JBR–BTR, 2013, 96: 123-126.

INVASIVE STAGING OF THE MEDIASTINUM*

W. De Wever, J. Coolen, J. Verschakelen[1]

Staging of patients with lung cancer provides accurate information on the extent of disease and guides the choice of treatment. Non-invasive imaging techniques are safe, however these imaging techniques have limited accuracy in detection of mediastinal lymph node metastases. The American College of Chest Physicians guidelines for lung cancer staging recommend that patients with abnormal lymph nodes on CT or PET, or centrally located tumors without mediastinal LNs, should undergo invasive staging. Mediastinal nodal sampling has traditionally been performed by cervical mediastinoscopy. However, with the development of endoscopic needle aspiration techniques such as endobronchial ultrasound (EBUS) to guide transbronchial needle aspiration (TBNA) and endoscopic ultrasound (EUS), the diagnostic algorithm for lung cancer is changing.

Key-word: Mediastinum, CT.

Correct staging of patients with lung cancer provides accurate information on the extent of disease, guides choice of treatment, gives an idea about prognosis and is necessary for comparison of studies. In patients with non-small cell lung cancer (NSCLC), surgical resection of the tumor is the treatment of choice in the absence of metastatic mediastinal lymph nodes (LN). Combined modality treatment is indicated for patients with mediastinal nodal metastases. CT, fluorodeoxyglucose PET (FDG-PET) and PET-CT are non-invasive imaging techniques to detect mediastinal metastases. Although CT and PET are safe, these imaging techniques have limited accuracy in detection of mediastinal LN metastases with positive predictive value (PPV) of only 56% to 79%, and negative predictive value (NPV) of 83% to 93% (1) (Table I). Tissue confirmation is usually recommended when there are abnormal findings with these non-invasive imaging modalities (2, 3). The American College of Chest Physicians (ACCP) guidelines for lung cancer staging recommend to limit the impact of false-positive and false-negative results, that patients with abnormal LNs on CT or PET, or centrally located tumors without mediastinal LNs, should undergo invasive staging (4). Mediastinal nodal sampling has traditionally been performed by cervical mediastinoscopy or anterior mediastinotomy (5). However, with the development of endoscopic needle aspiration techniques such as endobronchial ultrasound (EBUS) to guide transbronchial needle aspiration (TBNA) and endoscopic ultrasound (EUS) with needle aspiration (NA), the diagnostic algorithm for lung cancer is changing. In this paper we will give an overview of the possible staging techniques for invasive mediastinal staging.

Primary mediastinal invasive lymph node staging

Mediastinoscopy

Mediastinoscopy has traditionally been the gold standard for invasive mediastinal staging of patients with potentially operable lung cancer. Different forms of mediastinoscopy have been described. Cervical

Table I. — Sensitivities (%) and negative predictive values (%) for different invasive staging modalities in different studies and meta-analysis.

Study	Staging technique	Sensitivity	Negative predictive value
Toloza (1)	CT	57	83
	PET	84	93
Toloza (11)	Blind TBNA	76	71
	EUS-FNA	88	77
	Mediastinoscopy	81	91
Medford (19)	Cervical mediastinoscopy	78-81	91
	Conventional TBNA	76-78	71-72
	EBUS-TBNA	88-93	76
	EUS-FNA	84-88	77-81
Ernst (24)	EBUS	87	78
	Cervical mediastinoscopy	68	59
Yasufuku (25)	EBUS	76.9	85.9
	Cervical mediastinoscopy	84.6	90.4
Annema (26)	Surgical staging	79	86
	Endosonography and surgical staging	94	93
Mateu-Navarro (21)	Remediastinoscopy	70	
Van Schil (27)	Remediastinoscopy	73	75
De Leyn (22)	Remediastinoscopy	29	52

*Meeting "Lung Cancer Imaging in 2012: Updates and innovations", Tervuren, 10.11.2012.

1. Department of Radiology, University Hospitals Leuven, Belgium.

Table II. — Access to different lymph nodes with different staging techniques.

LN stations / Technique	2R	2L	4R	4L	5	6	7	8-9	10	11
Cervical mediastinoscopy	+	+	+	+	-	-	+	-	+ R	-
EUS-FNA	+/-	+	-	+	(+/-)	-	+	+	+/-	-
EBUS-TBNA	+	+	+	+	-	-	+	-	+	+
VATS left	-	-	-	-	+	+	-	+	-	-

EUS-FNA: Endo-oesophageal ultrasound with fine needle aspiration.
EBUS-TBNA: Endobronchial ultrasound with trans bronchial needle aspiration.
VATS: Video-assisted thoracoscopic surgery.

mediastinoscopy is the most commonly used. More recently, video-mediastinoscopy is introduced (5). Other modified techniques are mediastinal lymphadenectomy through a cervicotomy approach (VAMLA, video-assisted mediastinoscopic lymphadenectomy (6) -TEMLA, transcervical extended mediastinal lymphadenectomy (7)).

Cervical mediastinoscopy is a surgical open biopsy technique usually performed in an operating theatre under general anaesthesia. An incision is made just above the suprasternal notch and the mediastinoscope is inserted adjacent to the trachea to view and biopsy the accessible mediastinal nodes. Cervical mediastinoscopy has a reported morbidity (e.g. arrhythmia, haemorrhage and recurrent laryngeal nerve injury) and mortality rate of 2% and 0.08% respectively (8, 9). An advantage of mediastinoscopy over TBNA is the performing of a more complete mediastinal mapping, including contralateral LN stations (5). According to the LN map proposed by Mountain and Dresler (10) the following LN stations can be evaluated by cervical mediastinoscopy: the highest mediastinal LN station (level 1), the right and left superior paratracheal LN stations (level 2 right, level 2 left), the right and left inferior paratracheal LN stations (level 4 right, level 4 left) and the subcarinal LN station (level 7) (5) (Table II). Sensitivity of cervical mediastinoscopy varied between 72% and 89%, with an average of 81% with a NPV of 91% [11] (Table I). The results of the suboptimal sensitivity can partly be explained by the fact that some LN stations (levels 5, 6, posterior part of level 7 and levels 8 and 9) are not accessible by cervical mediastinoscopy.

Video mediastinoscopy allows better visualization and a more complete dissection of nodal tissue than cervical mediastinoscopy (4). A recent retrospective analysis of the two techniques revealed a lower incidence of recurrent laryngeal nerve palsies and postoperative bleeding with video mediastinoscopy. The number of nodes sampled was also higher with video mediastinoscopy. Existing studies show a higher sensitivity for video mediastinoscopy (86-93%) over the conventional version (81%) (8).

Transbrochial needle aspiration

TBNA has been shown to be safe and useful in patients with enlarged mediastinal LNs. Conventional TBNA has been long established as a minimally invasive method for diagnosing and staging patients with bulky subcarinal and paratracheal LNs at the same time as fibreoptic bronchoscopy. TBNA is performed under local anaesthesia with sedation as required as a day case procedure in the endoscopy suite. It is a well-tolerated procedure with no additional risks to a standard fibreoptic bronchoscopy. In reality, it is most often used to sample nodes at station 7. Stations 2 and 4 can also be sampled but these are technically more challenging due to the required angulation of the scope. Studies have reported sensitivity rates of 43-83% and positive predictive values of 89-100% (12) (Table I). The negative predictive value is low and does not obviate the requirement for further surgical staging.

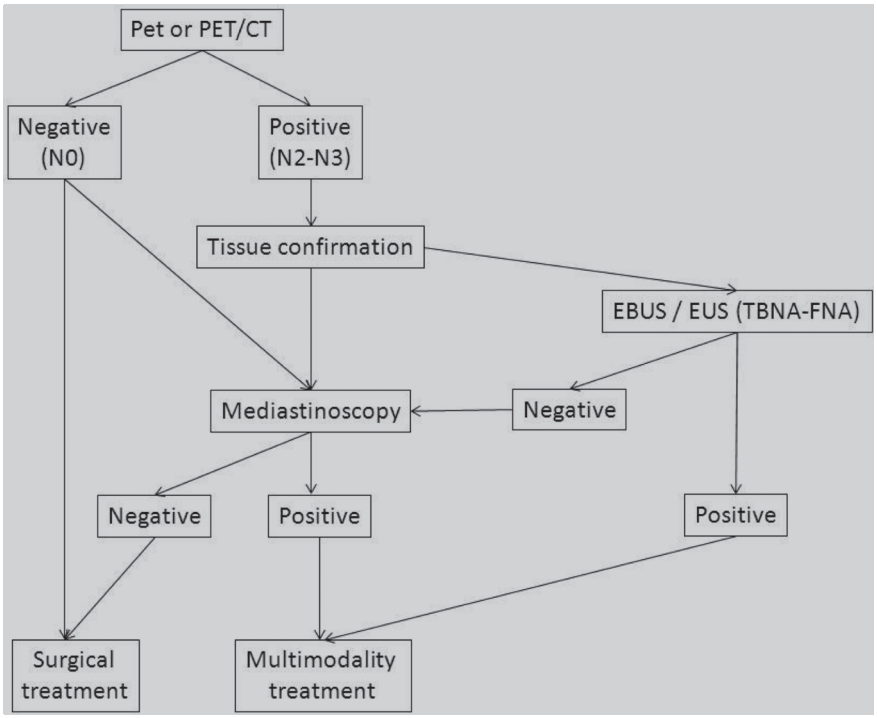
A potential limitation of mediastinal lymph node staging with TBNA is the blind character of this technique. Numerous papers confirm the safety of the procedure. The rare complications reported are: pneumothorax, pneumomediastinum, haemomediastinum, bacteraemia and pericarditis. One of the major complications of TBNA is the possible severe damage to the working channel of the scope (13).

Endo-oesophageal ultrasound with fine needle aspiration

Endo-oesophageal ultrasound (EUS) is a relatively new method first described in 1991 (14). The procedure is performed under local anaesthetic and conscious sedation. EUS and endo-oesophageal ultrasound with fine needle aspiration (EUS-FNA) are safe, simple and highly accurate in detecting and confirming nodal metastases and have been increasingly used for staging of potentially resectable NSCLC. EUS can visualise the posterior and inferior nodal stations 9, 8, 7 and 5 and also sometimes level 4 but cannot image anterior mediastinal nodes because of the interposition of the trachea (Table II). The left lobe of the liver and the left adrenal gland can also be studied and sampled for metastases if abnormalities are found with non-invasive imaging techniques. Morbidity from this technique is almost nihil and even patients with poor lung function tolerate it well. Visual assessment of mediastinal lymphnodes by EUS gave for various observers sensitivities of 54-75%, specificities of 71-98%, PPV of 46-77% and NPV of 85-93% (15) (Table I). Characteristics of lymph nodes indicating possible malignancy are hypoechoic core, sharp edges, round shape and a long axis diameter > 10 mm (15). Signs of benignancy are a hyperechoic core (fat), central calcification, ill-defined edges, a long and narrow shape and a long axis diameter up to 1 cm (16, 17).

Endobronchial ultrasound - TBNA

Endobronchial ultrasound (EBUS) is a procedure similar to conventional TBNA: it is a day case procedure using local anaesthesia and sedation with a similar gauge needle, sampling handling technique using four passes per node and similar or superior safety profile. There are, however, a



EUS: Endo-oesophageal ultrasound
EBUS: Endobronchial ultrasound
FNA: fine needle aspiration
TBNA: trans bronchial needle aspiration
N0: patients with a peripheral tumor with FDG uptake and with LN < 1 cm on CT and/or no FDG uptake in the mediastinum. If PET or PET/CT is negative, mediastinoscopy is still indicated in central tumors, tumors with low FDG uptake, tumors with LN > = 1.6 cm and / or PET N1 disease.

Fig. 1. — The proposed diagnostic algorithm for invasive mediastinal staging when PET or PET/CT is available adapted from P. De Leyn (5).

few differences. The patient is intubated orally from behind due to the larger external diameter of the EBUS bronchoscope (6.9 versus 4.9-5.1 mm in a standard fibroscopic bronchoscope). In general, a linear-type ultrasound probe is most commonly used for real-time imaging (8). EBUS-TBNA is a relatively quick, safe, minimally invasive and a day case procedure under conscious sedation performable by pulmonologists (18). Pneumomediastinum, pneumothorax and haemomediastinum can occur very rarely, but a postprocedure chest radiograph is not usually needed. Major vessel puncture is less likely because of real-time sampling. Infectious complications have rarely been reported, and bacteraemia is usually asymptomatic and clinically insignificant (19).

EBUS-TBNA has access to all the mediastinal lymph node stations accessible by mediastinoscopy. EBUS-TBNA can provide histology of the superior mediastinal LNs (levels 2 and 4, right and left) and the subcarinal LNs (level 7). Additionally, the hilar (station 10) and intrapulmonary nodal stations can be biopsied with TBNA (Table II). The nodes are directly visualised and sampled in real-time reducing the chances of major vessel puncture, and a larger tissue core is obtained.

The negative predictive value of EBUS-TBNA is lower than for mediastinoscopy. This is the reason that patients with a high pretest probability of lung cancer with a negative EBUS-TBNA currently still need a mediastinoscopy. A recent meta-analysis reported an impressive pooled sensitivity of 93% (Table I) (20).

Fig. 1 shows the proposed algorithm to follow primary mediastinal staging when PET or PET/CT scan is available. Proposition is based on the guidelines from the European Society of Thoracic Surgeons for preoperative lymph node staging for NSCLC (5).

Restaging of the mediastinum

Recent studies suggest that mainly patients with initial stage IIIA or IIIB and mediastinal downstaging will benefit from surgical resection. As a consequence, mediastinal restaging after induction therapy is required for selection of patients likely to benefit from surgical resection. Repeat mediastinoscopy offers the advantage of providing histological evidence of response after induction therapy. However repeat mediastinoscopy is technically more difficult than the first procedure. The sensitivity to detect residual mediastinal disease is about 70% (21). In a prospective study, evaluating the accuracy of re-mediastinoscopy and PET-CT in restaging the mediastinum after videomediastinoscopy proven N2 disease in 30 patients, De Leyn et al. concluded that, after a thoroughly performed initial videomediastinoscopy, repeat videomediastinoscopy was technically feasible but inaccurate due to severe adhesions and fibrosis. The sensitivity to detect residual positive mediastinal LNs was only 29%, with an accuracy of 60% (22). The degree of adhesions and mediastinal fibrosis is mainly secondary to preinduction mediastinoscopy rather than to induction treatment itself (22). An alternative, less invasive test to restage the mediastinum after induction chemotherapy is EBUS-TBNA or EUS-FNA. Annema et al. reported results in 19 patients with proven N2 disease which were restaged by EUS after induction chemotherapy. Diagnostic accuracy in this study was 83% (23).

Conclusion

The ACCP guidelines for lung cancer staging recommend that patients with abnormal LNs on CT or PET, or centrally located tumors without mediastinal LNs, should undergo invasive staging. Mediastinal nodal sampling has traditionally been performed by cervical mediastinoscopy. EBUS-TBNA and EUS-FNA are new techniques that provide cytohistological diagnosis and are minimally invasive techniques. They can be complementary to surgical invasive staging techniques. Their specificity is high, but their NPV is low. For this reason an invasive surgical technique is indicated if they yield negative results. However, if fine needle aspiration is positive, this result may be valid as proof of N2 or N3 disease.

References

1. Toloza E.M., Harpole L., McCrory D.C.: Noninvasive staging of non-small cell lung cancer: a review of the current evidence. *Chest*, 2003, 123: 137S-146S.
2. Silvestri G.A., Gould M.K., Margolis M.L., et al.: Noninvasive staging of non-small cell lung cancer: ACCP evidenced-based clinical practice guidelines (2nd edition). *Chest*, 2007, 132: 178S-201S.
3. Cerfolio R.J., Ojha B., Bryant A.S., et al.: The role of FDG-PET scan in staging patients with nonsmall cell carcinoma. *Ann Thorac Surg*, 2003, 76: 861-866.
4. Detterbeck F.C., Jantz M.A., Wallace M., et al.: Invasive mediastinal staging of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest*, 2007, 132: 202S-220S.
5. De Leyn P., Lardinois D., Van Schil P.E., et al.: ESTS guidelines for preoperative lymph node staging for non-small cell lung cancer. *Eur J Cardiothorac Surg*, 2007, 32: 1-8.
6. Hurtgen M., Friedel G, Toomes H, et al.: Radical video-assisted mediastinoscopic lymphadenectomy (VAMLA) – technique and first results. *Eur J Cardiothorac Surg*, 2002, 21: 348-351.
7. Kuzdzal J., Zielinski M., Papla B., et al.: Transcervical extended mediastinal lymphadenectomy – the new operative technique and early results in lung cancer staging. *Eur J Cardiothorac Surg*, 2005, 27: 384-390; discussion 390.
8. Medford A.R., Bennett J.A., Free C.M., et al.: Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. *Curr Opin Pulm Med*, 2009, 15: 334-342.
9. Khoo K.L., Ho K.Y.: Endoscopic mediastinal staging of lung cancer. *Respir Med*, 2011, 105: 515-518.
10. Mountain C.F., Dresler C.M.: Regional lymph node classification for lung cancer staging. *Chest*, 1997, 111: 1718-1723.
11. Toloza E.M., Harpole L., Detterbeck F., et al.: Invasive staging of non-small cell lung cancer: a review of the current evidence. *Chest*, 2003, 123: 157S-166S.
12. Utz J.P., Patel A.M., Edell E.S.: The role of transcarinal needle aspiration in the staging of bronchogenic carcinoma. *Chest*, 1993, 104: 1012-1016.
13. Dasgupta A., Mehta A.C.: Transbronchial needle aspiration. An underused diagnostic technique. *Clin Chest Med*, 1999, 20: 39-51.
14. Schuder G., Isringhaus H., Kubale B., et al.: Endoscopic ultrasonography of the mediastinum in the diagnosis of bronchial carcinoma. *Thorac Cardiovasc Surg*, 1991, 39: 299-303.
15. Micames C.G., McCrory D.C., Pavey D.A., et al.: Endoscopic ultrasound-guided fine-needle aspiration for non-small cell lung cancer staging: A systematic review and meta-analysis. *Chest*, 2007, 131: 539-548.
16. Fritscher-Ravens A., Sriram P.V., Bobrowski C., et al.: Mediastinal lymphadenopathy in patients with or without previous malignancy: EUS-FNA-based differential cytodiagnosis in 153 patients. *Am J Gastroenterol*, 2000, 95: 2278-2284.
17. Chang K.J., Erickson R.A., Nguyen P.: Endoscopic ultrasound (EUS) and EUS-guided fine-needle aspiration of the left adrenal gland. *Gastrointest Endosc*, 1996, 44: 568-572.
18. Herth F.J., Eberhardt R., Vilmann P., et al.: Real-time endobronchial ultrasound guided transbronchial needle aspiration for sampling mediastinal lymph nodes. *Thorax*, 2006, 61: 795-798.
19. Medford A.R.: Endobronchial ultrasound: what is it and when should it be used? *Clin Med*, 2010, 10: 458-463.
20. Gu P., Zhao Y.Z., Jiang L.Y., et al.: Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. *Eur J Cancer*, 2009, 45: 1389-1396.
21. Mateu-Navarro M., Rami-Porta R., Bastus-Piulats R., et al.: Remediastinoscopy after induction chemotherapy in non-small cell lung cancer. *Ann Thorac Surg*, 2000, 70: 391-395.
22. De Leyn P., Stroobants S., De Wever W., et al.: Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 Non-small-cell lung cancer: a Leuven Lung Cancer Group Study. *J Clin Oncol*, 2006, 24: 3333-3339.
23. Annema J.T., Veselic M., Versteegh M.I., et al.: Mediastinal restaging: EUS-FNA offers a new perspective. *Lung Cancer*, 2003, 42: 311-318.
24. Ernst A., Anantham D., Eberhardt R., et al.: Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. *J Thorac Oncol*, 2008, 3: 577-582.
25. Yasufuku K., Chiyo M., Koh E., et al.: Endobronchial ultrasound guided transbronchial needle aspiration for staging of lung cancer. *Lung Cancer*, 2005, 50: 347-354.
26. Annema J.T., van Meerbeeck J.P., Rintoul R.C., et al.: Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA*, 2010, 304: 2245-2252.
27. Van Schil P., van der Schoot J., Poniewierski J., et al.: Remediastinoscopy after neoadjuvant therapy for non-small cell lung cancer. *Lung Cancer*, 2002, 37: 281-285.