



Surgical mediastinal lymph node staging for non-small-cell lung carcinoma

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Background: The current preferred approach for surgical mediastinal staging of non-small-cell lung carcinoma is video-assisted mediastinoscopy. An alternative technique in which lymph nodes are resected instead of biopsied is video-assisted mediastinoscopic lymphadenectomy (VAMLA) that is suggested to be superior in detecting N2 disease. Yet, evidence is conflicting and furthermore limited by sample size. The objective was to compare mediastinal staging through VAMLA and video-assisted mediastinoscopy.

Methods: A single-center cohort study was conducted. All consecutive patients that underwent surgical mediastinal staging of non-small-cell lung carcinoma by VAMLA (2011 to 2018) were compared to historic video-assisted mediastinoscopy controls (2007 to 2011). Patients with negative surgical mediastinal staging underwent subsequent anatomical resection with systematic regional lymphadenectomy. Primary outcome was the sensitivity and negative predictive value for detecting N2 disease.

Results: Two-hundred-sixty-nine video-assisted mediastinoscopic lymphadenectomies and 118 video-assisted mediastinoscopies were performed. The prevalence of N2 disease was 20% and 26% respectively in the VAMLA and video-assisted mediastinoscopy group, while the rate of unforeseen pN2 resulting from lymph node dissection during anatomical resection was 4% and 11%, respectively. Invasive staging using VAMLA demonstrated superior sensitivity of 0.82 and a negative predictive value of 0.96 when compared to video-assisted mediastinoscopy (0.62 and 0.89, respectively), offering a 64% decrease in risk of unforeseen pN2 following anatomical resection. However, VAMLA is also associated with a 75% risk increase on complications (P=0.36).

Conclusions: We conclude that performing invasive mediastinal lymph node assessment for staging of non-small-cell lung carcinoma, VAMLA should be the preferred technique with superior sensitivity and negative predictive value in detecting N2 disease. Though, VAMLA is also associated with an increased risk of complications.

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Introduction

According to current American and European guidelines (1,2), mediastinal lymph node assessment plays a pivotal role in staging of non-small cell lung carcinoma (NSCLC). Patients suspected of NSCLC routinely undergo an ¹⁸F-deoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) scan. When imaging shows suspicious (i.e., enlarged or FDG-avid) ipsilateral or contralateral hilar or mediastinal lymph nodes, in absence of distant organ metastasis, mediastinal staging by endosonography [endo-bronchial (EBUS) and/or endo-esophageal ultrasonography (EUS)] is indicated as first best test (1,2). Though, if N2 disease is suspected on imaging and mediastinal lymph node sampling via E(B)US is negative, surgical mediastinal staging is advised by both the European and American guidelines (1,2). The standard approach for this diagnostic step is video-assisted mediastinoscopy (VAM), as advised by the European guidelines (1). In contrast, American guidelines do not advise on the preferred technique for surgical staging (2). The sensitivity of VAM ranges from 0.75 to 0.95 and NPV from 0.59 to 0.96 (3-7). An alternative technique for surgical mediastinal staging is video-assisted mediastinoscopic lymphadenectomy (VAMLA). In VAMLA, the mediastinal lymph node stations are resected compared to simple biopsy during VAM. Recent studies suggest a superior sensitivity and NPV up to 1.0. However, these series are limited by small sample sizes thereby impairing evidential value (8-10). In addition, the few studies comparing VAM and VAMLA show conflicting evidence regarding sensitivity and NPV (11,12).

The aim of this study is to compare mediastinal staging through VAMLA and VAM, focusing on their sensitivity and NPV in detecting N2 disease among patients suspected for NSCLC. We present the largest VAMLA cohort to date, evaluating its performance for the mediastinal evaluation of NSCLC compared to VAM. This report was written in compliance with the STARD (13) reporting checklist (available at <https://dx.doi.org/10.21037/tlcr-21-364>).

Methods

Study design

A single-center cohort study using prospectively collected, retrospectively reviewed data was conducted at Zuyderland Medical Center (Heerlen, the Netherlands). The study was approved by the local ethics and clinical research committee (METCZ; ID: METCZ20180090, approval date: August 15th, 2018) of Zuyderland Medical Center (Heerlen, the Netherlands). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients

All consecutive patients with histologically proven NSCLC who underwent surgical mediastinal staging through VAMLA or VAM between January 2007 (initiation of prospective data collection) and December 2018 at Zuyderland Medical Center (Heerlen, the Netherlands) were eligible for inclusion. Between May 2011 and December 2018 patients underwent VAMLA and were compared to historic VAM controls staged between January 2007 and April 2011. Those with prior mediastinal surgery, prior lung cancer, neoadjuvant therapy or oligometastasis were excluded.

Work-up and surgical techniques

All patients underwent similar pre-operative workup encompassing an FDG-PET-CT followed by EUS and/or EBUS in the presence of suspicious ipsilateral or contralateral hilar or mediastinal lymph nodes on imaging. The choice for either technique was based on the stations with suspected involvement. VAM(LA) was performed upon negative E(B)US. In addition, VAM(LA) was indicated in the presence of a non-FDG-avid tumor, central tumor location (defined as: middle one-third of the thorax) and tumor size larger than 3 centimeters, in accordance to European guidelines (1).

Table 1 Definitions of postoperative adverse events

Adverse event	Definition
Temporary recurrent laryngeal nerve palsy	Postoperative dysphagia and/or dysphonia with laryngoscopically confirmed standstill of one or both vocal cords, recovered within 1 year after VAM(LA)
Permanent recurrent laryngeal nerve palsy	Persistent postoperative dysphagia and/or dysphonia with laryngoscopically confirmed standstill of one or both vocal cords that is still present after 1 year after VAM(LA)
Mediastinitis	Radiographically confirmed and symptomatic mediastinitis requiring antibiotic treatment within 30 days after surgery
Pneumonia	The presence of a (new) radiographic infiltrate combined with a decline in oxygenation, fever, purulent sputum, and leukocytosis within 30 days following surgery (11)
Superficial surgical wound infection	The presence of purulent surgical wound drainage, a positive culture and/or requiring surgical drainage or reoperation within 30 days after surgery (12)

VAM, video-assisted mediastinoscopy; VAMLA, video-assisted mediastinoscopic lymphadenectomy.

VAM was performed using a standard mediastinoscope with integrated optics connected to a video system. Lymph node stations 2R-L, 4R-L and 7 were biopsied. VAMLA was performed according to the technique comprehensively described by Hürtgen *et al.* (3), using a twin-bladed speculum with integrated optics providing enhanced exposure and facilitating bimanual resection (*Video 1*). During VAMLA, the same nodal stations were completely resected that were sampled with VAM.

In the absence of N2 disease after VAM(LA), anatomical resection was performed within one week. During anatomical resection, intraoperative completing systematic nodal resection was performed in adherence to European guidelines (i.e., adjuvant resection of stations 8 and 9 for the right lower lobe, stations 5 and 6 for the left upper lobe and stations 8 and 9 for the left lower lobe) (14). Station 2, 4 and 7 were solely re-evaluated during anatomical resection in the VAM-group, given that they were already resected in toto by VAMLA. Nevertheless, if adenectomy was not possible during initial VAMLA due to for example dense adhesions, they were re-evaluated during anatomical resection.

All tissue samples were processed and evaluated by a pathologist using similar protocols encompassing hematoxylin-eosin staining without additional immunohistochemical analysis. In order to maintain uniformity, all TNM stages were classified according to the 7th edition (15) and were converted if defined in a previous edition.

Variables and data acquisition

Prospectively collected patient charts were retrospectively reviewed for (I) clinical characteristics (gender, age, body

mass index, comorbidities, indication for mediastinal staging, tumor location, tumor histology and clinical TNM (cTNM) stage); (II) mediastinal staging characteristics [mean number and location of lymph node stations resected/biopsied, adherence to the European (i.e., at least resection or biopsy of 4R-L and 7) (1) and American guidelines (i.e., level B: at least resection or biopsy of 2R-L, 4R-L and 7) (2) for mediastinal lymph node staging, presence of positive mediastinal nodes, cTNM stage after VAM(LA), and postoperative adverse events (see *Table 1* for definitions) including severity score according to the Clavien-Dindo Classification (CDC) (13)]; (III) characteristics of subsequent anatomical resection [adherence to the European guidelines on systematic lymph node dissection during anatomical resection (as mentioned above), final pathological (pTNM) stage and unforeseen pN2 disease (i.e., false-negative VAM(LA)]. Unforeseen pN2 disease was defined as N2 metastasis resulting from lobe-specific intraoperative systematic nodal resection, when nodal stations evaluated by VAM(LA) demonstrated no N2 metastasis. For example, metastases in station 5, 6, 8 or 9, found after anatomical resection were also considered as unforeseen pN2. Although American guidelines recommend systematic lymph node evaluation at the time of anatomical resection, they do not specify stations to be sampled or dissected (14). Consequently, adherence to the American guidelines could not be assessed

Statistical analyses

Statistical analyses were performed by SPSS statistics (IBM Corp. IBM SPSS Statistics for MacOS, Version 27.0,

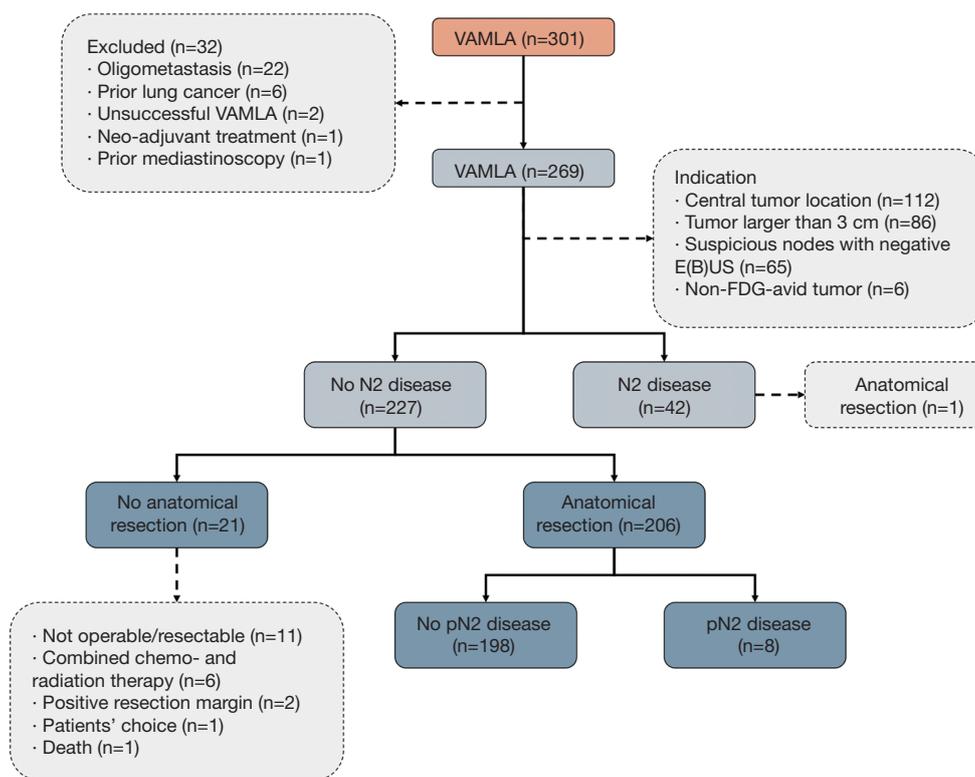


Figure 1 STARD flow chart of patients with histologically proven NSCLC who underwent surgical mediastinal staging through VAMLA and, if applicable, subsequent anatomical resection. NSCLC, non-small-cell lung carcinoma; VAMLA, video-assisted mediastinoscopic lymphadenectomy; EBUS, endo-bronchial ultrasonography; EUS, endo-esophageal ultrasonography; FDG, 18F-deoxyglucose; pN2, pathological N2 disease.

Armonk, NY, USA). Continuous variables were denoted as mean and standard deviation (SD) and assessed for differences by the independent samples *t*-test. Categorical variables were depicted as frequency and percentage and compared using the chi-square-test with post-hoc analyses (by Fisher's exact test) and Bonferroni correction or Fisher's exact test alone. The sensitivity and NPV of VAM(LA) were calculated. These calculations were based on the assumption that the fraction of patients with unforeseen pN2 disease who underwent an anatomical resection was the same as in patients with negative VAM(LA) who did not receive an anatomical resection. In addition, patients with positive VAM(LA) did not undergo anatomical resection and were considered to be true positives. Calculating the overall prevalence of N2 disease [i.e., N2 metastasis found during VAM(LA) combined with unforeseen pN2 disease after anatomical resection], patients who had a negative VAM(LA) without subsequent anatomical resection were not considered. Missing data was reported as such. A P

value <0.05 was considered statistically significant.

Results

Between January 2007 and December 2018, 436 consecutive patients underwent surgical mediastinal staging, of whom 49 were primarily excluded due to prior mediastinal surgery, prior lung cancer, neoadjuvant treatment and oligometastasis (see the STARD flow charts in *Figures 1,2*). The remaining 387 patients were divided into a VAMLA (n=269) and VAM (n=118) group. Baseline characteristics are presented in *Table 2*. Suspicious lymph nodes were significantly ($P=0.007$) more often the reason to perform invasive mediastinal staging in the VAM group [38% (n=45/118)] when compared to the VAMLA group [24% (n=65/269)]. An indication based on tumors larger than 3 centimeters was significantly more frequently observed in the VAMLA group [32% (n=86/269); versus VAM: 19% (n=22/118); $P=0.007$]. Adenocarcinoma was significantly

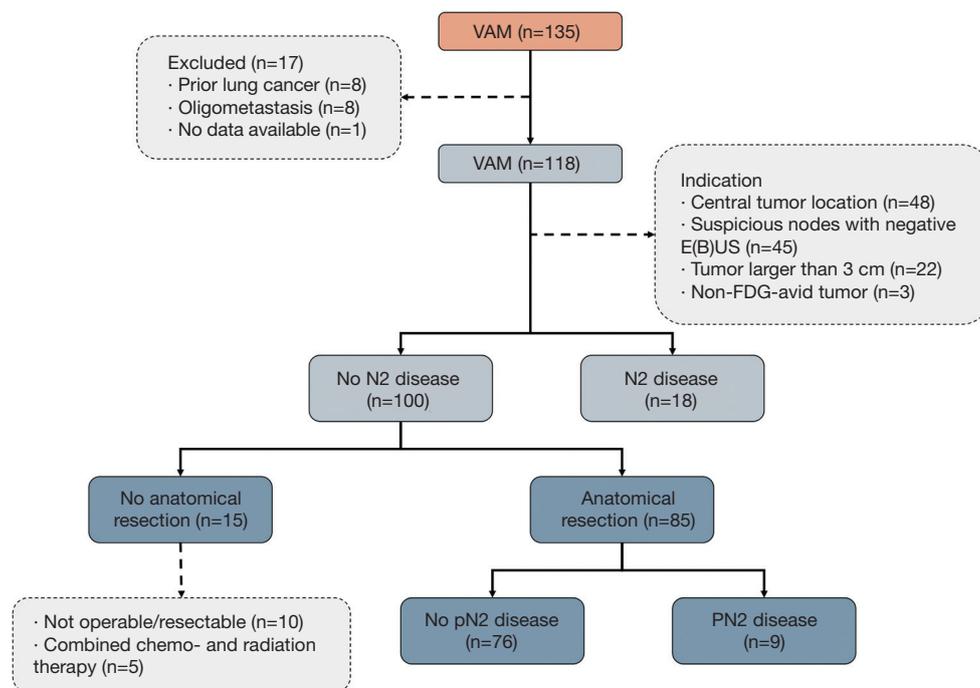


Figure 2 STARD flow chart of patients with histologically proven NSCLC who underwent surgical mediastinal staging through VAM and, if applicable, subsequent anatomical resection. NSCLC, non-small-cell lung carcinoma; VAM, video-assisted mediastinoscopy; EBUS, endobronchial ultrasonography; EUS, endo-esophageal ultrasonography; FDG, 18F-deoxyglucose; pN2, pathological N2 disease.

more common in the VAMLA group ($P=0.004$) and large cell carcinoma in the VAM group ($P<0.001$).

More lymph node stations were resected during VAMLA [mean: 4.4 (SD: 0.7)] compared to stations biopsied during VAM [mean: 3.5 (SD: 1.0)]. This difference was mainly due to the fact that stations 2R-L, and 4R-L were significantly more often resected in VAMLA (all $P<0.001$, *Table 3*). Compliance with the current European and American mediastinal staging guidelines was superior in VAMLA [91% ($n=246/269$) and 53% ($n=143/269$)] compared to VAM [71% ($n=84/118$) and 18% ($n=21/118$); both $P<0.001$].

The risk of adverse events demonstrated an increase of 75% for VAMLA ($n=19/269$), compared to VAM ($n=5/118$; $P=0.36$). Events encompassed temporary recurrent laryngeal nerve palsy (VAMLA =10, VAM =4; CDC-III_a; i.e., neuropraxia), permanent recurrent laryngeal nerve palsy (VAMLA =3; CDC-III_a), mediastinitis (VAMLA =3; CDC-II), pneumonia (VAMLA =3; CDC-II) and superficial surgical site infection (VAM =1; CDC-I).

Since the overall prevalence of N2 metastasis (i.e., N2 disease found during VAM(LA) combined with unforeseen pN2 disease after anatomical resection) was 20% ($n=50/248$)

in the VAMLA and 26% in the VAM ($n=27/103$) group, results should be interpreted in the light of a relative risk of 1.31 on N2 disease in the VAM group.

A positive VAM(LA) was most often observed among patients who underwent mediastinal staging due to suspected nodes on imaging with negative E(B)US [VAMLA: 38% ($n=18/65$), VAM: 29% ($n=13/45$)]. Among patients with an indication for mediastinal staging based on a central tumor and tumor size larger than 3 cm, the frequency of a positive VAM(LA) respectively ranged from 6% to 11% and 5% to 14% (*Table 3*). A non-FDG-avid tumor as indication for mediastinal staging was not encountered frequently enough ($n=9$ total) to allow interpretation.

Of the 227 negative VAMLA cases (i.e., no N2 metastasis found during mediastinal staging), 206 underwent subsequent anatomical resection (*Table 4*). In this group unforeseen pN2 disease (i.e., false negative VAMLA) was found in 4% ($n=8/206$) of cases. Inoperability due to evolving medical conditions or unresectability were the most frequent reasons for withholding surgical resections in patients without N2 metastasis (*Figure 1*). One patient with a positive VAMLA (based on micrometastasis in nodal station 7)

Table 2 Clinical patient characteristics

Characteristics	VAMLA		VAM		P value
	n	Value	n	Value	
Gender, male, n (%)	269	171 [64]	118	79 [67]	0.57
Age, years, mean [SD]	269	67 [9]	118	66 [9]	0.16
BMI, kg/m ² , mean [SD]	269	26 [5]	118	26 [5]	0.31
Comorbidities [†] , n [%]	269	158 [59]	118	66 [56]	0.61
Cardiac		38 [14]		16 [14]	
Pulmonary		90 [33]		36 [31]	
Oncologic (i.e., any prior cancer but basal cell carcinoma)		50 [19]		16 [14]	
Diabetes		32 [12]		17 [14]	
Prior stroke		15 [6]		8 [7]	
Indication, n [%]	269		118		0.012*
Suspicious nodes		65 [24]		45 [38]	0.007**
Non-FDG-avid tumor		6 [2]		3 [2]	1
Central tumor		112 [42]		48 [41]	0.91
Tumor >3 cm		86 [32]		22 [19]	0.007**
Tumor location, n [%]	269		118		0.99
RUL		74 [27]		34 [29]	
RML		16 [6]		7 [6]	
RLL		51 [19]		24 [20]	
LUL		78 [29]		33 [28]	
LLL		50 [19]		20 [17]	
Tumor histology, n [%]	269		117		<0.001*
Adeno		112 [42]		31 [27]	0.004***
Squamous		138 [51]		59 [50]	0.83
Large cell		19 [7]		27 [23]	<0.001***
cTNM stage after imaging, n [%]	269		118		0.47
Ia		54 [20]		21 [18]	
Ib		84 [31]		47 [40]	
IIa		49 [18]		20 [17]	
IIb		64 [24]		21 [18]	
IIIa		18 [7]		9 [7]	

*, statistically significant at $P < 0.05$. **, statistically significant at $P < 0.013$ after Bonferroni correction. ***, statistically significant at $P < 0.017$ after Bonferroni correction. †, a single patient can have multiple comorbidities. VAMLA, video-assisted mediastinoscopic lymphadenectomy; VAM, video-assisted mediastinoscopy; SD, standard deviation; BMI, body mass index; FDG, 18F-deoxyglucose; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; cTNM, clinical TNM.

Table 3 Characteristics of mediastinal staging

Characteristics	VAMLA		VAM		P value
	n	Value	n	Value	
Total number of lymph node stations resected/biopsied, mean (SD)	269	4.4 [0.7]	118	3.5 [1.0]	<0.001*
Frequency of lymph node stations resected/biopsied, n [%]	269		118		
2L		157 [58]		35 [30]	<0.001*
2R		251 [93]		63 [53]	<0.001*
4L		250 [93]		93 [79]	<0.001*
4R		266 [99]		110 [93]	0.004a
7		266 [99]		116 [98]	0.64
Adherence to European guidelines for mediastinal staging (at least 4L-R and 7), n [%]	269	246 [91]	118	84 [71]	<0.001*
Adherence to American guidelines for mediastinal staging (level B: at least 2L-R, 4L-R and 7), n [%]	269	143 [53]	118	21 [18]	<0.001*
cTNM stage after VAM(LA), n [%]	269		118		<0.001*
Ia		39 [14]		9 [8]	0.066
Ib		60 [22]		25 [21]	0.89
IIa		51 [19]		18 [15]	0.47
IIb		50 [19]		9 [8]	0.005**
IIIa		59 [22]		56 [47]	<0.001**
IIIb		10 [4]		1 [1]	0.18
Positive mediastinal staging, n [%]	269	42 [16]	118	18 [15]	0.086
Suspicious nodes	65	18 [38]	45	13 [29]	
Non-FDG-avid tumor	6	0 [0]	3	1 [33]	
Central tumor	112	12 [11]	48	3 [6]	
Tumor >3 cm	86	12 [14]	22	1 [5]	
Adverse events, n [%]	269	19 [7]	118	5 [4]	0.36
Temporary recurrent laryngeal nerve palsy (CDC-IIIa)		10 [4]		4 [3]	
Permanent recurrent laryngeal nerve palsy (CDC-IIIa)		3 [1]		0 [0]	
Mediastinitis (CDC-II)		3 [1]		0 [0]	
Pneumonia (CDC-II)		3 [1]		0 [0]	
Superficial surgical wound infection (CDC-I)		0 [0]		1 [1]	

*, statistically significant at $P < 0.05$. **, statistically significant at $P < 0.008$ after Bonferroni correction. VAMLA, video-assisted mediastinoscopic lymphadenectomy; VAM, video-assisted mediastinoscopy; SD, standard deviation; CDC, Clavien-Dindo.

underwent resection but was excluded from sensitivity and NPV analyses. Of the 100 negative VAM cases, fifteen patients had no subsequent surgical intervention due to similar reasons in the VAMLA group (inoperability or

irresectability). Unforeseen pN2 disease in the VAM group after anatomical resection was observed in 11% ($n=9/85$) of patients (*Figure 2*). The prevalence of unforeseen pN2 disease did significantly differ in favor of VAMLA, when

Table 4 Characteristics of anatomical resections after negative VAM[LA]

Characteristics	VAMLA		VAM		P value
	n	Value	n	Value	
Subsequent anatomical resection, n [%]	269	206 [77]	118	85 [72]	0.31
Adherence to lobe specific European guidelines for lymph node resection, n [%]	206	142 [69]	85	15 [18]	<0.001*
Final pTNM stage, n [%]	206		84		0.011*
Ia		46 [22]		20 [24]	1
Ib		33 [16]		26 [31]	0.02
IIa		59 [29]		10 [12]	0.001**
IIb		36 [17]		13 [15]	0.62
IIIa		30 [15]		15 [18]	0.74
IIIb		2 [1]		0 [0]	1
Unforeseen pN2, n [%]	206	8 [4]	85	9 [11]	0.049*

*, statistically significant at $P < 0.05$. **, statistically significant at $P < 0.008$ after Bonferroni correction. VAMLA, video-assisted mediastinoscopic lymphadenectomy; VAM, video-assisted mediastinoscopy; SD, standard deviation; pTNM, pathological TNM; pN2, pathological N2 disease.

being compared to VAM ($P = 0.049$).

The sensitivity of VAMLA for detecting N2 disease was 0.82 ($n = 42/51$; 95% CI: 0.69 to 0.92) with a NPV of 0.96 (95% CI: 0.93 to 0.98). Corresponding values for VAM were 0.62 ($n = 18/29$; 95% CI: 0.42 to 0.79) and 0.89 (95% CI: 0.84 to 0.93).

Clinical characteristics of patients with unforeseen pN2 disease are depicted in *Table 5*. Missed mediastinal metastases were single station in all but one patient. In 5 out of 9 VAM patients this concerned lymph node stations that were accessible by VAM. In the remaining four VAM patients, metastases were found in station 5, which cannot be reached via standard VAM(LA). In 2 of the 8 false negative cases in the VAMLA group metastasis were found in nodal stations that should have been resected. This included one patient in whom N7 was only partially resected due to extensive peri-nodal tissue induration.

The lobe specific European guidelines for lymph node resection during anatomical resection were adhered to in 69% ($n = 142/206$) and 18% ($n = 15/85$) of patients in the VAMLA and VAM group, respectively.

Discussion

The objective of this single-center cohort study was to compare surgical mediastinal staging for NSCLC through

VAMLA and VAM, focusing on their ability to detect N2 disease.

Based on our data we found superior sensitivity and NPV for VAMLA (0.82 and 0.96, respectively) for detecting N2 disease, compared with VAM (0.62 and 0.89, respectively). The rate of unforeseen pN2 was 4% ($n = 8/206$) for VAMLA and 11% ($n = 9/85$) for VAM. VAMLA thus offers a significantly better staging that results in a 64% risk reduction in unforeseen pN2. However, VAMLA is also associated with an increased complication rate of 75% ($n = 19/269$) compared to VAM ($n = 5/118$; $P = 0.36$), predominantly due to a 66% [VAMLA: 5% (13/269); VAM: 3% (3/118)] increase in the risk of recurrent laryngeal nerve palsies. Though, the majority of these concerned neuropraxia and thus were of temporary nature. Whether this increased complication rate justifies the risk reduction in unforeseen pN2 may be questioned. It could potentially be justified for patients with a high prior probability of N2 disease in combination, such as patients with suspected mediastinal lymph nodes and negative E(B)US. Though, the morbidity associated with VAM(LA) has made it an unattractive option for North American surgeons who favor the sole use of E(B)US which is associated with negligible morbidity (15).

The NPV in the VAM group falls within the range of previously reported series (0.59 to 0.96) (16-20). Similar

Table 5 Characteristics of individual patients with unforeseen pN2 following anatomical resection

Surgical modality	Tumor location	Indication for VAM(LA)	cTNM stage after imaging	Tumor histology	2L	2R	4L	4R	7	Positive node(s)
VAMLA	LLL	Central tumor	Ib	Adeno	Yes	Yes	Yes	Yes	Yes	6 and 7
	LUL	Central tumor	Ib	Adeno	Yes	Yes	Yes	Yes	Yes	5
	LUL	Central tumor	IIb	Adeno	Yes	Yes	Yes	Yes	Yes	5
	LUL	Suspicious nodes	Ia	Squamous	Yes	Yes	Yes	Yes	Yes	6
	LUL	Central tumor	IIb	Squamous	Yes	Yes	Yes	Yes	Yes	5
	LUL	Central tumor	Ia	Squamous	No	Yes	Yes	Yes	Yes	6
	LUL	Central tumor	IIb	Squamous	Yes	Yes	Yes	Yes	Yes	9
	RLL	Tumor >3 cm	IIa	Squamous	No	Yes	Yes	Yes	Yes	7
VAM	LUL	Suspicious nodes	IIb	Adeno	No	No	No	Yes	Yes	5
	RUL	Central tumor	Ib	Squamous	No	Yes	No	Yes	Yes	4R
	RUL	Central tumor	IIIa	Squamous	No	Yes	Yes	Yes	Yes	7
	RLL	Central tumor	Ib	Squamous	No	Yes	Yes	Yes	Yes	7
	RLL	Suspicious nodes	Ib	Squamous	No	No	Yes	Yes	Yes	7
	LUL	Suspicious nodes	IIb	Squamous	Yes	Yes	Yes	Yes	Yes	5
	LUL	Tumor >3 cm	IIb	Large cell	No	Yes	Yes	Yes	Yes	5
	LUL	Central tumor	IIa	Large cell	No	No	Yes	Yes	Yes	5
	LLL	Suspicious nodes	IIb	Large cell	No	No	Yes	Yes	Yes	7

VAM, video-assisted mediastinoscopy; VAMLA, video-assisted mediastinoscopic lymphadenectomy; cTNM, clinical TNM; LUL, left upper lobe; LLL, left lower lobe; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe.

observations are made for VAMLA with reported NPVs ranging from 0.84 up to 1.0 (3,4,6,7,21,22). These variations demonstrate considerable heterogeneity among studies, that might possibly be explained by differences in sample size, inclusion criteria, work-up and use of additional diagnostics (e.g., extended mediastinoscopy or mediastinotomy). The NPV reported in the current series should thus be interpreted within the context that all patients suspected for NSCLC underwent E(B)US in the presence of reachable suspicious lymph nodes on FDG-PET-CT. In addition, VAM(LA) was indicated after negative E(B)US, or in the presence of a non-FDG-avid tumor, central tumor location and tumor size larger than 3 centimeters.

Suspicious lymph nodes were more often the reason to perform invasive mediastinal staging in the VAM group, while a tumor larger than 3 centimeters was more frequently observed as an indication in the VAMLA group. The indication for mediastinal staging in tumors larger than 3 cm was not applied compellingly during the

early enrollment period (i.e., at the time when surgical mediastinal staging was performed through VAM) as this recommendation had not been embodied in the national Dutch guidelines at that time. Gradually, adherence to European guidelines (that included the indication in tumors >3 cm) intensified and a shift was made to VAMLA, potentially explaining its increased frequency.

Regarding the differences in tumor histology: adenocarcinoma was more often observed in the VAMLA and large cell carcinoma in the VAM group. However, both definitions have an overlap and their institutional use shifted during the enrollment period.

In the VAMLA and VAM group, respectively 5% and 10% of patients without N2 disease found after surgical mediastinal staging did not undergo subsequent anatomical lung resection. This resulted from the primary objective for mediastinal staging being assessment of nodal status to determine chemoradiation treatment strategy in these selected patients who were already deemed inoperable/

unresectable.

As reported earlier (6), we demonstrated that VAMLA led to an increase in the number of stations evaluated and thus improved adherence to current guidelines for mediastinal staging (1,2). This may be due to the use of a twin-bladed scope enabling bimanual dissection and enlarging the field of dissection, thereby improving visibility and identification of lymph nodes. Alternatively, these increased number of stations evaluated may be biased due to the use of historical controls which do not account for enhanced awareness and, as mentioned previously, improved guideline adherence over time. Though, the latter may be challenged given that the adherence to anatomical resection guidelines was also superior for the VAMLA group (69%; compared to 18% for VAM) and was, moreover, considerably higher compared to a nationwide study in the Netherlands by van der Woude *et al.* (23). During the same enrollment period as our VAMLA group, van der Woude *et al.*, revealed a complete N2 lymph node dissection rate (defined as: at least three mediastinal lymph node stations including station 7) of approximately 27% for anatomical resections through a minimally invasive approach among patients with cN0-1 disease staged by E(B)US and/or mediastinoscopy (23). Albeit a partial effect of improved adherence over time is, next to the potential superiority of VAMLA, likely to be present since we also intensified our adherence to European guidelines on indications for surgical mediastinal staging as above-mentioned.

Anatomical resection within one week following VAM(LA), as performed in the present study, may be technically more demanding due to the presence of mediastinal tissue reaction and induration. At this point, VAMLA is at advantage since lymph node stations 2, 4 and 7 are already being resected in toto during mediastinal staging, because of which the touched stations do not require re-evaluation upon anatomical resection. In addition, the stations which still require resection during anatomical resection (i.e., station 5, 6, 8 and/or 9 depending on tumor location) are in previously untouched areas, not directly complicating their resection. In contrast VAM requires re-evaluation of stations 2, 4 and 7. Evaluating the difference regarding complications after anatomical resection may be of great interest for future research given the preceding differences between anatomical resection after respectively VAM and VAMLA.

The traditional 'Achilles-heel' of both VAM and VAMLA (4) consists of station 2L due to its direct anatomical relation with the recurrent laryngeal nerve and aortic arch. In

addition, ipsilateral station 2 is known for being difficult to reach when performing lobe-specific lymph node dissection during anatomical resection through conventional video-assisted thoracoscopy (24), potentially leading to a (microscopic) incomplete lymphadenectomy. Though, this potential issue can be circumvented by complete resection of stations 2L-R during VAMLA.

We reported a complication rate of 7% (n=19/269) and 4% (n=5/118) for VAMLA and VAM, respectively. These complication rates are both slightly higher than in previously published VAMLA- (3,5,21,22) and VAM-cohorts (17,20). The most observed complication after VAMLA was laryngeal recurrent nerve palsy in 5% (n=13/269) of cases, versus 3% (n=4/118) in VAM cases (temporary and permanent combined). Appropriate visualization of the recurrent nerve, systematic sampling of the left paratracheal nodes instead of *en bloc* resection and the use of endoclips for hemostasis instead of electrocautery are all measures that can be taken in order to prevent laryngeal recurrent nerve palsies during VAMLA (5,21).

In addition, we recently published our learning process of VAMLA and demonstrated a considerable drop in complication rates with frequent exposure after an initial 16 to 17 cases, advocating a minimal volume-limit for surgeons (25). In contrast to this positive effect on complications, no relation was found between the occurrence of unforeseen pN2 and learning process of VAMLA. However, it should be noted that this study reported a lower unforeseen pN2 rate of 3% that was based on a more heterogeneous patient population (25).

We reported an overall N2 metastasis prevalence of 22% (n=77/251). This is relatively low in comparison to rates reported in current literature (21% to 32%) (6,7). The diagnostic yield of E(B)US in our center may possibly be higher but is unknown at this time. In addition, the indications for E(B)US may differ among centers, affecting the rate of N2 disease found during surgical mediastinal staging and subsequent resection. In the current series, E(B)US was only indicated in the presence of suspicious ipsilateral or contralateral hilar or mediastinal lymph nodes on imaging. In cases with a non-FDG-avid tumor, centrally located tumor and a tumor size larger than 3 centimeters without suspicious nodes, invasive mediastinal staging was not preceded by E(B)US. However, experience with E(B)US is expanding and several centers already perform E(B)US for all the aforementioned indications to rule out mediastinal disease.

Although the unforeseen pN2 rate after VAMLA of 4%

is considered acceptable and is in agreement with the revised European guidelines that aim at a rate below 10% (1), improvements are possible. As pointed out in *Table 5*, twelve out of 17 combined VAM(LA) patients with unforeseen pN2 had left-sided tumors with the main indication for surgical staging being a central tumor location. Transcervical extended mediastinal lymphadenectomy (TEMLA) aimed at station 5 and 6 theoretically could have reduced the false negative rate of VAMLA, as 5 out of 8 patients had single station tumor spread in these para-aortic and sub-aortic nodes that are not sampled through VAM(LA). However, given the concern on morbidity and mortality associated with TEMLA (1) leading to >20% of patients becoming medically inoperable (26), video-assisted thoracoscopic surgery (VATS) may provide a safer approach to sample station 5 and 6 before committing to anatomical resection (27). Moreover, station 5 and 6 could in theory also be sampled via EUS in expert hands (28). Evaluation of these stations is of great interest for future research to reduce the occurrence of futile surgical interventions. Though, patients with isolated sub-aortic nodal metastases often behave more like N1-disease and might be eligible for primary anatomical resection with improved survival compared to survival following anatomical resection of metastatic disease in other mediastinal lymph node stations (29).

Finally, missed mediastinal metastases were single station in all but one patient, requiring these patients to undergo adjuvant treatment following surgery. It is well known that there is a wide variety in the prognosis of multilevel or single station N2 disease in NSCLC (30), whereas the latter is associated with a significantly better prognosis and are thus often operated. Neo-adjuvant treatment in these patients is not associated with better outcomes in comparison with adjuvant treatment (31) and might thus question the added benefit of surgical mediastinal staging procedures and their associated complication risks. In its turn, complete mediastinal staging might provide a mediastinal nodes ratio, showing potential in patient tailored treatment (32-34), whereas optimal non-invasive endosonography may even omit the need for surgical mediastinal staging. In order to choose optimal therapy, patient counselling may start to play a bigger role in future diagnostic strategies for NSCLC.

Limitations

We present the largest VAMLA cohort to date with 269 patients and compared its performance to VAM (n=118).

Other comparative studies included a maximum of 89 VAMLA patients (6,7). However, this also directly imposes a concern for the external applicability of our results, considering the relatively large experience of surgeons in VAMLA. The majority of VAMLA (n=243/269) were performed by 6 distinct surgeons, while the majority of VAMs were performed by 4 different surgeons (n=92/118). The remaining procedures were performed by residents or surgeons who performed less than 10 procedures each, potentially affecting outcome. Less experienced hands may show higher complication rates; however, this applies for both techniques. Another limitation concerns that the study was not powered to detect the statistical significance of clinically important differences in the rates of uncommon complications. The study was, moreover, limited by the use of historic controls and a relatively lengthy enrollment period of 11 years inducing potential heterogeneity due to the introduction of pathological, radiological and surgical innovations and the fact that emphasis shifted in the work-up and treatment of patients with NSCLC. The use of multivariate analysis techniques or matching of participants could have reduced the amount of bias, however, the sample size was deemed inadequately. During the course of this study, we switched from VAM to VAMLA (in 2011) for mediastinal staging and from multiportal to uniportal VATS (in 2015) for anatomical resection. Adoption of both new procedures necessitated a learning process. In addition, although prospectively collected data were used, missing data regarding tumor histology and final pTNM stage were present in one patient. Given the above-mentioned limitations, the current evidence should be corroborated by future, adequately powered, randomized controlled trials.

Future perspectives

The combination of E(B)US (11) has led to a further refinement in the diagnostic work-up for NSCLC as described in the combined European Society of Gastrointestinal Endoscopy (ESGE)/European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) guideline on combined endobronchial and esophageal endosonography (12). A diagnostic work-up combining negative dual endosonography followed by surgical mediastinoscopy, led to the detection of mediastinal metastatic disease in 9% of patients with a sensitivity of 0.94 (35). Although we found a higher mediastinal disease rate after both VAMLA and VAM [16% (n=42/269) and 15% (n=18/118), respectively], our reported unforeseen

pN2 rate was considerably lower in the VAMLA group [4% (n=8/206)] compared to reported rates following negative dual endosonography only (23%) (35). Following the results of Annema *et al.* (35), the ongoing MEDIASTrial investigates whether dual endosonography alone is non-inferior to the addition of subsequent surgical mediastinoscopy, thereby potentially reducing morbidity and treatment delay (36). However, we advocate careful subgroup analyses as the rates of N2 disease are likely to differ among indications for mediastinal staging (e.g., suspicious nodes on pre-operative imaging).

In the present study, the absence of N2-disease after VAM(LA), either minimal or multi-level, selected candidates for subsequent anatomical resection, while its presence indicated non-surgical therapy [i.e., chemo(radiation) therapy] as initial treatment course. Though, in future practice the involved mediastinal nodes ratio might prove to be a better criterium for tailored treatment (32-34). This in turn may result in an increased interest for mediastinal lymphadenectomies. For example, in inoperable patients undergoing mediastinal staging to rule out N2 disease to have non-surgical treatment such as stereotactic body radiation therapy. Moreover, with advancing insight and techniques, space was created for resection after neoadjuvant treatment or anatomical resection followed by adjuvant therapy in the presence of minimal N2 disease.

In the present study, anatomical resection was performed within 1 week in the absence of N2 disease after VAM(LA). Theoretically speaking, both procedures could be performed in the same setting. Consequently, the patient only requires a single surgery which may ease surgical planning and enhance overall recovery, but also eliminates the patient's uncertainty while waiting for the VAM(LA) results. However, frozen sections are associated with limited reliability for the analysis of lymph node metastases. An alternative may be to use One Step Nucleic Acid Amplification, a novel molecular-based diagnostic to detect lymph node metastases, which takes around 30 minutes to obtain a final result. Its first results in NSCLC patients are promising (37,38). The concept of performing both procedures in the same setting is promising and should be subject of future research.

Conclusions

We evaluated the value of surgical mediastinal staging using VAMLA versus VAM in a NSCLC population to detect N2 disease. Invasive staging using VAMLA should be the

preferred technique given its superior sensitivity and NPV when compared to VAM, depicted by a 64% decrease in the risk of unforeseen pN2 following anatomical resection in patients undergoing VAMLA. However, VAMLA was also associated with a 75% increase in the risk of complications including a 66% increase in the risk of recurrent laryngeal nerve palsies. Though, the majority were of temporary nature. Future studies should aim to corroborate this evidence by adequately powered randomized controlled trials.

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