Mediastinal staging by videomediastinoscopy in clinical N1 non-small cell lung cancer: a prospective multicentre study

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Videomediastinoscopy reaches a sensitivity of 73% detecting N2 disease in cN1 NSCLC patients; N2 prevalence is 26% http://ow.ly/VrzL30gIOWm

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ABSTRACT A quarter of patients with clinical N1 (cN1) non-small cell lung cancer (NSCLC) based on positron emission tomography–computed tomography (PET-CT) imaging have occult mediastinal nodal involvement (N2 disease). In a prospective study, endosonography alone had an unsatisfactory sensitivity (38%) in detecting N2 disease. The current prospective multicentre trial investigated the sensitivity of preoperative mediastinal staging by video-assisted mediastinoscopy (VAM) or VAM-lymphadenectomy (VAMLA).

Consecutive patients with operable and resectable (suspected) NSCLC and cN1 after PET-CT imaging underwent VAM(LA). The primary study outcome was sensitivity to detect N2 disease. Secondary endpoints were the prevalence of N2 disease, negative predictive value (NPV) and accuracy of VAM(LA).

Out of 105 patients with cN1 on imaging, 26% eventually developed N2 disease. Invasive mediastinal staging with VAM(LA) had a sensitivity of 73% to detect N2 disease. The NPV was 92% and accuracy 93%. Median number of assessed lymph node stations during VAM(LA) was 4 (IQR 3–5), and in 96%, at least three stations were assessed.

VAM(LA) has a satisfactory sensitivity of 73% to detect mediastinal nodal disease in cN1 lung cancer, and could be the technique of choice for pre-resection mediastinal lymph node assessment in this patient group with a one in four chance of occult-positive mediastinal nodes after negative PET-CT.

Introduction

In patients with suspected non-small cell lung cancer (NSCLC) and enlarged or 18F-fluorodeoxyglucose (FDG)-avid hilar or intrapulmonary lymph nodes (clinical N1 disease, cN1), the risk of unforeseen positive mediastinal nodes (N2 disease) at resection is estimated at between 20% and 30% [1–5].

Guidelines recommend invasive preoperative mediastinal staging in these patients with cN1, *e.g.* videomediastinoscopy (VAM) or endosonography [6, 7].

In a previous prospective multicentre study, we demonstrated that the sensitivity to detect mediastinal positive nodes in cN1 lung cancer was only 38% with endosonography alone. This was increased to 73% by adding a confirmation mediastinoscopy if endosonography was negative [1]. This double approach might not be cost-effective in the context of an occult N2 prevalence of less than 30% and sensitivity of endosonography of 38% to detect N2 disease.

In the absence of prospective multicentre data for VAM, we evaluated VAM as a proposed strategy in the European Society of Thoracic Surgeon (ESTS) guidelines for patients with cN1 [7]. The objective of this multicentre prospective study was to assess the sensitivity, negative predictive value (NPV) and accuracy of VAM in a well-defined group of patients with cN1.

Patients and methods

Patients

Patients were eligible if all of the following applied: 18 years or older; able to give informed consent; had medically operable, surgically resectable (suspected) NSCLC and clinical N1 disease based on integrated FDG-positron emission tomography-computed tomography (FDG-PET-CT). The following definition of cN1 was used: enlarged lymph nodes (defined as $\geqslant$10 mm on the largest short axis on CT) or FDG-PET-positive lymph node in an N1 position, in accordance with the International Association for the Study of Lung Cancer lymph node map (*i.e.* lymph node stations 10–14) [8]. Lymph nodes were considered positive on FDG-PET if FDG uptake was higher than background uptake in the mediastinal blood pool. Tumours with clinical T categories T1, T2 and selected T3 (*i.e.* intraparenchymal tumour >7 cm, T3 invading the chest wall, or T3 based on additional nodule in the lobe of the primary tumour) were allowed (TNM Classification of Malignant Tumors, seventh edition). Patients with previous therapy for lung cancer; presence of unresectable disease, cT4 or a central tumour staged as cT3 (*i.e.* invasion of mediastinal pleura, invasion of phrenic nerve or parietal pericardium, tumour in the main bronchus less than 2 cm from the main carina), enlarged or FDG-positive mediastinal nodes or distant metastases (cM1); or previous endobronchial ultrasound assessment of mediastinal nodes were excluded from the study.

Cervical VAM

VAM was performed in a dedicated thoracic operating room by experienced thoracic surgeons, in accordance with institutional practice. A transverse cervical incision was made above the jugular notch, and the pretracheal muscles were separated in the midline to expose the anterior surface of the trachea. The pretracheal fascia was incised and a plane under this fascia was made. Palpation was used so as not to miss any proximal pretracheal nodes. Further dissection was performed under a video-assisted mediastinoscope. In accordance with ESTS guidelines, all accessible mediastinal nodes were to be sampled, with the minimal stations being 4L-4R-7. VAM-lymphadenectomy (VAMLA) was allowed, depending on surgeon's discretion. In a standard VAM, lymph nodes at the different stations are assessed by sampling and not necessarily removed completely [9], whereas during VAMLA, typically the subcarinal nodes and right paratracheal nodes are removed completely with the surrounding fat, while the left paratracheal nodes are removed separately, respecting the left recurrent nerve [10]. Video-assisted thoracic surgery (VATS) or parasternal mediastinoscopy were not considered part of the preoperative mediastinal staging. The case report form included a lymph node map querying which nodal stations were not sampled, partially sampled or completely resected.

Surgical resection

If mediastinoscopy was negative, the patient underwent primary surgery with resection and surgical verification by systematic nodal dissection [11]. If frozen sections taken during VAM(LA) were negative,

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resection during the same anaesthesia period was allowed. Resection could be performed by VATS or thoracotomy. The ESTS guidelines on intraoperative systematic nodal dissection were followed [11]. The case report form questioned which stations were assessed during surgery, how many nodes were removed and whether the station was completely resected.

Study design

This was a non-randomised prospective multicentre trial on the sensitivity of VAM(LA) (index test) for mediastinal staging of consecutive patients with operable and resectable cT1–3N1M0 (suspected) NSCLC based on integrated FDG-PET/CT. Surgical resection with systematic nodal dissection was the reference standard. Institutional review board approval was obtained. The coordinating centre was the University Hospital of Leuven. The case report form incorporated cross-checking of data, *e.g.* by comparison of cTNM after imaging, cTNM after VAM, final pTNM, questions about whether the results of VAM(LA) and/or resection changed the TNM stage, and the results at the individual nodal station level. The procedures were performed and data obtained and anonymized in accordance with the International Conference on Harmonization Guidelines of Good Clinical Practice. The study was registered at ClinicalTrials.gov with identifier number NCT02222194 (ASTER 3).

Endpoints

The primary endpoint was sensitivity in detecting mediastinal nodal involvement (N2 disease) by VAM(LA). Sensitivity was defined as the proportion of patients with positive mediastinal staging by VAM(LA) out of all patients with mediastinal nodal disease. Surgical resection with lymphadenectomy (by thoracotomy or VATS) was considered the reference standard for patients without mediastinal nodal

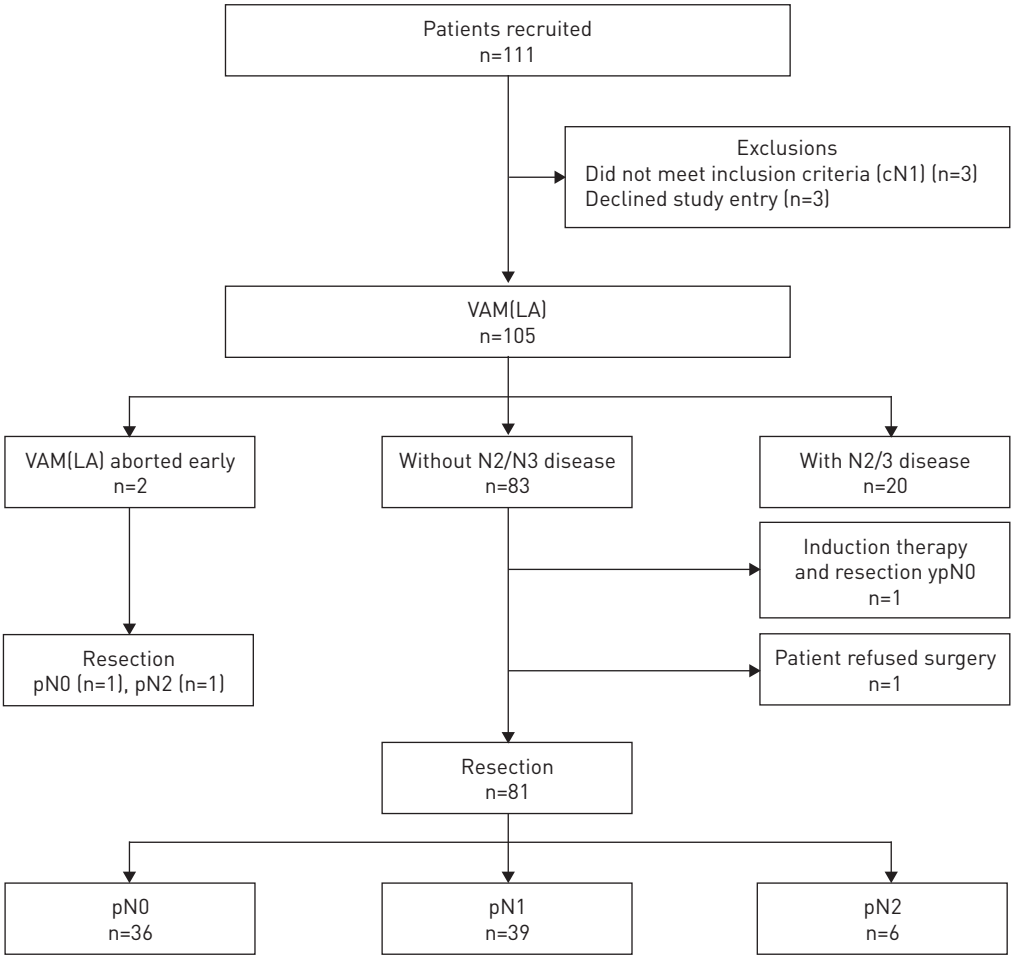

FIGURE 1 STARD flow chart of patients undergoing mediastinal nodal staging for clinical N1 (suspected) non-small cell lung cancer. Two VAM(LA) were aborted early: no lymph nodes were assessed. VAM: video-assisted mediastinoscopy; VAM(LA): video-assisted mediastinoscopic lymphadenectomy; STARD: Standards for Reporting Diagnostic accuracy studies [23].

TABLE 1 Clinical patient characteristics

Patients n	105
Mean±SD age years	66±8.9
Male sex	87 (83%)
Right side	68 (65%)
Tumour location	
Right upper lobe	40 (38%)
Right middle lobe	6 (6%)
Right lower lobe	22 (21%)
Left upper lobe	20 (19%)
Left lower lobe	17 (16%)
Clinical T category	
1a	13 (12%)
1b	21 (20%)
2a	24 (23%)
2b	19 (18%)
3	28 (27%)
Clinical N1 category	
By CT (short axis ⩾1 cm)	91 (87%)
By PET	96 (91%)
By CT and PET	82 (78%)
By CT or PET	105 (100%)
Final pathology	
Adenocarcinoma	51 (49%)
Squamous cell carcinoma	38 (36%)
Adenosquamous carcinoma	1 (1%)
Large cell carcinoma	3 (3%)
Pleiomorphic carcinoma	2 (2%)
NSCLC-NOS	2 (2%)
LCNEC	1 (1%)
SCLC	1 (1%)
Lymphoma	1 (1%)
No malignancy	4 (4%)
Unknown[#]	1 (1%)

CT: computed tomography; PET: positron emission tomography; NSCLC-NOS: non-small cell lung cancer, not otherwise specified; LCNEC: large cell neuroendocrine carcinoma; SCLC: small cell lung cancer. [#]: patient refused surgery after negative mediastinoscopy.

disease after VAM(LA). Secondary endpoints were NPV, accuracy, negative post-test probability and assessment of the prevalence of N2/3 disease.

Statistics

Setting the total sample size at 250 patients, 50 patients with N2 were expected, based on a prevalence of 20%. Assuming a sensitivity of 70%, we calculated a greater than 90% probability that the half-width of the confidence interval (CI) for the sensitivity would be at most 13%. The calculation of the two-sided (Wilson-score) CI was based on the binomial distribution.

Sensitivity, prevalence, NPV and negative post-test probability were calculated on an intent-to-treat basis for all included patients. For patients with missing reference standard (*i.e.* no primary surgery after negative VAM), a multiple imputation analysis was used to obtain estimates for sensitivity, prevalence, NPV and accuracy for all subjects. A result for positive mediastinal staging was imputed assuming a maximum probability for mediastinal disease. This was calculated as follows: ((n false negatives after successful VAM)+(n missing reference standard))/(n negative result after successful VAM). Results from 1000 imputed datasets were combined using Rubin's rule. All analyses were performed using SAS software, version 9.4 of the SAS System for Windows. p-values <0.05 were considered significant.

Results

Between June 2014 and March 2017, 105 patients with operable and resectable (suspected) clinical N1 NSCLC were included (figure 1). The accrual rate was lower than initially expected, and the study was closed early in April 2017. The clinical patient characteristics are shown in table 1.

Results of VAM

Positive mediastinal nodes were identified by VAM(LA) in 20 patients. This was single-level N2 disease in 13, multi-level N2 disease in four and N3 disease in three patients. The mean number of biopsied lymph node stations was 3.9 (standard deviation 1.2), with median being 4 (interquartile range 3–5). Distribution of the total number of lymph node stations biopsied per patient and the frequency of biopsy of different lymph node stations are shown in tables 2 and 3. In 31% (n=33) of cases the procedure was labelled as VAMLA. In two patients, the procedure was aborted before any lymph node was assessed; in one, the mediastinoscope could not be introduced due to severe kyphosis, while in the other, early cessation was due to tracheomalacia and ventilatory problems during the procedure. In one patient, only one node was assessed as N3 disease was found. An adverse event related to VAM was reported in four patients (4%): one case of bleeding of <200 mL, one case of uncomplicated wound infection and two cases of transient recurrent nerve paralysis.

Resection and lymphadenectomy

In total, 85 patients were referred to surgery. One refused and one underwent neo-adjuvant treatment first (figure 1), thus 83 patients underwent primary surgery (68 lobectomies, seven bilobectomies and seven pneumonectomies). Surgery was performed the same day as VAM(LA) in 46% (n=48) or during a second stage in 37% (n=39); in the latter group the median delay between surgery and VAM(LA) was 14 days (IQR 7–27). In seven patients, positive mediastinal nodes were found at resection (figure 1). One of these was a patient for whom the mediastinoscopy was aborted prematurely. The missed mediastinal metastases were single-level N2 disease in five patients, and multi-level N2 disease in two patients. Clinical characteristics can be found in table 4, and details on completeness of the lymphadenectomy during resection in table 5. Analysis of the number of lymph nodes removed per station proved to be impractical due to fragmentation; up to 16 lymph nodes (*i.e.* fragments) in one station were reported. A mean of four lymph node stations was resected. The ESTS guideline recommending systematic nodal dissection with excision of a minimum of three stations (including the subcarinal nodes), was attained in 92% of the right-sided and 97% of the left-sided tumours.

Multiple imputation

For two patients, the reference standard after negative VAM(LA), *i.e.* primary surgery with assessment of mediastinal nodes, was missing. Of 83 patients with a negative test result after successful (not aborted) VAM(LA), six had pN2/N3 at resection. If both patients with missing pN2/N3 information (no primary resection) were positive, the probability of pN2/N3 after successful VAM(LA) would be equal to 0.0964 (n=(6+2)/83). This number was used in the multiple imputation as maximum probability for mediastinal disease in the two patients with missing reference standard.

Study endpoints for VAM(LA)

According to an intent-to-treat analysis with multiple imputation, the prevalence of mediastinal nodal metastases was 0.26 (95% CI: 0.18–0.35) overall, with sensitivity being 0.73 (95% CI: 0.54–0.86), accuracy 0.93 (95% CI: 0.86–0.97), NPV 0.92 (95% CI: 0.83–0.97) and negative post-test probability 0.08

TABLE 2 Distribution of total number of lymph node stations biopsied per patient by videomediastinoscopy

Total number of lymph node stations biopsied	Patients
0[#]	2 (2%)
1[¶]	1 (1%)
2	1 (1%)
3	35 (33%)
4	39 (37%)
5	18 (17%)
6	8 (8%)
7	1 (1%)
Mean±SD	3.9±1.2
Median (interquartile range)	4 (3–5)
At least three stations	101 (96%)

Total number of patients=105. [#]: in two patients, videomediastinoscopy was aborted early before lymph nodes were assessed; [¶]: in one patient the procedure was aborted after the finding of a contralateral positive node (N3).

TABLE 3 Frequency of biopsy of different lymph node stations by videomediastinoscopy

Lymph node station	Patients
1	1 (1%)
2R	58 (55%)
2L	17 (16%)
3	1 (1%)
4R	103 (98%)
4L	96 (91%)
5	2 (2%)
6	0 (0%)
7	100 (95%)
8	3 (3%)
9	0 (0%)
10	29 (28%)
At least stations 4L-4R-7	95 (90%)

Total number of patients=105.

(95% CI: 0.03–0.17) (table 6). Therefore, a patient with a negative VAM(LA) had a probability of 8% of having positive mediastinal nodes at resection with lymphadenectomy.

Discussion

This is the first prospective study evaluating performance of surgical mediastinal staging in patients with cN1 (suspected) NSCLC. Our main findings were that a quarter of patients with cN1 lung cancer eventually had N2 disease and that sensitivity of VAM(LA) to detect positive mediastinal nodes in these patients was 73%.

Current guidelines recommend invasive pre-resection staging in patients with cN1 disease and negative mediastinum on imaging [7, 12, 13]. However, the choice between VAM or endosonography as first choice is left open [7]. These recommendations are based on subgroup analysis of trials that included patients with clinical stage I-III lung cancer [14]. The vast majority of patients had clinical N2 disease, with only a minority of the patients having cN1 disease with a normal mediastinum on imaging [15–17]. In a previous study, we prospectively measured the performance of endosonography in a selected patient group with cN1 (suspected) NSCLC. We reported a prevalence of 24% N2 disease and sensitivity of 38% for endosonography alone in detecting mediastinal disease. This was raised to 73% if VAM was added (table 6) [1]. The post-test probability that a patient had N2 disease after a negative endosonography was 19%. In the current study, we report a prevalence of 26% N2 disease, sensitivity of 73% for mediastinoscopy and post-test probability of 8%. One could therefore argue for omitting endosonography to evaluate mediastinal nodes and instead selecting a surgical pre-resection staging by VAM(LA) in this patient group.

Few reports in the literature have evaluated the final pathological stage distribution of patients with resectable and operable NSCLC with clinical stage cN1. Hishida *et al.* and Watanabe *et al.* reported that

TABLE 4 Characteristics of patients with false-negative results on videomediastinoscopy.

Location	cT	VAM/ VAM(LA)	2R	2L	4R	4L	5	6	7	Time min	Aborted	Final pathology	Positive nodes
RLL	1b	Aborted	Not	Not	**Not**	Not	Not	Not	**Not**	15	Yes	Adenocarcinoma	4R, 7
LLL	2b	VAM	Part	Not	Part	Part	Not	**Not**	Part	30	No	SCLC	6
RLL	3	VAM	Part	Part	Part	Part	Not	Not	**Part**	90	No	Adenocarcinoma	7
RLL	2a	VAM	Not	Not	**Part**	Part	Not	Not	**Part**	45	No	Adenocarcinoma	4R, 7
LUL	1b	VAM	Not	Not	Part	Part	Not	**Not**	Part	45	No	Adenocarcinoma	6
LLL	2b	VAM	Not	Not	Part	Part	Not	Not	**Part**	35	No	Squamous cell carcinoma	7
LLL	2a	VAM	Not	Not	Part	Part	Not	Not	**Part**	40	No	Adenocarcinoma	7

False-negative lymph node stations are shown in bold. VAM: video-assisted mediastinoscopy; VAM(LA): video-assisted mediastinoscopy–lymphadenectomy; RLL: right lower lobe; LLL: left lower lobe; LUL: left upper lobe; Part: partially resected; Not: not biopsied or resected; SCLC: small cell lung cancer.

TABLE 5 Findings during primary surgical resection after negative mediastinoscopy (n=83): number and type of lymph node stations resected during resection of right-sided and left-sided tumours

	Right tumour (n=50)	Left tumour (n=33)
Number of lymph node stations resected		
Mean±SD	3.8±1.1	4.8±1.3
Median (interquartile range)	4 (3–5)	5 (4–6)
Frequency of resection per lymph node station		
2R/2L	36 (72%)	4 (12%)
3	7 (14%)	0
4R/4L	48 (96%)	27 (82%)
5		28 (85%)
6		25 (76%)
7	48 (96%)	32 (97%)
8	23 (46%)	19 (58%)
9	30 (60%)	25 (76%)
3 stations including station 7	46 (92%)	46 (92%)

30–37% of patients with cN1 based on CT alone had positive mediastinal nodes after mediastinoscopy [2, 3]. Kim *et al.* reported that 19% of 99 patients with cN1 after imaging, including FDG-PET, were found to have pathological N2 disease at pulmonary resection with mediastinal lymph node dissection [5]. In this study, we found a prevalence of 26%, with single-level N2 disease in two-thirds, multi-level N2 disease in 22% and N3 disease in 11%.

Our study has several limitations. Recruitment stopped at 105 of 250 patients owing to a slower accrual rate than originally anticipated. Possibly, potential patients were not included during the study period due to increasing referral for endosonography for staging of mediastinal nodes, which was an exclusion criterion. The lower number of patients increased the width of the 95% confidence intervals for the diagnostic indices. Nevertheless, this is the largest prospective study on mediastinal staging in patients with cN1 disease with solid analyses and results. Second, as the study was performed by the institutions willing to participate in a prospective study on surgical staging, results may be different from the performance of the surgical pre-resection staging in daily practice [18]. Third, we did not report the number of resected lymph nodes, as fragmentation of the nodes and variation between patients diminished its value [19–21]. Standard systematic nodal dissection was performed in accordance with ESTS guidelines. Fourth, in 31% of patients, the mediastinoscopy was VAMLA. In theory VAM and VAMLA are different procedures, but in reality, procedures can often be labelled as "in-between" as some stations are removed completely and others sampled within the same operation. The reliability of VAM hugely depends on its thoroughness [13]. In four patients, the false-negative station was partially sampled during VAM, and would have been positive if the station had been removed completely. VAMLA produced excellent results in this study, with no reported complications and no false-negative results (table 4). Call *et al.* recently published a sensitivity of 96% and NPV of 99% after VAMLA in patients with cN0-1 NSCLC [22]. However, VAMLA is only performed in certain centres. Future studies should address whether this technique can be adopted in more centres with similar results.

In conclusion, we prospectively analysed the performance of surgical pre-resection mediastinal staging with VAM(LA) in a cohort of patients with cN1 (suspected) NSCLC. We confirmed that a quarter of patients eventually had N2 disease and we found a sensitivity of 73% after VAM(LA). As endosonography

TABLE 6 Prevalence and diagnostic performance based on multiple imputation analysis of endosonography alone, endosonography if negative followed by cervical mediastinoscopy and mediastinoscopy alone

		Subjects n	Prevalence of mediastinal disease	Sensitivity (95 % CI)	Negative predictive value (95 % CI)	Negative post-test probability (95 % CI)
Dooms *et al.* [1]	Endosonography alone	100	24%	0.38 (0.18–0.57)	0.81 (0.71–0.91)	0.19 (0.13–0.27)
	Endosonograpy, followed by mediastinoscopy if negative			0.73 (0.55–0.91)	0.91 (0.83–0.98)	0.09 (0.04–0.17)
Current study	Mediastinoscopy	105	26%	0.73 (0.54–0.86)	0.92 (0.83–0.97)	0.08 (0.03–0.17)

alone had an unsatisfactory sensitivity in detecting mediastinal disease in a previous prospective study, we suggest VAM(LA) as the preferred technique for pre-resection mediastinal nodal staging in patients with cN1 NSCLC.

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