INVASIVE STAGING OF THE MEDIASTINUM*

W. De Wever, J. Coolen, J. Verschakelen

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), 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.

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

1. Department of Radiology, University Hospitals Leuven, Belgium.
mediastinoscopy is the most commonly used. More recently, video-
mediastinoscopy is introduced (8). Other modified techniques are medi-
astinal lymphadenectomy through a cervicotomy approach (VAMLA), video-assisted mediastinoscopic lymphadenectomy (6) - TEMLA, trans-
cervical - 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 supra-
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Table II. — Access to different lymph nodes with different staging techniques.

<table>
<thead>
<tr>
<th>Technique</th>
<th>LN stations</th>
<th>2R</th>
<th>2L</th>
<th>4R</th>
<th>4L</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8-9</th>
<th>10</th>
<th>11</th>
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<tbody>
<tr>
<td>Cervical mediastinoscopy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUS-FNA</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EBUS-TBNA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>VATS left</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>


cent retrospective analysis of the two techniques revealed a lower in-
cidence 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 mediastinosco-
py (86-93%) over the conventional version (81%) (8).

Transbronchial 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 mini-

Surgical staging

The potential limitation of mediasti-
nal lymph node staging with TBNA is the blind character of this technique. Numerous papers confirm the safety of the procedure. The rare complica-
tions reported are: pneumothorax, pneumomediastinum, haemomedi-
astinum, bacteremia and pericardi-
tis. One of the major complications of TBNA is the possible severe dam-
age 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 proce-
dure is performed under local anaes-
thetic and conscious sedation. EUS
and endo-oesophageal ultrasound with fine needle aspiration (EUS-
FNA) are safe, simple and highly ac-
curate in detecting and confirming nodal metastases and have been in-
creasingly used for staging of poten-
tially resectable NSCLC. EUS can vi-
sualise 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 metasta-
ses if abnormalities are found with non-invasive imaging techniques. Morbidity from this technique is almost nil 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 indic-
ating possible malignancy are hypo-
echoic 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 convention-
al 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

endothelial cells that are said to have a common precursor in the mesenchyme (18, 19) and there is evidence that they can form similar structures in vitro (20) and in vivo in congenital malformations (21). The potential role of these cells in vascular development is thus currently under investigation.
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 induction chemotherapy 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


