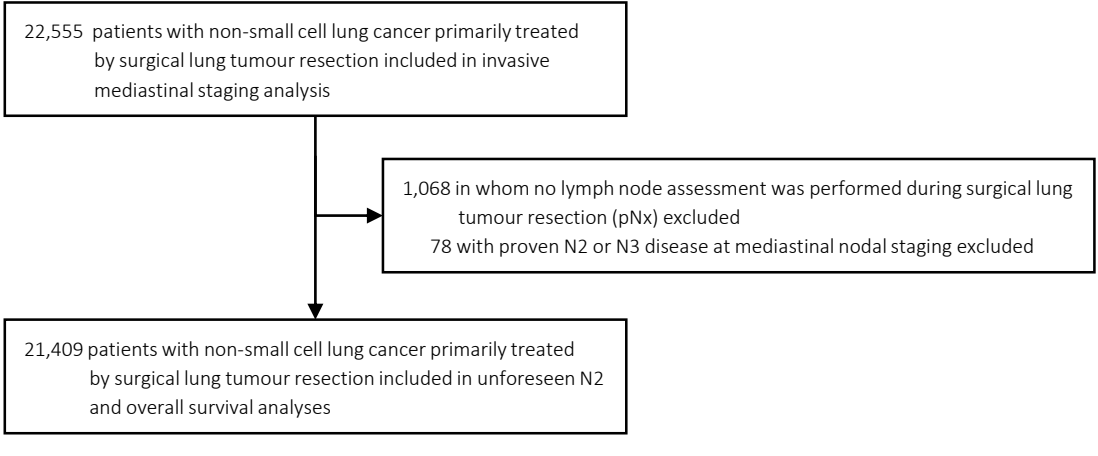
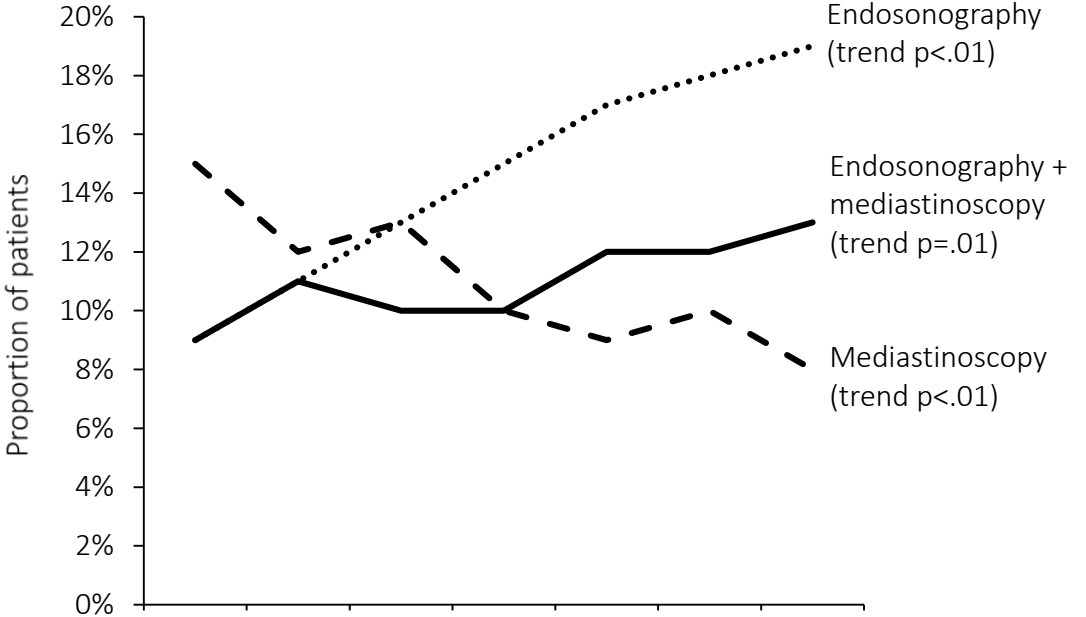
Figure legends

Figure 1. Flowchart of patient selection.

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)


22,555 patients with non-small cell lung cancer primarily treated by surgical lung tumour resection included in invasive mediastinal staging analysis
1,068 in whom no lymph node assessment was performed during surgical lung tumour resection (pNx) excluded
78 with proven N2 or N3 disease at mediastinal nodal staging excluded
21,409 patients with non-small cell lung cancer primarily treated by surgical lung tumour resection included in unforeseen N2 and overall survival analyses



year	2011	2012	2013	2014	2015	2016	2017
n	1,725	1,683	1,784	1,694	1,828	1,782	1,825
uN2, %	7.8	8.0	9.0	9.3	9.5	8.5	8.9

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
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

x^2 =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;