Lung Cancer 134 (2019) 254–258

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

UPSTAGING, CENTRALITY AND SURVIVAL IN EARLY STAGE NON-SMALL CELL LUNG CANCER VIDEO-ASSISTED SURGERY★

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ARTICLE INFO

Keywords:
VATS
Lung Cancer
Lymph Nodes
Early stage

ABSTRACT

OBJECTIVES: Hiliar (pN1) and mediastinal lymph (pN2) nodal upstaging after surgery for early stage (< IIB) non-small cell lung cancer (NSCLC) is a quality marker of surgical lymphadenectomy. It has been suggested that Video-Assisted Thoracoscopic Surgery (VATS) may result in suboptimal lymphadenctomy because nodal upstaging was lower than after open thoracothomy (THO).

We sought to: (1) compare the prevalence of nodal upstaging after VATS and THO in NSCLC < IIB; (2) investigate potential risk factors of nodal upstaging; and, (3) assess the impact of nodal upstaging on survival.
METHODS: Retrospective analysis of all anatomical resections for NSCLC < IIB in our center (n = 323) from 2011 to 2017. The surgical procedure [THO (60.4%) or VATS (39.4%)] was chosen by the surgeon on the basis of experience and tumor characteristics (centrality and size).
RESULTS: Baseline characteristics were similar between the two groups except for larger and more central tumors in THO ($p < 0.05$). The prevalence of pN1 upstaging was higher after THO (20.5%) than after VATS (8.6%, $p < 0.05$), but that of pN2 was similar in both groups (6% (THO) and 6.5% (VATS). Tumor centrality was an independent risk factor for pN1. Survival after THO or VATS was similar, irrespectively of nodal upstaging.
CONCLUSIONS: In conclusion, VATS is as useful as THO to detect upstaging. Lower upstaging after VATS is attributable to bias selection. Central tumors are more often approached by thoracotomy and centrality is a risk factor for hiliar upstaging.

1. Introduction

Non-small cell lung cancer (NSCLC) staging determines both treatment and prognosis. Anatomic resection (with lymphadenectomy) is indicated in patients with early-stage NSCLC (< IIB) [1,2]. In these patients, nodal upstaging after surgery (pN+) occurs in about 20% of patients [3]. This is a surgical quality marker since under diagnosis of nodal involvement leads to under adjuvant therapy and, therefore, may have significant prognostic implications.

Video-Assisted Thoracic Surgery (VATS) lobectomy is currently recommended over open surgery (THO) for the treatment of patients with < IIB NSCLC because long-term survival is similar but post-operative pain and hospital stay are reduced [4]. However, the ability of VATS to adequately perform lymphadenectomy has been questioned. In fact, some recent studies reported that, in patients with < IIB NSCLC, the incidence of nodal (pN1) upstaging after VATS was lower than after THO [5,6]. Others suggested that this may be related to tumor centrality and not to the specific surgical procedure used [7]. To address these questions, we investigated: (1) the prevalence of pN+, pN1 and pN2 (mediastinal) in patients with < IIB NSCLC treated with VATS or THO in our center; (2) potential risk factors for nodal upstaging; and (3) survival after VATS and THO in patients with (pN+, pN1, pN2) or without (pN0) nodal upstaging.

★ Meeting presentation: Accepted as a poster in the World Conference in Lung Cancer, Toronto 2018.

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https://doi.org/10.1016/j.lungcan.2019.06.030
Received 3 May 2019; Received in revised form 28 June 2019; Accepted 30 June 2019

2. Methods

2.1. Study design, Patients and Ethics

We retrospectively analyzed the results of all clinical stage < IIB NSCLC patients, according to the 8th edition of the international TNM classification [8] operated in our center between January 2011 and December 2017. We excluded from the analysis wedge resections, metastatic disease, neuroendocrine tumors, synchronous lung cancer or patients previously treated with neoadjuvant chemo-radiotherapy. Anatomical segmentectomies were excluded too. All participants signed informed surgical consent. Specific surgical approach (THO or VATS) was decided by each one of the five experienced thoracic surgeons based on their own experience, tumor location and size. Anatomical resection and systematic lymph node dissection were performed in all patients. After surgery, patients were followed up regularly in outpatient clinic.

2.2. Pre-operative lung cancer staging

Pre-operative lung cancer staging was done according to international recommendations [9]. All patients were initially staged using CT and PET-CT. Mediastinal lymph nodes were considered positive when their short axis was larger than 1 cm in CT scans and/or were evaluated as positive in PET-CT by dedicated thoracic radiologists and nuclear medicine specialists. Tumor size and centrality (operationally defined here as a tumor growing in the inner third of the thorax in CT scan) were recorded. Finally, if deemed necessary by the multi-disciplinary lung cancer committee of our institution, pre-surgical mediastinal staging was done using endoscopic ultrasound (EBUS) and/or mediastinoscopy (Fig. 1).

2.3. Post-operative pathological staging

Post-operative pathological staging was done following international recommendations [10]. We recorded the number of lymph node stations examined, general lymph node (pN+), hiliar (pN1) and mediastinal (pN2) upstaging. Skip metastases (pN2 in absence of pN1) were registered too.

2.4. Statistical analysis

Results are presented as n (proportion), mean ± standard deviation or median [interquartile range] as appropriate. The THO and VATS groups were compared using Fisher's exact test, Chi-Square, Student's t-test or ANOVA as appropriate. Univariate and multivariate (logistic regression) correlation analysis were used to investigate risk factors of nodal upstaging. Kaplan-Meier curves were used to compare survival after THO or VATS in pN+, pN0, pN1 and pN2 groups. A p value < 0.05 was considered statistically significant. All analyses were done using SPSS 20.0 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Patient characteristics

Out of the 323 anatomical resections for < IIB NSCLC included in the analysis (311 lobectomies (96.3%), 4 bi-lobectomies (1.2%) and 8 pneumonectomies (2.5%)), 195 (60.4 %) were done by THO and 128 (39.4 %) by VATS (p < 0.05). As shown in Table 1, by and large, the main clinical characteristics of these two groups before surgery were similar, except that tumor size was larger (p = 0.006) and centrality more frequent (p = 0.0001) in THO. Peri-operative mortality was zero in both groups.

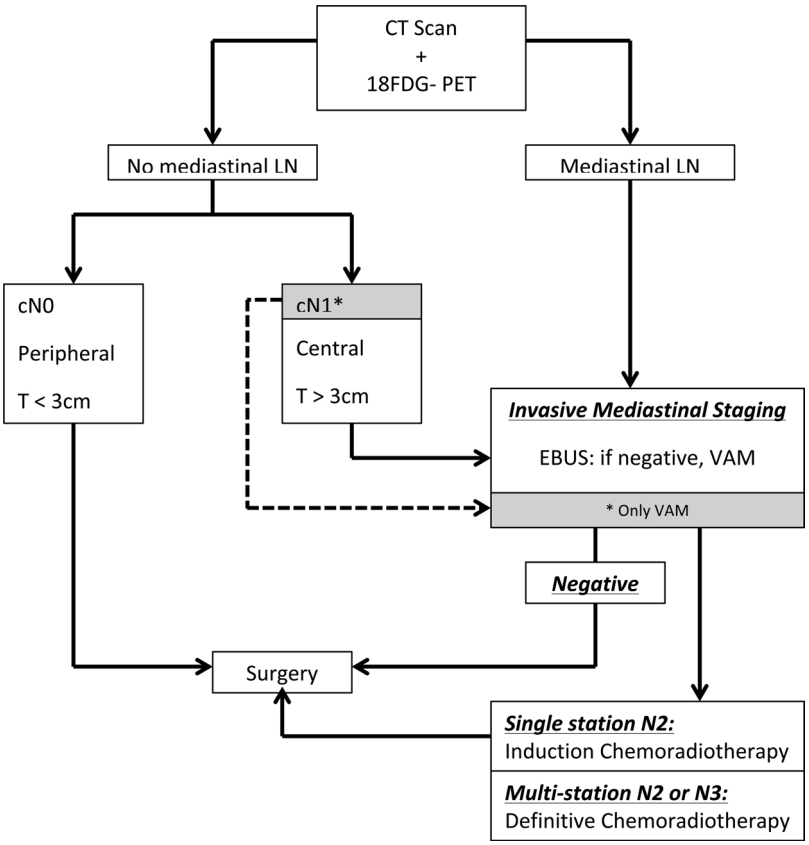

Fig. 1. Mediastinal staging algorithm. [CT, computerized tomography; 18FDG-PET, 18 fluoro-deoxy-glucose positron emission tomography; LN, lymph nodes; EBUS, endobronchial ultrasound; VAM, video-assisted mediastinoscopy].

Table 1
Main baseline characteristics of the two groups of patients studied.

	THO 195 (60 .4%)	VATS 128 (39 .6%)	p value
Age, years	65 .2 (± 10 .1)	66 .5 (± 9 .4)	0 .255
Male, n (%)	136 (69 .7%)	92 (71 .9%)	0 .709
Non Smoker, n (%)	25 (12 .8%)	13 (10 .2%)	0 .608
FEV1, % reference	77 .2 (± 17.3)	81 .8 (± 19.1)	0 .028
FVC, % reference	88.3 (± 15.5)	89.3 (± 16.6)	0 .602
FEV1/FVC, %	66.9 (± 15.4)	68.6 (± 11.9)	0.278
DLCO, % reference	s70 .7 (± 16.4)	72 .4 (± 18.3)	0 .412
Tumor type			0.172
Adenocarcinoma	119 (61%)	90 (79.3%)	
Squamous	68 (34 .9%)	32 (25%)	
Other	8 (4.1%)	6 (4.7%)	
Tumor size			0.006
0-1 (T1a)	8 (4.1%)	11 (8.6%)	
1-2 (T1b)	56 (28.7%)	50 (38.8%)	
2-3 (T1c)	61 (31.3%)	43 (33.6%)	
3-4 (T2a)	46 (23.6%)	19 (14.8%)	
4-5 (T2b)	24 (12.3%)	5 (3.9%)	
Tumor centrality criteria	45 (23.1%)	7 (5.5%)	0.005
pN+	41 (22%)	19 (13.6%)	< 0.005
pN0	150 (76.9%)	113 (88.3%)	0.01
pN1	40 (20.5%)	11 (8.6%)	0.004
pN2	11 (6%)	9 (6.5%)	0.972

FEV1: Forced Expiratory Volume 1 st second; FVC: Forced Vital Capacity; DLCO: Carbon Monoxide Lung Diffusion Capacity; THO: Thoracotomoy; VATS: Video Assisted Thoracic Surgery.

3.2. Pathologic staging

After surgery 150 patients in THO (76,9%) and 113 in VATS (88,3%) were not upstaged (pN0) (p = 0.01). Lymph node involvement (pN+) was observed in 41 patients (22%) in the THO group and in 19 patients (13,6%) in the VATS group (p < 0.005). This was due to hiliar lymph node upstaging (pN1), which was higher after THO (20.5%) than after VATS (8.6%) (p = 0.004), whereas mediastinal lymph node upstaging (pN2) was similar in both groups (6 vs. 6.5% after THO and VATS respectively; p = 0.972). When central and peripheral tumors were analyzed separately (Table 2) differences on prevalence of upstaging by the surgical access employed (THO or VATS) vanished. Hiliar metastases were identified more frequently using THO than VATS in peripheral tumors (14.7% vs. 7.4%) albeit differences did not reach statistical significance.

3.3. Risk factors for nodal upstaging

Male gender, diabetes mellitus, low FEV1, tumor centrality and size as well as surgical technique were significantly associated with pN1 upstaging in the univariate analysis (Table 3). Among them, multivariate logistic regression analysis identified male gender (p = 0.003) and tumor centrality (p = 0.006) as independent risk factors for pN1.

Table 2
Prevalence of lack of (pN0) or nodal upstaging (pN1 or pN2) by tumor location (all tumors vs. excluding central tumors) and surgical technique (THO vs. VATS).

	All tumors			Central Tumors Excluded		
	THO (n = 195)	VATS (n = 128)	P value	THO (n = 150)	VATS (n = 121)	P value
pN0	76.9%	88.3%	0.01	82.0%	90.1%	0.06
pN1	20.5%	8.6%	0.04	14.7%	7.4 %	0.06
pN2	6%	6.5%	0.97	8%	5.8 %	0.48

THO: Thoracotomoy; VATS: Video Assisted Thoracic Surgery.

Table 3
Univariate and multivariate risk factors for pN1 upstaging.

	Univariate		Multivariate
	Correlation coefficient (Rho)	P value	P value
Age, years	0.012	0.863	-
Male	0.149	0.007	0.003
Diabetes mellitus	−0 .139	0.013	0.070
FEV1, % reference	0.140	0.012	0.964
FVC, % reference	0.089	0.120	-
DLCO, % reference	−0.003	0.959	-
Tumor size (clinical), cm	−0.172	0.002	0.393
Tumor centrality	−0.272	< 0.001	0.006
Performed surgical access	0.160	0.004	0.441

FEV1: Forced Expiratory Volume 1 st second; FVC: Forced Vital Capacity; DLCO: Carbon Monoxide Lung Diffusion Capacity; THO: Thoracotomoy; VATS: Video Assisted Thoracic Surgery.

3.4. Survival

Fig. 2 present the Kaplan Meier survival curves by nodal upstaging (pN+, pN0, pN1 and pN2) and surgical technique used (THO and VATS). There were no significant differences in overall survival in any of these groups.

4. COMMENT

This study shows that pN1 (but not pN2) was lower after VATS than after THO, that this is mostly related to tumor centrality and that, in any case, this does not influence long-term survival after surgery.

4.1. Previous studies

There is current controversy on the recommended approach for early stage lung cancer surgery. Several reports have shown that the incidence lymph node upstaging was lower after VATS than after THO [5,11]. For instance, Martin et al. reported 4.8% pN1 after VATS as compared to 9.9% after THO [12]; notably, however, despite this lower pN1, long-term survival after VATS was higher than after THO [12]. Likewise, Licht et al analyzed the national Danish Registry and found similar differences in hiliar nodal upstaging after VATS but, again, no differences in survival were observed [13]. Finally, a recent meta-analysis suggested that VATS was less effective for adequate lymphadenectomy than THO [6], but Watanabe et al. concluded that improvements in VATS lymphadenectomy technique coupled with better survival results should make it preferable to THO [14].

4.2. Interpretation of current findings

Our results confirm that nodal upstaging (pN+) is lower after VATS than after THO (13.6 vs. 22%, p < 0.005). The upstaging rate observed in our THO group is similar to that reported by others [3]. We observed that nodal upstaging was due to pN1 and not to pN2 (Table 1), as previously reported too [3,15]. In our series, pN2 was similar in both groups (6% after THO vs. 6.5% after VATS, p > 0.05). These figures are similar to those reported by Decaluwé (8.2% after THO and 4.5% after VATS) [16] but lower than those published by Lincht et al [13]. The latter can be explained by the extensive non invasive mediastinal staging that we obtain in all surgical candidates as recommended by international guidelines, including CT and PET-CT in all plus EBUS and/or mediastinoscopy in highly suspicious N2 patients or high-risk N2 patients [17].

The lower prevalence of central tumors in the VATS group (5.5% vs. 23.1%, p = 0.005) is likely related to the fact that the surgeon might have chosen not to use VATS previously to surgery or, once in the

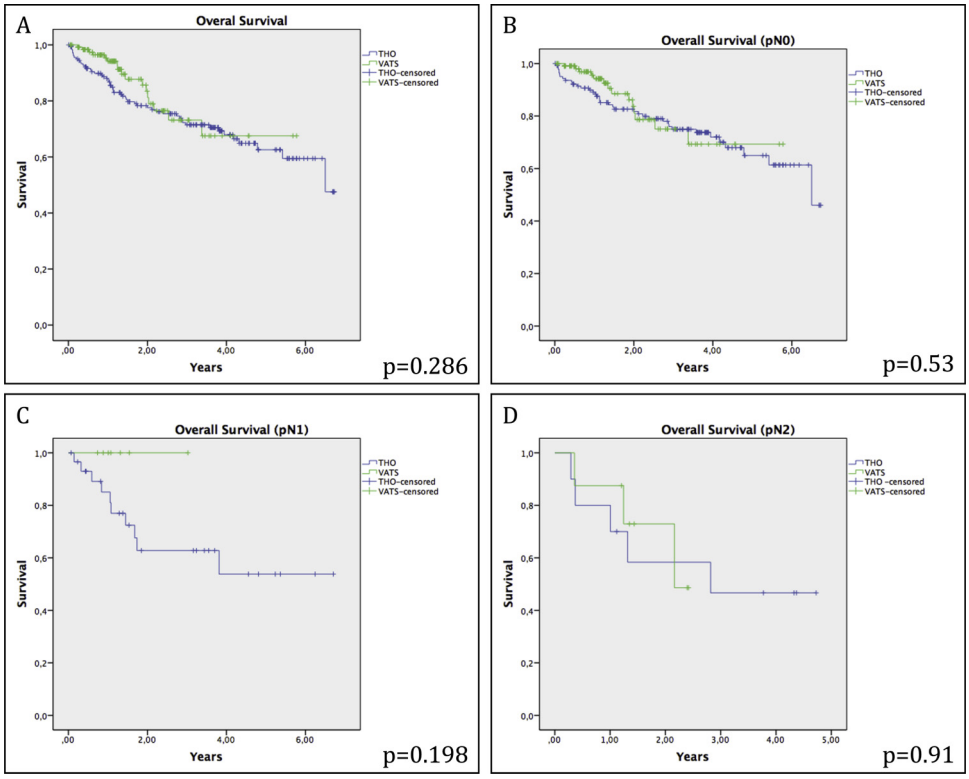

Fig. 2. Post-operative survival (Kaplan-Meier analysis) by surgical procedure (THOR (blue) or VATS (green). (A) All patients; (B) pN0 patients; (C) pN1 patients; (D) pN2 patients. For further explanations, see text.

operating room switch to THO at her/his discretion after having observed, for instance, the presence of large hiliar lymph nodes. In fact, differences in pN1 after THO or VATS vanished when central tumors were excluded from the analysis (Table 2). We think that this is likely to be the most important reason for the lower pN1 observed in our analysis after VATS, as also suggested by some previous studies [12,16,18].

Tumor centrality is considered an independent risk factor for lymph node metastasis and has been included in the last ESTS guidelines update as a criteria for invasive preoperative staging in NSCLC with EBUS and/or mediastinoscopy [9]. In keeping with Decaluwé et al [16], our analysis identified tumor centrality as an independent risk factors for pN1 after VATS (Table 3). By contrast, at variance to Marulli et al., we did not find that tumor size or tumor cell type were risk factors for nodal upstaging after VATS [15]. In this context, it should be noted that, in our series, tumor size was significantly smaller in the VATS group (Table 1).

Finally, it is well established that lymph node involvement worsens survival in patients with NSCLC [19] and it is actually an indication for adjuvant therapy [1]. Maximizing nodal upstaging after surgery is, therefore, of paramount clinical importance. We found that, despite lower pN1 after VATS, overall survival was similar after VATS or THO (Fig. 1). This is in keeping with previously published data [12,13] and suggests that no patients were left under-staged after VATS.

5. Conclusions

This study identified tumor centrality as a risk factor for hiliar upstaging as well as a determinant factor for surgical technique selection. Both could explain lower incidence of nodal hiliar upstaging (pN1) after VATS (vs. THO) and the absence of differences on long-term survival among techniques. In conclusion, VATS is as effective as THO to detect hiliar upstaging and should be considered the election technique in early stage lung cancer.

Declaration of Competing Interest

None.

Acknowledgments

Authors thank the multidisciplinary Lung Cancer Committee of our institution as well as the anesthesiology and critical care and ward team (doctors and nurses) for their daily work.

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