Invasive Staging of Mediastinal Lymph Nodes: Mediastinoscopy and Remediastinoscopy

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KEYWORDS

• Lung cancer staging • Mediastinal lymph nodes
• Mediastinoscopy • Remediastinoscopy

Confirmation of nodal status in lung cancer is essential for planning treatment and assessing prognosis. Nodal involvement is associated with poor prognosis. This is especially true for ipsilateral and subcarinal nodal involvement (N2 disease) and for contralateral hilar, mediastinal, and contralateral and ipsilateral supraclavicular nodal involvement (N3 disease). For clinically staged non–small cell lung cancer, 5-year survival rates for N2 and N3 disease are 16% and 7%, respectively. Those for pathologically staged tumors are 22% and 6%, respectively.[1] As for small cell lung cancer, the corresponding rates for clinically staged N2 and N3 tumors are 12% and 9%, respectively,[2] and 6% and 0% for pathologically staged tumors, respectively.[3]

Treatment failures after complete resection of stage III tumors are mainly caused by distant metastasis or by a combination of distant metastasis and locoregional recurrence.[4] To improve survival by controlling subclinical distant metastases, multimodality treatment protocols, including induction chemotherapy followed by lung resection, were introduced in clinical practice. The results of the first published reports showing that induction chemotherapy followed by lung resection was associated with significantly better survival than resection alone[5,6] have been recently confirmed by a meta-analysis of 13 randomized clinical trials: the hazard ratio for those patients with stage III tumors who received combined therapy was 0.84 (confidence interval, 0.75–0.95).[7] It was generally agreed that the administration of induction therapy had to be based on pathologic evidence of nodal disease, either by transbronchial needle aspiration, by transparietal needle aspiration, or by mediastinoscopy, by far the most used procedure.

More than a decade later, two clinical trials tried to establish the role of resection after induction chemotherapy[8] or chemoradiotherapy[9] for pathologically proved stage III-N2 non–small cell lung cancer. The results of these trials showed that resection did not add any benefit to the whole group of patients. However, subgroup analyses in both trials showed that 5-year survival rates for patients with tumors that had been downstaged from clinical N2 to either pathologic N0 or N1 after induction were significantly higher than those for patients with tumors with persistent mediastinal nodal disease. In one of the studies, 5-year survival rates for pathologic N0-1 and N2 tumors, and for incompletely resected tumors, either with microscopic (R1) or macroscopic (R2) residual disease, were 29%, 7%, and 7% (P = .001), respectively.[8] In the other study, 5-year survival rates for pathologic N0, N1–3, and unresectable tumors were 41%, 24%, and 8% (P = .0001),

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respectively.[9] These results showed that resection after induction chemotherapy or chemoradiotherapy cannot be performed indiscriminately. Some selection after induction therapy is necessary, especially the identification of those patients whose tumors have been downstaged from clinical N2 to N0 or N1, because these patients are most likely to benefit from tumor resection. Restaging of these tumors after induction is essential to determine objective tumor response and downstaging. The same methods used for staging can be applied at restaging,[10] but only those providing cytologic or pathologic proof of tumor response and downstaging are reliable enough to make further therapeutic decisions.

In the past decade, less invasive procedures, such as endobronchial ultrasound-guided fine-needle aspiration (EBUS-FNA)[11] and esophageal ultrasound-guided FNA (EUS-FNA)[12] have been progressively introduced in clinical practice. However, more thorough mediastinal explorations have been developed with the objective to remove the upper mediastinal nodes: video-assisted mediastinoscopic lymphadenectomy[13,14] and transcervical extended mediastinal lymphadenectomy.[15] These procedures are described elsewhere in this issue.

Currently, mediastinoscopy and remediastinoscopy must be thoughtfully integrated in clinical practice with all the other procedures that provide cytohistologic evidence of nodal status. They still have an important role in the invasive staging of mediastinal lymph nodes not only in patients with lung cancer, but also in those with mesothelioma and with potentially resectable lung metastases with radiologic or metabolic evidence of mediastinal nodal disease.

MEDIASTINOSCOPY

Historical Note

Mediastinoscopy was first described by Carlens in 1959.[16] Carlens had started mediastinoscopy in 1957 and had performed over 100 procedures without complications by the time he wrote his report. He described the technique and six cases as examples. In cases of suspected or diagnosed lung cancer, he indicated mediastinoscopy if the carina was fixed at rigid bronchoscopy or there was mediastinal widening on chest radiographs. Positive nodes at mediastinoscopy precluded resection. He duly acknowledged his predecessors, Daniels, Harken, and Radner, who also had tried to diagnose intrathoracic diseases without relying to thoracotomy. Daniels described the biopsy of scalene lymph nodes, which could be involved by the same intrathoracic disease and thus avoid exploratory thoracotomy.[17] Harken and colleagues[18] took advantage of the supraclavicular incision used by Daniels to insert a laryngoscope and perform a rudimentary unilateral mediastinoscopy. Radner[19] favored a suprasternal incision to reach paratracheal lymph nodes on both sides. Two of the six cases described by Carlens were for benign diseases: tracheal narrowing and paratracheal cyst. In one of the reported cases, diagnosis of lung cancer was obtained at mediastinoscopy, because there were no endobronchial lesions to biopsy. Carlens already pointed out the advantages of mediastinoscopy, not only as a staging procedure, but also as a diagnostic one for lung cancer and for other mediastinal diseases, such as lymphoma, lymph node metastasis from gastric and breast cancer, amyloidosis of the tracheal wall, and benign tracheal tumors. Reading Carlen's report more than half a century after publication gives the reader the impression of a very timely article and not of an outdated historical relic.

Indications and Contraindications

The European Society of Thoracic Surgeons (ESTS) has published guidelines on preoperative mediastinal staging in lung cancer that consider the computed tomography (CT) and the positron emission tomography (PET) or integrated PET-CT scans as leading imaging techniques in the staging process.[20] Any abnormality suggestive of N2 or N3 disease on CT has to undergo biopsy. Mediastinoscopy is the procedure of choice, but EBUS-FNA and EUS-FNA can provide cytologic confirmation that may be enough to start a multidisciplinary treatment protocol or to exclude resection. However, if these endoscopic procedures are negative, mediastinoscopy is still recommended, because the negative predictive value of EBUS-FNA and EUS-FNA is low. When there is no mediastinal abnormality on CT and the tumor is a peripheral T1N0M0 squamous cell carcinoma, mediastinal exploration can be avoided. However, in T1N0M0 tumors of other histologic types or more advanced tumors, mediastinoscopy is recommended. If the leading imaging technique is PET or PET-CT, any abnormal uptake suggestive of mediastinal nodal disease should undergo biopsy by mediastinoscopy or by endoscopic techniques, but if the latter are negative, a confirmatory mediastinoscopy is indicated. When there is no abnormal mediastinal uptake, exploration with mediastinoscopy is still indicated when there are signs of N1 disease, in central tumors, in tumors with low standardized uptake value, and in tumors with mediastinal nodes larger than 1.6 cm in the shortest diameter. In a recent prospective validation, sensitivity, specificity, and