Editor's note:
In the era of personalized medicine, a critical appraisal new developments and controversies are essential in order to derived tailored approaches. In addition to its educative aspect, we expect these discussions to help younger researchers to refine their own research strategies.

Controversies on Lung Cancer: Pros and Cons

# Pros: should a patient with stage IA non-small cell lung cancer undergo invasive mediastinal staging?

**Carme Obiols, Sergi Call**

Department of Thoracic Surgery, Hospital Universitari Mútua Terrassa, University of Barcelona, Terrassa, Barcelona, Spain
*Correspondence to:* Carme Obiols, MD, PhD, FEBTS. Department of Thoracic Surgery, Hospital Universitari Mútua Terrassa, University of Barcelona, Plaza del Dr. Robert, 5, 08221 Terrassa, Barcelona, Spain. Email: carme_obiols@hotmail.com.

Submitted Mar 17, 2016. Accepted for publication May 17, 2016.
doi: 10.21037/tlcr.2016.06.05
**View this article at:** http://dx.doi.org/10.21037/tlcr.2016.06.05

## Introduction

Mediastinal lymph node involvement is an important prognostic factor in patients with non-small cell lung cancer (NSCLC). The American and European guidelines for preoperative mediastinal lymph node staging agree in which situations a pre-surgical exploration of the mediastinum is required in order to avoid futile pulmonary resections (1,2). Invasive mediastinal staging with cyto-histological confirmation is indicated when computed tomography (CT) shows enlarged mediastinal or hilar lymph nodes, when positron emission tomography (PET) shows an increase uptake in the mediastinum or hilum, when the tumour is centrally located and when the tumour size is more than 3 cm, especially in adenocarcinoma with high 18F-Fluorodeoxyglucose (FDG) uptake. In general, a minimally invasive technique (endobronchial or endoesophageal ultrasound fine needle aspiration) is indicated of first choice, but when negative, a surgical exploration of the mediastinum (mainly a video mediastinoscopy) is required. In some particular situation, like clinical (c) staged N1 tumours, with normal mediastinum on imaging techniques, it was suggested to proceed directly to surgical resection when preoperative endosonography was negative. However, this issue has been analyzed, concluding that in cN1 NSCLC, endosonography alone has an unsatisfactory sensitivity to detect mediastinal involvement and, therefore, a confirmatory video mediastinoscopy is mandatory when endoscopic techniques show a negative result (3).

Although stage cIA NSCLC is the main situation in which invasive mediastinal staging might be omitted, this paper will analyze the established indications and other particular situations in which performing a pre-surgical mediastinal staging in this group of patients can add a benefit in terms of accurate staging.

## Invasive mediastinal staging in cIA NSCLC

In cIA tumours, situation without suspicious of hilar or mediastinal lymph node metastases, an invasive exploration of the mediastinum is consensually recommended when the tumour is centrally located (1,2). The definition of central tumour is usually based on radiologic features, but also on bronchoscopic findings. The ESTS guidelines for preoperative mediastinal staging defined a peripheral tumour as the one located in the outer third of the lung (2), based on the publication of Lee *et al.* (4). These authors studied the risk factors for occult mediastinal metastases in stage cI NSCLC and observed that the prevalence of pathologic (p) N2 disease was 21.6% for central tumours compared with 2.9% for peripheral tumours. Gómez-Caro *et al.* (5) defined central tumour as a tumour in contact with the intrapulmonary main bronchi, pulmonary artery, pulmonary

veins or the origin of the first segmental branches. In this study, the negative predictive value of CT and PET-CT for staging patients with cIA NSCLC and excluding centrally located tumours was 92%. Decaluwé *et al.* (6) have recently published a series of patients with stage I NSCLC observing that the subgroup with central primary tumour location, defined as a lesion visible by standard video-bronchoscopy, were upstaged to pN1 in 32.6% of the cases.

Regarding the histological subtype of the tumour, adenocarcinoma has been associated with a higher risk of mediastinal metastases. In a meta-analysis by Wang *et al.* (7), PET-CT staging in cI tumours had a negative predictive value of 92%, but a higher risk of occult mediastinal metastases was observed in pT2 tumours, adenocarcinomas, and primary tumours with high uptake. Ye *et al.* (8) retrospectively studied 651 patients with stage cIA adenocarcinoma, observing that those presenting with a pure solid pattern, serum carcinoembryonic antigen (CEA) level exceeding 5 ng/dL and maximum standardized uptake value (SUVmax) exceeding 5 were at a higher risk of presenting lymph node metastases. Similarly, Koike *et al.* (9) retrospectively analyzed 894 patients with peripheral cIA NSCLC encountering these four predictors for mediastinal nodal metastases: age (≤67 years), preoperative serum CEA level (≥3.5 ng/mL), tumour size (≥2 cm) and consolidation/tumour ratio on high resolution CT (≥89%). Among patients presenting with all these four predictors identified in the multivariate analyses, the prevalence of mediastinal nodal metastases was 33.8% and, therefore, invasive preoperative staging is recommended.

The association between FDG uptake on PET and the incidence of mediastinal metastases has also been analyzed. Many authors, as mentioned above (7,8), have encountered a high SUVmax value as a predictor of mediastinal metastases in combination with other factors, but also higher uptake values have been associated with worse survival and increased risk of recurrence in patients with stage I NSCLC (10). The main limitation of these studies is that not all of them report a multivariate analysis of the different prognostic factors, the difficulty to standardize the PET uptake values and to define a prognostic SUV cut-off, which leads to confusion when comparing studies (11).

Finally, tumour size has also been associated with the risk of presenting mediastinal lymph node metastases. Stage IA, which involves tumours of 3 cm or less, includes T1a (≤1 cm), T1b (>1 to ≤2 cm) and T1c (>2 to ≤3 cm) tumours in the eight edition of the TNM classification of lung cancer, showing a progressive degradation of survival as tumour size increases (12). European guidelines recommend invasive mediastinal staging in tumours >3 cm, especially in adenocarcinomas. Therefore, in clinical stage IA, invasive mediastinal staging is not recommended according to tumour size alone. But when taking into consideration tumour size (>2 cm) in combination with other factors, an increased risk of mediastinal metastases has been observed (9). More studies are needed to determine an inferior cut-off of the primary tumour size, probably in combination with other preoperative risk factors, to predict mediastinal involvement in stage cIA.

## The role of transcervical lymphadenectomies in early stage NSCLC

Transcervical lymphadenectomies have been developed in the last decades allowing a step forward beyond classic mediastinoscopy. Video-assisted mediastinoscopic lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA), also known as "supermediastinocopies" (13), allow a complete mediastinal lymphadenectomy. VAMLA is a totally endoscopic procedure performed with the video mediastinoscope. Its aim is to remove en bloc the lymph nodes and the surrounding fatty tissue of the right and left paratracheal and subcarinal nodal stations (14). TEMLA is a mainly open procedure, more extensive than VAMLA because it also includes the highest mediastinal, subaortic, anterior mediastinal and paraesophageal nodes (15). Both techniques are not indicated when there is an evident mediastinal involvement, in which situation a minimally invasive technique would be of first choice. In the last years, these techniques, especially VAMLA, have been adopted by other departments besides the institutions where the technique was originally developed, and new indications have been described. In a recent report on 160 VAMLAs for staging NSCLC, a high rate of unsuspected mediastinal involvement was observed in patients with cN1 tumours (40.7%) and in cN0 and tumour size >3 cm (22.2%) (16). The differentiation between central primary tumour and cN1 involvement is not easy to assess by imaging techniques. Although in this study central tumours were not analyzed separately, some of them may overlap with cN1.

These are the described indications for VAMLA which also includes cIA NSCLC: central tumours, left sided tumours, bilateral synchronous lung cancer, preresectional lymphadenectomy in video-assisted thoracoscopic lobectomy (17) and in elderly patients and

 

patients with poor performance status (16). In all these situations, VAMLA provides an accurate preoperative mediastinal staging and lymphadenectomy. Turna *et al*. observed a survival benefit of patients who underwent VAMLA in comparison with video mediastinoscopy (18). Although this effect on survival could be explained by the low rate of unsuspected pN2 disease after performing VAMLA, it also can reflect the effect of a more extensive lymphadenectomy, which is bilateral. This is especially important in left sided tumours in which left paratracheal nodes are not usually explored due to the interposition of the aorta. Finally, in bilateral synchronous lung tumours, an invasive mediastinal staging is recommended because of the difficulty to distinguish between two primary tumours versus a metastatic lesion. Therefore, ruling out mediastinal involvement is important before proceeding to bilateral lung resections (19).

## Conclusions

Invasive mediastinal staging in cIA NSCLC is not routinely performed and has very particular indications. In central tumours, according to its high rate of unsuspected pN2 disease, invasive mediastinal staging is consensually indicated (1,2). There are other parameters and tumour characteristics that increase the risk of mediastinal nodal involvement, especially when combining them. This is the situation of adenocarcinoma histological type, combined with tumour size, FDG uptake value or serum CEA level (7-10).

The role of transcervical lymphadenectomies in early stage lung cancer has been described, showing better staging values than standard mediastinoscopy and endoscopic ultrasound fine needle aspiration techniques (14-18). Therefore, in case of central tumours, the accuracy of these techniques adds value to rule out mediastinal disease, enhancing, therefore, clinical staging. Other challenging situations like bilateral synchronous lung cancer (16,19) and elderly patients or patients with poor performance status (16) can benefit from VAMLA/TEMLA in order to avoid unnecessary lung resections and its complications. Finally, these pre-resectional lymphadenectomies can be indicated in cIA tumours located in the left lung or in combination with VATS lobectomy to achieve a radical lymphadenectomy, even better than by open surgery (16,17).

## Acknowledgements

None.

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

## References

1. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e211S-50S.
2. De Leyn P, Dooms C, Kuzdzal J, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg 2014;45:787-98.
3. Dooms C, Tournoy KG, Schuurbiers O, et al. Endosonography for mediastinal nodal staging of clinical N1 non-small cell lung cancer: a prospective multicenter study. Chest 2015;147:209-15.
4. Lee PC, Port JL, Korst RJ, et al. Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. Ann Thorac Surg 2007;84:177-81.
5. Gómez-Caro A, Boada M, Cabañas M, et al. False-negative rate after positron emission tomography/computer tomography scan for mediastinal staging in cI stage non-small-cell lung cancer. Eur J Cardiothorac Surg 2012;42:93-100; discussion 100.
6. Decaluwé H, Stanzi A, Dooms C, et al. Central tumour location should be considered when comparing N1 upstaging between thoracoscopic and open surgery for clinical stage I non-small-cell lung cancer†. Eur J Cardiothorac Surg 2016;50:110-7.
7. Wang J, Welch K, Wang L, et al. Negative predictive value of positron emission tomography and computed tomography for stage T1-2N0 non-small-cell lung cancer: a meta-analysis. Clin Lung Cancer 2012;13:81-9.
8. Ye B, Cheng M, Li W, et al. Predictive factors for lymph node metastasis in clinical stage IA lung adenocarcinoma. Ann Thorac Surg 2014;98:217-23.
9. Koike T, Koike T, Yamato Y, et al. Predictive risk factors for mediastinal lymph node metastasis in clinical stage IA non-small-cell lung cancer patients. J Thorac Oncol 2012;7:1246-51.
10. Nair VS, Krupitskaya Y, Gould MK. Positron emission tomography 18F-fluorodeoxyglucose uptake and prognosis in patients with surgically treated, stage I non-small cell lung cancer: a systematic review. J Thorac Oncol

 

2009;4:1473-9.
11. Dooms C, Vansteenkiste J. Prognostic value of fluorodeoxyglucose uptake in non-small cell lung cancer: time for standardization and validation. J Thorac Oncol 2010;5:583-4.
12. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.
13. Rami-Porta R. Supermediastinoscopies: a step forward in lung cancer staging. J Thorac Oncol 2007;2:355-6.
14. Hürtgen M, Friedel G, Toomes H, et al. Radical video-assisted mediastinoscopic lymphadenectomy (VAMLA)--technique and first results. Eur J Cardiothorac Surg 2002;21:348-51.
15. Zieliński M. Transcervical extended mediastinal lymphadenectomy: results of staging in two hundred fifty-six patients with non-small cell lung cancer. J Thorac Oncol 2007;2:370-2.
16. Call S, Obiols C, Rami-Porta R, et al. Video-Assisted Mediastinoscopic Lymphadenectomy for Staging Non-Small Cell Lung Cancer. Ann Thorac Surg 2016;101:1326-33.
17. Witte B, Messerschmidt A, Hillebrand H, et al. Combined videothoracoscopic and videomediastinoscopic approach improves radicality of minimally invasive mediastinal lymphadenectomy for early stage lung carcinoma. Eur J Cardiothorac Surg 2009;35:343-7.
18. Turna A, Demirkaya A, Ozkul S, et al. Video-assisted mediastinoscopic lymphadenectomy is associated with better survival than mediastinoscopy in patients with resected non-small cell lung cancer. J Thorac Cardiovasc Surg 2013;146:774-80.
19. Kozower BD, Larner JM, Detterbeck FC, et al. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-99S.

**Cite this article as:** Obiols C, Call S. Pros: should a patient with stage IA non-small cell lung cancer undergo invasive mediastinal staging? Transl Lung Cancer Res 2016;5(3):247-250. doi: 10.21037/tlcr.2016.06.05

 