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Video-assisted thoracic surgery systematic mediastinal nodal dissection and stage migration: impact on clinical pathway☆,☆☆

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Abstract

Objectives: The aim of this study is to investigate the role of routine systematic mediastinal nodal dissection (SND) performed during video-assisted thoracic surgery (VATS) major pulmonary resections (VMPRs) as a staging strategy for non-small-cell lung cancer (NSCLC), compared with preoperative staging by conventional positron emission tomography (PET) and computed tomography (CT) imaging. **Methods:** All patients suspected of having early lung cancer (T1—2, N0—1 and M0) were staged preoperatively by CT/PET. During VMPR, all lymph nodes on the right side at stations 2—4, 7, 8, 9, 10 and 11 and on the left stations 4—6, 7, 8, 9, 10, 11 and 3 when indicated were dissected *en bloc*. Histology was provided on the paraffin-embedded nodes, and patients staged accordingly. Preoperative and postoperative stagings were compared. Stage migration and impact on clinical pathway were noted. Stage IIa and higher were referred for adjuvant chemotherapy. **Results:** Between April 2007 and January 2011, 106 consecutive patients with suspected primary NSCLC proceeded to VMPR + SND. Histology confirmed NSCLC in 96 patients. Forty-five were men and 51 women. Median age was 68.6 (range 42.8—84.7) years. As many as 91 (94.8%) patients underwent lobectomy, three (3.1%) bilobectomy and two (2.1%) pneumonectomy. PET accurately correlated with SND histological diagnosis in 42 (43.8%) patients. The unexpected N2 disease in cN0—1 was 9/86 (10.5%). SND resulted in 25 stage migrations, upstaged 16 (16.6%) and down-staged nine (9.4%) patients. All upstagings were adenocarcinoma. Four (4.2%) PET-negative patients had multi-station N2 disease. SND resulted in changing the clinical pathway for 19 (20%) patients. Fourteen (14.6%) patients upstaged to qualify for chemotherapy, and 5/9 (5.2%) down-staged patients were saved the chemotherapy. There was no morbidity or mortality attributable to this added procedure. **Conclusions:** SND during VMPR is safe and should be routinely performed even when nodal metastases is considered unlikely. VATS-SND is more accurate than PET in staging the mediastinum for NSCLC. PET sensitivity is significantly reduced in adenocarcinoma and might result in stage migration. Adjuvant multidisciplinary treatment should be based on SND staging.

Keywords: Video-assisted thoracic surgery; Non-small-cell lung cancer; Systematic nodal dissection; Positron emission tomography; Stage migration

1. Introduction

Video-assisted thoracic surgery (VATS) lobectomy and major pulmonary resection is growing in popularity. Positron emission tomography (PET) is the most convenient non-invasive staging tool for a fast-track keyhole surgery. However, video-assisted thoracic surgery major pulmonary resection (VMPR) is designed for early lung cancer, and PET was expected to identify nodal disease in computed tomography (CT)-negative and normal-looking mediastinum. Recent publications have shown a significant statistical gain in 5-year survival, if stage IIa and higher were treated by adjuvant chemotherapy [1,2]. It is therefore mandatory to get the staging right in early lung cancer; otherwise, patients would be denied a significant chance of cure. Oncological randomised controlled trials rely on final histological staging obtained at surgery, and therefore surgeons have a moral duty to put in maximal effort to obtain correct staging. Stage migration could be a source of misleading statistics for survival in lung cancer.

2. Materials and methods

In this series, VMPR was considered for early lung cancer T1—2, N0—1 and M0. The decision to include these patients in the VATS series was based on CT/PET studies. Preoperative

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☆☆ Updated results presented at the Society for Cardiothoracic Surgeons of Great Britain and Ireland, Liverpool 7—9 March 2010.

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investigations included pulmonary function tests (forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC) and transfer factor of the lung for carbon monoxide (TLCO)), CT chest and abdomen and image fusion of CT on PET scan using ^{18}F-fluorodeoxyglucose (FDG) as a substrate from orbits of skull to mid-thighs. Either CT or magnetic resonance imaging (MRI) of the brain was used to screen for metastases. Mediastinoscopy was performed selectively on single-station N2 disease suggested by CT nodal enlargement >1.5 cm at its shortest diameter or low-to-moderate FDG avidity on the PET/CT scan. Preoperative intense FDG uptake by N2 nodes precluded surgery, as these patients were treated by chemo-radiotherapy (Fig. 1). However, cases of N1 were included as they were deemed removable during the VATS procedure.

All cases were performed under general anaesthesia, using single-lung ventilation. Two ports (2 × 1 cm) were fashioned, as was a utility port 3—4-cm long at the midaxillary line over the 5th or 6th intercostal space. Histological confirmation of the diagnosis, if not already available, was obtained by frozen section. Resection was performed by individual anatomic dissection of the hilar structures, without rib spreading. Systematic mediastinal nodal dissection (SND) was performed according to published European and international standards [3—5]. We harvest nodes *en bloc*, stations 2—4, 7, 8, 9, 10 and 11 on the right, preserving the azygos vein, and 4, 5, 6, 7, 8, 9, 10 and 11 on the left side. We do not harvest #1 bilaterally, or #2 on the left. However, we harvest #3, when indicated, on the left chest without dividing the ligamentum arteriosum by retracting the main pulmonary artery up and pushing the carina down (Fig. 2). Subcarinal nodes #7 were mandatory for the definition of SND, and if these were not harvested the procedure would have been classified as 'nodal sampling' and not SND [3]. Current evidence suggests that complete mediastinal lymph node dissection is associated with improved survival compared with node sampling in patients with stage I—IIIa non-small-cell lung cancer (NSCLC) undergoing resection [6]. Nodal dissection is performed before, during or after the planned lung resection. SND was also completed if the case was converted to thoracotomy. All lung specimens were extracted within a polythene bag, but not the nodes. Final histological diagnosis was obtained on the paraffin-embedded block using haematoxylin—eosin and a battery of immunohistochemistry stains. No intra-operative

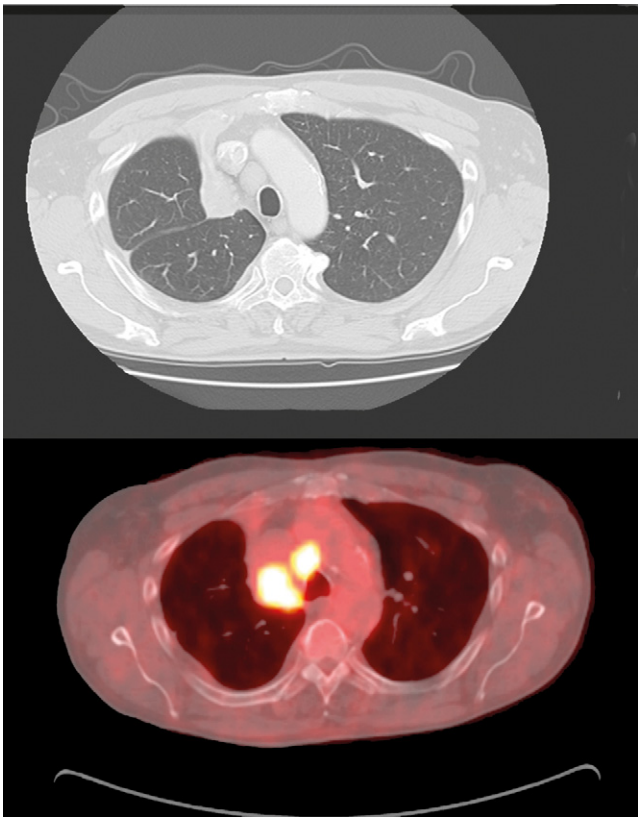

Fig. 1. CT/PET of a patient with right upper lobe lesion. Bronchoscopy obtained Squamous cancerous cells. The high intake of ^{18}FDG seen in pre-carinal node #3 was sufficient evidence not to proceed with mediastinoscopy. The patient was treated by chemo-radiotherapy.

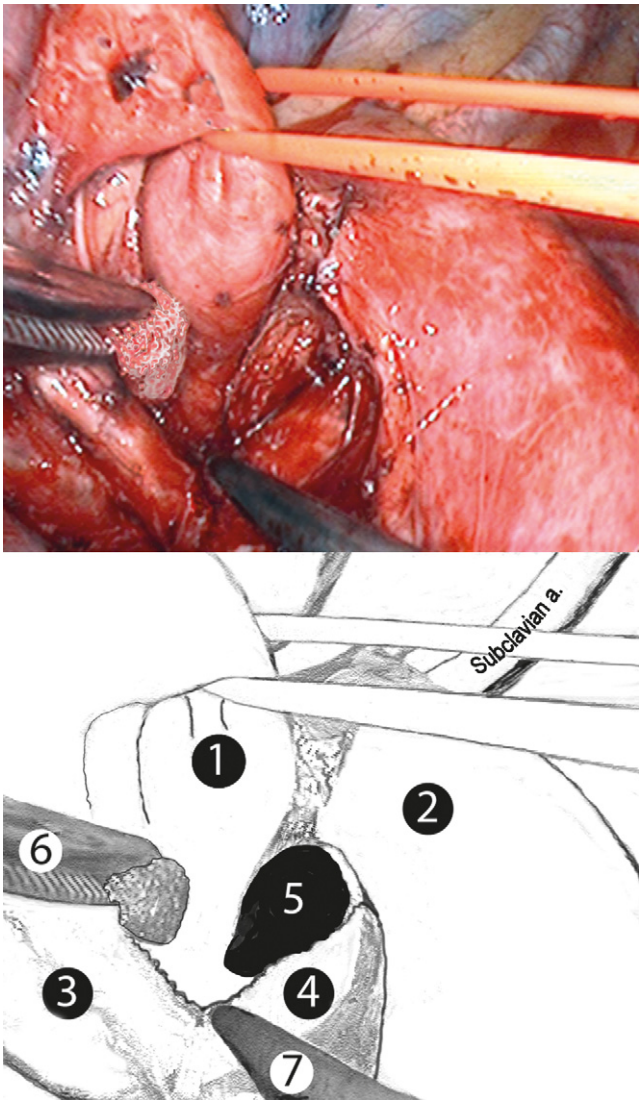

Fig. 2. Access to pretracheal lymph nodes in station 3 during a left VATS procedure.
1: Left main pulmonary artery; 2: Arch of aorta; 3: Left main bronchus; 4: Main stem trachea; 5: Precarinal nodes #3; 6: Peanut on a Robert as a retracting instrument, pushing the pulmonary artery up; 7: Sucker as a retracting instrument, pushing the carina down.

assessment by frozen section of the nodes was practiced. The tumour, node, metastasis (TNM) classification was determined, according to the Union Internationale Contre le Cancer (UICC) staging system (TNM6) [7]. This series precedes the new TNM7 classification system introduced to the UK in January 2010, which leaves the N descriptor unchanged [8]. Stage IIa and higher NSCLC patients were referred for adjuvant chemotherapy, in accordance with recent publications [1,2]. Follow-up of patients was scheduled at 4 weeks from surgery, at 3 months and yearly thereafter.

3. Results

At our institution, 200 patients proceeded to VMPR between April 2005 and January 2011 (Fig. 3). As experience with this comprehensive nodal dissection was lacking in the earlier phase of our VATS programme, only the last consecutive 106 cases underwent SND during VMPR for presumed lung cancer. Histology showed 98 patients to have primary lung cancer, four metastatic lung cancer, three benign lesions and one MALToma (Extranodal Marginal zone Non-Hodgkins B-cell lymphoma arising in mucosa-associated lymphoid tissue). Analysis of the 98 primary lung-cancer patients revealed 96 NSCLC and one patient with small-cell lung cancer. An additional patient proved to have malignant solitary fibrous tumour.

Of the NSCLC group, 45 were men and 51 women; the median age was 68.6 (range 42.8—84.7) years. As many as 91 (94.8%) patients underwent lobectomy, three (3.1%) bilobectomy and two (2.1%) pneumonectomy. SND was 65 (67%) on the right and 31 (33%) on the left chest. Four (4.2%) were not suitable for VATS on initial videoscopic inspection and had early thoracotomy, 79 (82.3%) proceeded to completion of planned VATS resection and 13 (13.5%) were converted to thoracotomy. The median operative time for completed VMPR-SND was 3 h 30 min (range 2 h 05 min—06 h 55 min). On average, right-sided SND added 30 min, whereas left-sided SND added 45—60 min to the planned VATS resection.

3.1. Length of hospital stay

The median length of hospital stay (LOS) in the NSCLC VMPR-SND completed group (n = 79) was 4 days (range 1—25 days, mode 3 days). Thirty-four (35.4%) patients were discharged on or before the third postoperative day. There was no delay in discharge from hospital attributable to SND. Eight (8.3%) patients were re-admitted to their local regional hospitals for various reasons within 2 weeks from discharge. All eight re-admissions had prolonged air leak $\geq$7 days, and two patients required surgical rib resection to drain an empyema.

3.2. Blood loss and transfusion

The median blood loss in the operating theatre was 100 ml (range 20—1000 ml) in the 79 patients, who completed the VMPR-SND procedure. The median postoperative drainage via the intercostal drain for the same group was 450 ml (range 100—1320 ml). Median dwell time of chest tube was 2 days (range 1—17 days, mode 1 day). Four patients (4.2%) required transfusion with blood, two units each.

3.3. Preoperative histological confirmation

Bronchoscopy or CT-guided needle biopsy obtained preoperative histological diagnosis in 27/96 (28.1%) patients. The low preoperative diagnostic attempt reflects reluctance to provide CT-guided radiological biopsy. It is argued that a negative biopsy would not change the clinical pathway of treatment. Mediastinoscopy was performed in six patients suspected of having N2/N3 disease by PET/CT. Sampled nodes (#2—4, #3, #7 and #10) were negative in all cases, down-staging disease to permit proceeding to VMPR-SND. In four patients, SND confirmed the negative state of nodes and revealed involvement of unexpected N1 nodes in two patients. A patient undergoing left-VATS-sleeve upper lobectomy was staged by a combined mediastinoscopy and VATS-SND as a separate initial procedure, and nodal clearance allowed proceeding to VMPR-SND.

Frozen section was used 29 times, proving useful in all cases. It proved malignancy in 25/29 cases, and negated

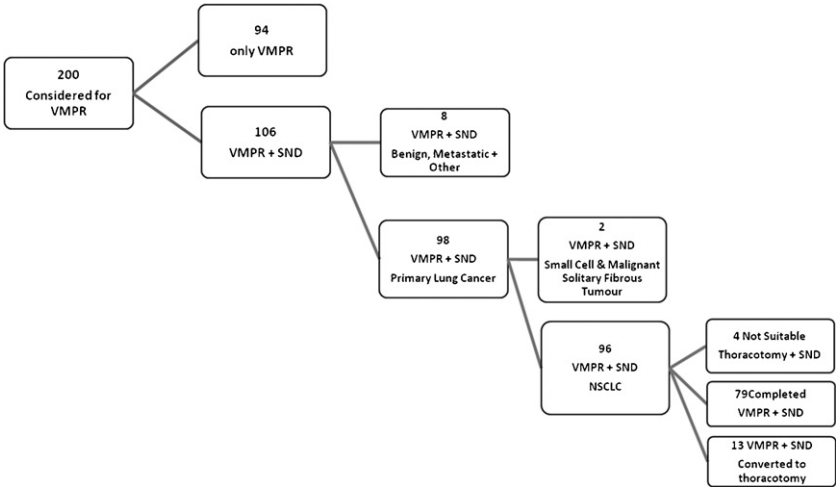

Fig. 3. Schema of results of the Southampton VATS Lobectomy Programme 2005—2011.

extrapulmonary extension of tumour in the other four cases.

3.4. Histology

Of the primary lung cancer group that underwent VATS-SND, final histology documented 96 NSCLC. Histological subtypes of NSCLC were 68 (70.8%) adenocarcinoma, 19 (19.8%) squamous cell carcinoma, four (4.2%) adenosquamous carcinoma, four (4.2%) bronchioloalveolar carcinoma and one (1%) large cell carcinoma.

The median number of nodes harvested by SND on the right chest was 12 (range 5—33), and a median number of 10 nodes (range 7—21) on the left chest. As many as 95 of 96 (98.9%) had ≥6 nodes harvested from three stations and 70/96 (72.9%) had ≥10 nodes harvested from three stations. The median number of nodes invaded by malignant cells was 1.5 nodes (range 1—8) per patient.

3.5. Stage migration

Stage migration is extrapolated from Table 1, which shows the distribution of clinical and pathological staging of 96 patients undergoing VMPR-SND for NSCLC. PET was concordant in 42 (43.8%) cases and discordant in 54 (56.2%) cases. Of the latter group, nodal status upstaged 16 (16.6%) and down-staged nine (9.4%), resulting in 25 (26%) stage migrations. Table 2 shows the nodal and lobar distribution of these patients. All upstagings were adenocarcinoma, and six of nine (66.6%) down-stagings were squamous cell carcinoma. In addition to the 25 patients, one patient with solitary brain metastasis, removed by neurosurgeons (T3N0M1 right-upper-lobe lesion), had VATS upper lobectomy and SND. Histology revealed unexpected N2 nodes (#2—4). The staging did not change for obvious reasons, but the TNM was reclassified as T4N2M1. Patient had disease progression 4 weeks later and new brain secondaries were discovered. She died 6 months later of disseminated disease.

PET mistook the T status in 9/96 (9.4%) satellite lesions (T4). N1 nodes were missed in 11 (11.5%) patients (#10 and 11), whereas N2 nodes were missed in nine (9.4%) patients (five single station and four multistation). There were 86 patients qualifying as cN0—1, and the unexpected N2 in this group was 9/86 (10.5%). There were six (6.3%) skip lesions, where SND revealed positive N2 nodes in the absence of positive N1 nodes. In five (5.2%) patients with cN0 by PET, a combination of N1 + N2 nodes was revealed, four of whom had positive #7. PET failed to identify knee metastases in one patient due to the fact that the knees were not included in the screening fields. It also failed to identify pleural secondary deposits in one patient (M1) with adenocarcinoma, who had VATS-inspection-only operation.

Table 1. Concordant lung cancer staging between PET and SND in 96 patients with NSCLC.

Clinical stage	PET/CT stage	SND stage	Concordant PET = SND
Ia	38 (39.6%)	26 (27.1%)	19 (73.1%)
Ib	33 (34.4%)	31 (32.3%)	17 (54.8%)
IIa	3 (3.1%)	5 (5.2%)	0 (0%)
IIb	6 (6.2%)	11 (11.5%)	1 (9%)
IIIa	9 (9.4%)	12 (12.5%)	2 (16.6%)
IIIb	5 (5.2%)	8 (8.3%)	2 (25%)
IV	2 (2.1%)	3 (3.1%)	0 (0%)

3.6. Impact on clinical pathway

SND staging resulted in changing the postoperative clinical pathway for 19 (20%) patients. Fourteen (14.6%) patients were upstaged to qualify for chemotherapy, who would have otherwise been denied the chance of cure. Five out of nine down-staged patients were saved the chemotherapy.

3.7. Morbidity and mortality

There was no in-hospital mortality for the 96 patients with NSCLC and one case of <30 days' mortality due to pneumonia and pulmonary embolism. Table 3 shows details of 16 patients, who died during a median follow-up period of 10.9 months (range 0.3—39.7 months). The commonest cause for death was disease progression in 9/16 (56%). However, 38/96 (39.6%) patients had no surgical or non-surgical complications during their short hospital stay.

Intra-operative bleeding occurred in 23 (23.9%) patients. Intra-operative bleeding was defined as bleeding in excess of 500 ml, irrespective of brisk bleeding due to vascular injury or slow bleeding due to release of adhesions. There has not been a single case of re-opening for bleeding, chyle leak or pleural collection requiring drainage in this series. However, there was one case of unexplained delayed recurrent laryngeal nerve palsy. The patient recovered with a normal postoperative voice for 2 weeks, and was seen in clinic 4 weeks later with left vocal cord palsy, without evidence of disease progression. A similar complication was reported by Watanabe et al. [9]. There was one case of port-site seedling in a lady, who previously underwent resection of a sigmoid carcinoma, ending in a permanent stoma. Port-site metastases occurred early after 3 months, and were confirmed histologically to be of lung origin. Incidentally, the lobe was retrieved within a polythene bag, but none of the nodes. However, none of the nine nodes retrieved was involved with malignancy. Simple contact theory cannot explain this port-site metastases and a humoral mechanism is contemplated.

3.8. Learning curve

VATS-SND during VMPR requires patience. Whereas *en bloc* dissection on the right is straightforward, that on the left is more taxing. Subcarinal #7 on the left is the most time-consuming, as the space has to be clearly displayed. We routinely access it from the back of the hilum, starting with SND before resecting the lung. Precarinal #3 nodes are also accessible without the need for cutting the ligamentum arteriosum. Currently, we are perfecting dissection of #2 on the left, as described by Alper Toker[1] during open thoracotomy. Despite exercising care during VATS dissection of mediastinal nodes, it is very difficult sometimes to avoid fragmenting the nodes. We found great variation in the

[1] Alper Toker, Serkan Kaya, Suat Erus, Serhan Tanju. Dissection of superior mediastinum in patients with left sided hilar lung cancer (2009). Available http://www.ctsnet.org/sections/clinicalresources/videos/vg2009_TokerA_-DissectnSuperMediastnm.html [last accessed 16 January 2011].

Table 2. Stage migration and impact on clinical pathway: SND versus PET staging in 96 patients with NSCLC.

Patient number	PET staging	SND staging	Stage migration	Lobe removed	Histology	Clinical pathway
Upstaging						
1	N0	N1 (#10)	Ia to IIa	RUL	Adenocarcinoma	Completed chemotherapy
2	N0	N1 (#11)	Ia to IIa	RLL	Adenocarcinoma	Completed chemotherapy
3	N0	N1 (#10)	Ia to IIa	LUL	Adenocarcinoma	Chemotherapy curtailed
4	N0	N1 (#10 and #11)	Ia to IIa	RUL	Adenocarcinoma	Completed chemotherapy
5	N0	N1 (#11)	Ib to IIb	LLL	Adenocarcinoma	3/4 cycles of chemotherapy
6	N0	N1 (#10)	Ib to IIb	RUL	Adenocarcinoma	Completed chemotherapy
7	N0	N1 (#11)	Ib to IIIa	RL Bilobectomy	Adenocarcinoma	Radiotherapy
8	N0	N1 (#11)	IIb (T3N0) to IIIa (T3N1)	L pneumonectomy	Adenocarcinoma	Died in neutropenic sepsis after chemotherapy
9	N0	N2 (#4) skip lesion	Ib to IIIa	RLL	Adenocarcinoma	Completed chemotherapy
10	N0	N2 (#R2-4 and #9) skip lesion	Ib to IIIa	RLL	Adenocarcinoma	Completed chemotherapy and radiotherapy
11	N0	N2 (#R2-4) skip lesion	Ib to IIIa	RUL	Adenocarcinoma	Completed chemotherapy
12	N0	N1 (#10 and #11) + N2 (#7)	Ib to IIIa	RL Bilobectomy	Adenocarcinoma	Completed chemotherapy
13	N0	N1 (#10 and #11) + N2 (#R2-4)	Ia to IIIa	RUL	Adenocarcinoma	Chemotherapy curtailed
14	N0	N1 (#11) + Multilevel N2 (#R2-4 and #7)	Ib to IIIa	RUL	Adenocarcinoma	Completed chemotherapy
15	N0	N1 (#10 and #11) + Multilevel N2 (#9 and #7)	Ia to IIIa	LLL	Adenocarcinoma	Completed chemotherapy
16	N1	N1 (#10 and #11) + Multilevel N2 (#2-4 and #7)	IIa to IIIa	RUL	Adenocarcinoma	Completed chemotherapy
Downstaging						
1	N1 (#10)	N0	IIb to Ia	RUL	Adenocarcinoma	No adjuvant therapy
2	N1 (#10)	N0	IIb to Ib	RLL	Squamous	No adjuvant therapy
3	N2 (#9)	N0	IIb to Ib	RL Bilobectomy	Squamous	No adjuvant therapy
4	N2 (#R2-4)	N1 #10	IIIa to IIb	RUL	Squamous	Completed chemotherapy
5	N2 (#4 and #7)	N0	IIIa to Ia	RLL	Squamous	No adjuvant therapy
6	N1(#11) and N2 (#5-6)	N1(#11)	IIIa to IIa	LUL	Adenocarcinoma	Chemotherapy curtailed
7	N1(#10) + N2(#4-5)	N0	IIIa to Ib	LUL (Sleeve)	Squamous	No adjuvant therapy
8	N1 (#10) + N2 (#7) + N3 (#3)	N1	IIIb to IIb	LUL	Adenocarcinoma	Completed chemotherapy
9	N2 (#2) and N3 (preaortic #5)	N0	IIIb to Ia	RLL (Bronchoplasty)	Squamous	No adjuvant therapy
Concordant staging but different N stage						
1	T2 N1 M0	T3 N0 M0	Stage IIb	RLL	Squamous	Completed chemotherapy
2	T3 N0 M1	T4 N2 M1	Stage IV	RUL	Adenocarcinoma	Radiotherapy (not fit for chemo)

RUL = right upper lobe, RLL = right lower lobe, LUL = left upper lobe.

number and consistency of nodal groups, especially #8 and #9. Nodes could be completely absent, discrete or lumped in a fibrofatty tissue amenable to block dissection. Early in our experience of SND, we had the chance of revisiting one area of block dissection. A patient with right upper lobe lesion had, in addition, high FDG uptake in R4 nodes. There was no histological diagnosis; therefore, he underwent wedge resection of the primary lesion and block dissection of #2–4 as a first stage. All harvested nodes were free from metastases. Lung isolation was difficult on the first-stage operation; therefore, he was deemed not suitable for VATS on the second-stage lobectomy. He proceeded to open thoracotomy, lobectomy and SND when two more nodes were found at station #R4 and both were invaded by metastases, as predicted by PET. Clearly, this was a false-negative SND. Clearance of nodal tissue has to be thorough and complete, and the VATS-SND should not be any different from open SND, as described by Watanabe [10].

Technically, PET was performed from orbits to mid-thighs initially in this series. As a result, bone metastasis (M1) in a knee joint was missed in one patient. This was discovered 2 weeks postoperatively, and was treated by local radiotherapy followed by total knee replacement. The patient is alive and well 3 years later with no recurrence on CT. Total body CT is now practiced in our unit.

4. Discussion

A review article by Connolly et al. [11] suggested that outcome of lung cancer appears poorer in the UK than elsewhere in Europe. This may be due to a less aggressive approach in treatment, especially N2 disease. There are no data in the literature to reflect on the current practice of SND in the UK; however, a study conducted by Tsang and Watson in 1992 [12] suggested that 51% of UK thoracic surgeons did not sample mediastinal nodes routinely. Conversely, Goldstraw (Royal Brompton Hospital) has advocated as early as 1996 the routine use of SND as the method of choice to stage the mediastinum [13]. In a pressurised service where commis-

Table 3. Mortality in 96 patients with NSCLC undergoing VMPR + SND.

	VATS procedure	Stage migration	PET staging	SND staging	Histology	Cause of death	Survival in days
1	LUL	Upstaged Ia to IIa	T1 N0	T1 N1 (#10)	Adenocarcinoma	Disseminated disease	394
2	RUL	Concordant Ia	T1N0	T1N0	Adenocarcinoma	Disseminated disease	172
3	LUL	Upstaged Ia to Ib	T1 N0	T2 N0	Adenocarcinoma	Ethanol toxicity	63
4	RUL	Concordant Ia	T1 N0	T1 N0	Adenocarcinoma	Disseminated disease	398
5	LLL	Upstaged Ia to IIIa	T1 N0	T2 N2 (#10,#11,#7 and #9)	Adenocarcinoma	Complications of chemotherapy	238
6	RLL	Upstaged Ib to IV	T2 N0	T3 N0 M1	Squamous cell	Disseminated disease	305
7	RLL	Upstaged Ib to IIIa	T2 N0	T2 N2 (#R4 and #9)	Adenocarcinoma	Disseminated disease	777
8	RL Bilobectomy	Upstaged Ib to IIIa	T2 N0	T2 N2 (#10, #11, #7)	Adenocarcinoma	Pneumonia and pulmonary embolism	35
9	LUL	Concordant Ib	T2 N0	T2 N0	Squamous cell	Disseminated disease	296
10	RUL	Upstaged Ib to IIIa	T2 N0	T2 Multilevel N2 (#11,#2-4,#7)	Adenocarcinoma	Disseminated disease	239
11	RLL	Concordant Ib	T2 N0	T2 N0	Adenocarcinoma	Pneumonia and pulmonary embolism	29
12	RL Bilobectomy	Upstaged Ib to IIIa	T2 N0	T3 N1 (#11)	Adenocarcinoma	Unknown	288
13	RLL	Concordant IIb	T2 N1	T3 N0	Squamous cell	Disseminated disease	171
14	LUL	Downstaged IIIb to IIb	T2 N3	T2 N1 (#10)	Adenocarcinoma	Unknown	330
15	Pneumonectomy	Upstaged IIb to IIIa	T3N0	T3N1 (#11)	Adenocarcinoma	Neutropenic sepsis after chemotherapy	63
16	RUL	Concordant IV	T3 N0 M1	T4 N2 M1	Adenocarcinoma	Disseminated disease	115

sioning is governed by patients' waiting times, targets and cost-effectiveness, UK surgeons might feel reluctant to extend operating time by an hour or so looking for mediastinal nodes. The risk of improper mediastinal staging in our view is by far greater than extending the duration of the operation. The long-term results of stage migration lead to faulty comparison, and might dictate the wrong management, ending in completely erroneous survival statistics. In our view, the only contraindication to SND would be technical difficulty with dissection in the presence of severe adhesions.

The significance of preoperative as opposed to postoperative staging in resectable early lung cancer is tied to what the clinician wants to do with the information. There might be little disagreement about the N1 disease, but controversy surrounds N2 disease. The choices are: (1) avoid surgery all together and opt for chemo-radiotherapy, (2) induce chemotherapy before surgery or (3) make a run for surgery while the tumour is operable and follow that by adjuvant chemotherapy/radiotherapy. The first approach is advocated by Albain et al. [14] who showed that lobectomy will add little to chemo-radiotherapy for patients with stage IIIa (N2) NSCLC, at the expense of higher mortality. The second approach is supported by the S9900 trial follow-up published in 2010, which continues to show that the best treatment for N2-resectable lung cancer would be induction chemotherapy followed by surgery [15]. Rocco et al. [16] is supportive of the third approach, concluding that standard treatment of initially resectable stage IIIa NSCLC remains surgery followed by adjuvant chemotherapy. The subject remains controversial. Currently, we rely on CT/PET, mediastinoscopy or endobronchial ultrasound (EBUS) either to direct the patient to one form of treatment or prevent unnecessary operation. However, Lim et al. conducted a systematic review of all the published meta-analysis of randomised trials in preoperative versus postoperative chemotherapy in patients with resectable lung cancer [17]. They concluded that in patients with resectable lung cancer, there was no difference in overall and disease-free survival between the timing of administration of chemotherapy (postoperative vs preoperative). Clearly, this sends a strong message that earnest preoperative investigation of the mediastinum in PET-negative resectable early lung cancer might be unnecessary. Meyers et al. [18] specifically considered the cost-effectiveness of routine mediastinoscopy in CT-negative, PET-negative patients with stage I lung cancer. They concluded that routine mediastinoscopy would add an average of 0.01 years (3.65 days) of life at a cost of $201,918 per life-year gained. Therefore, they do not recommend routine mediastinoscopy in PET-negative patients. Our results show that SND is a safe and comprehensive way to stage the mediastinum during the resection procedure, and we therefore recommend the third approach of VMPR-SND followed by adjuvant chemotherapy based on proper SND staging.

One of the serious disappointments of PET scanning in lung cancer is the low uptake of carcinoids, adenocarcinoma and bronchioloalveolar carcinomas, in some series up to 40%. The PLUS meta-analysis reporting the PET/CT mediastinal staging in patients with NSCLC found the median sensitivity to be 85% (range 67—91%) and specificity of 90% (range 82—96%) [19]. In our series, all 16 (16.6%) upstaged cancers were adenocarcinoma. Clearly, this suggests that PET has low sensitivity to detect metastatic adenocarcinoma in mediastinal nodes. Gillies et al. [20] and Plathow et al. [21] summarised the current views about the elevated glucose metabolism in cancers. Tumour cells adapt to hypoxia by up-regulation of glucose transporter (GLUTs) and increased activity of hexokinase. GLUT is the first energy-independent glucose transporter across the cell membrane down the concentration gradient. Tumours increase their level of energy production by engaging in glycolysis, which is a relatively inefficient way to produce energy compared with aerobic oxidation (two ATP molecules vs 30 ATPs). The toxic acidic tumour microenvironment results in death of normal tissue, whereas tumour cells evade apoptosis by maintaining normal intracellular pH. It is thought that this process gives the tumour cells a competitive advantage for local growth, ultimately leading to invasion of basement membrane and distant metastases. Primary tumours and their nodal secondaries express high GLUT1 up-regulation, which in turn

is tied to ^{18}F-FDG accumulation in the tumour cell, and hence directly related to maximum standard uptake value (SUV_{max}). GLUT expression is tied to tumour cell type and differentiation, and there is some phenotypic variation by which GLUT3 and GLUT5 overexpression is mainly in metastatic nodes. Squamous cell carcinoma exhibits overexpression of GLUT1, whereas adenocarcinoma does not. This tumour biological behaviour explains why PET is blinded to adenocarcinoma, and why all our upstaged tumours were adenocarcinoma. For the same reason, the importance of the SUVmax as a surrogate value for malignancy has been played down. The role of PET will continue to evolve with further clinical studies using other new tracers, such as the thymidine analogue 3′-deoxy-3′-^{18}F-fluorothymidine, which more specifically targets the proliferative activity of malignant lesions and can differentiate them from the false-positive inflammatory lesions, as seen with FDG [22].

Another important difficulty about the uptake of the FDG metabolite is the mass of active tissue. A node under 1 cm in diameter is unlikely to show up as a hot spot on PET, even if it was replaced by secondary malignant tissue. Al-Sarraf et al. [23] found that integrated CT/PET images had reduced sensitivity for non-enlarged <1 cm nodes (40%). In our series, false negativity was experienced at five levels, T descriptor (nine), N1 (eleven), N2 single station (five) and N2 multi-station (four) as well as M1 descriptor (two). All the false-negative N1 nodes were <1 cm in diameter. Skip lesions were expressed in six cases, but the true importance of this is unknown [24]. It is likely that micrometastases are missed by our current methods of investigating nodal metastases. This is not a problem with the practice of systematic dissection, but can be a serious problem for mediastinal nodal sampling, as it can lead to erroneous staging.

There are few published studies that attest to completeness of VATS-SND, but the most impressive was that of Sagawa et al. [25]. After VATS lobectomy-SND, a standard thoracotomy was subsequently opened by a different surgeon to complete systematic nodal dissection and revisit the VATS-SND dissection. The average addition to VATS-SND was 1.2 nodes. Comprehensive radical nodal dissection is possible by VATS and should not be different to open thoracotomy [10]. In our series, 98.9% of patients had six or more nodes harvested from three stations, which compares favourably with the 99% reported in the American College of Surgeons Oncology Group (ACOSOG) Z0030 Trial [5]. Our median number of harvested nodes (right = 12, range 5–33; left = 10, range 7–21) is consistent with the Z0030 trial, but is much lower than the Japanese series of Watanabe (23.4 nodes for right lower lobectomy) [9]. This might be attributable to racial variation. The Goldstraw series of SND by thoracotomy is the only benchmark series from the UK, quoting a median of seven nodes per patient (range 3–13) [13]. We conclude therefore that the video-assisted surgical approach did not adversely affect the lymph node yield. Our occult N2 disease is double the 4% reported in the Z0030 Trial, and in line with the current literature (unexpected N2 in cN0–1 = 10.5%). A prospective study is required to look into the number of lymph nodes harvested by open thoracotomy versus VATS-SND in the Anglo-Saxon predominant population in the UK.

5. Conclusions

We conclude therefore that VATS-SND is technically feasible and safe, and does not add to the morbidity or mortality of the originally planned operation. SND should be performed routinely even if nodal involvement is unlikely. We found PET to be blinded to adenocarcinoma nodal metastases in 16.6% of cases; therefore, a negative PET should not be an excuse against mediastinal nodal dissection. Multidisciplinary management of NSCLC has to accept the limitations of PET when constructing clinical pathways, and adjuvant therapy should be based on SND. Relying on PET alone for mediastinal staging can lead to significant stage migration, and would result in misleading survival statistics.

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Editorial comment

Clinical pathways: mediastinoscopy and mediastinal lymph node dissection

Keywords: Lung cancer; Mediastinum

Mediastinal lymph node (MLN) staging is integral to the assessment and management of patients with operable non-small-cell lung cancer (NSCLC) and is necessary to achieve complete resection. Current guidelines suggest that mediastinoscopy should be performed regardless of the clinical N status in patients with stage Ib and greater, and that assessment of a minimum of three N2 nodes, in addition to the removal of regional N1 nodes, should be included during the anatomic resection of NSCLC [1]. A recent study by Amer and colleagues compared the staging accuracy of preoperative positron emission tomography (PET) with MLN dissection (MLND) during thoracoscopic lobectomy. In this study, video-assisted thoracoscopic surgery (VATS) MLND resulted in a change in pathologic stage in approximately 20% of patients, with 15% of patients upstaged and 5% downstaged. This study adds to the literature that supports the absolute necessity to confirm N-status with pathologic staging prior to assigning therapy: patients who are clinical stage III are sometimes stage I—II, and should not be denied surgical resection, and patients who are clinical stage I—II are sometimes stage III, and should receive induction therapy or definitive chemoradiotherapy.

The authors, however, seem to have ignored the data that support the use of mediastinoscopy prior to VATS lobectomy, even in clinical stage I disease [2—4]. In a study of 202 patients with clinical stage I NSCLC, the role of PET for MLN staging was challenged [3]. Of the 65 patients with positive results of PET, only 29 patients (45%) had positive results of mediastinoscopy in the corresponding nodal station. More importantly, of the 137 patients with a negative PET scan, 16 patients (12%) were demonstrated to have N2 or N3 disease. Thus, it is unclear why all patients in the study by Amer and colleagues were not offered mediastinoscopy [1].

The implementation of MLN dissection (as performed in this study) versus MLN sampling (MLNS) is still controversial; MLND may be associated with more accurate staging, but it is not clear whether it is associated with improved survival. This debate was recently addressed by the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial, which assessed patients with clinical stage I NSCLC randomized to MLNS or MLND [5]. In this trial, there was no difference in survival, and MLND demonstrated an improvement in staging of only 4%. However, it must be noted that this trial mandated systematic sampling in all patients and included only early stage patients. In addition, the patients in this study, who underwent MLNS, underwent complete systematic sampling, as opposed to selective biopsies.

Finally, the authors support the use VATS MLND, which has been demonstrated to be as effective as MLND with thoracotomy in comparative studies. Of note, recent multi-institutional study compared the efficacy of MLND during lobectomy performed with thoracoscopy or thoracotomy [6]. Overall, the majority of patients in both groups had at least three MLN stations assessed, and MLND with thoracoscopy was as effective as thoracotomy as assessed by the number of N2 stations, the total number of LN stations resected, and the degree of upstaging and downstaging.