Disciplined Practice and Improving Clinical and Pathologic Staging for Non-Small Cell Lung Cancer

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Clinical staging techniques for non-small cell lung cancer (NSCLC) are commonly used to evaluate the patient for resection, and are based upon anatomic characteristics as a surrogate for biological aggressiveness and survival. The clinician defines the clinical stage—the best and final estimate of the extent of disease before the initiation of definitive therapy—for treatment recommendations [1]. Despite significant improvements in preoperative clinical and invasive staging, occult N2 disease—metastasis to the mediastinal lymph nodes—continues to be identified. Intraoperatively, a systematic node dissection (SND), an integral component of every operation for NSCLC, provides otherwise unachievable pathologic staging information to guide subsequent treatment recommendations [2, 3].

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In this issue of The Annals, Obiols and colleagues [4] present their results of patients with occult N2 disease using a standardized clinical staging protocol and resection with SND. Patients with histologically confirmed N2 disease by mediastinoscopy were excluded from subsequent analysis. The investigators used the European Society of Thoracic Surgeons (ESTS) guidelines for clinical staging [5]. Endobronchial ultrasonography (EBUS) was not available during this study period; invasive staging was with cervical mediastinoscopy. Approximately 75% of their patients underwent invasive staging before resection, and 25% proceeded directly to resection without invasive staging. Obiols and colleagues [4] demonstrated a better than expected 3-year and 5-year survival of patients with occult N2 disease after their preoperative staging algorithm and resection with SND: 3-year and 5-year survival was 79% and 40%, respectively, for patients with resected occult N2 disease, compared with international 5-year survival norms of 24% for pStage IIIA NSCLC [6]. Even with a structured preoperative staging strategy including mediastinoscopy, 5.5% of these patients had unsuspected N2 disease. Patients, who proceeded directly to surgery based on a negative clinical staging result, had a false negative rate of 7.5%, whereas patients who had previous invasive clinical staging of the mediastinum had a false negative rate of 5%.

Should every patient have invasive staging of the mediastinum? Use of guidelines can direct patients with specific characteristics (suspicious mediastinal lymph nodes, clinical N1, central tumors, and so forth) toward invasive staging. In this study, there was only a small difference between the direct-to-surgery group and the surgically staged mediastinum group (7.5% and 5% false negative N2 rate, respectively). Selective mediastinoscopy seemed to be an effective strategy in this population, although only a minority of patients (25%) proceeded directly to resection without invasive surgical staging. Ancillary studies, including [18F]fluorodeoxyglucose positron emission tomography, performed relatively well in the noninvasively staged population (false negative rate 7.5%). With such a low number of false negative patients, should SND be abandoned or only limited to more advanced clinical stages? No—optimizing pathologic staging even for early stage disease limits stage migration and most accurately guides subsequent treatment recommendations [7].

Most patients with occult N2 disease were subsequently found to have only one lymph node station positive (typically, level 7 or 4R). Although many of these patients had clinical early stage disease, a SND was still performed and provided significant nodal tissue for analysis. It is interesting that for the 8 patients with 2 or more mediastinal lymph nodes, the 5-year survival was 0%. Granted, this is a small number of patients, but implies a greater negative impact on survival of patients with 2 or more mediastinal lymph nodes—even with complete resection. All patients in this study with pathologically staged N2 disease had adjuvant chemotherapy as per current guidelines [8].

Endobronchial ultrasonography with transbronchial biopsy of the lymph nodes has more recently been applied as the initial invasive staging modality for patients with suspicious mediastinal lymph nodes; however, negative EBUS does not completely eliminate the need for cervical mediastinoscopy for patients with suspicious mediastinal lymph nodes nor does it limit the requirement for SND during the operation. In patients with a negative EBUS and suspicious lymph nodes by size, [18F]fluorodeoxyglucose avidity, or presence of clinical N1 disease, surgical staging of the mediastinum would still be appropriate [1]. Refinements in invasive staging such as EBUS will facilitate the invasive clinical staging of the mediastinum, thereby improving treatment recommendations.

In contrast to many practices of general thoracic surgery in the United States, these patients were treated with an open thoracotomy rather than with a minimally invasive or video-assisted thoracic surgery (VATS) approach. Analyses of aggregate data for the extent of lymph nodes dissected for VATS compared with open
techniques describe more variability in the number of lymph nodes resected with VATS (typically fewer) than with more traditional open techniques.

A recent single-institution study in *The Annals* evaluated the completeness of lymph node dissection or sampling for patients undergoing open lobectomy by open thoracotomy or VATS approach for clinical stage N0 NSCLC. Lee and colleagues [9] found that the open approach was superior to VATS in the mean number of nodes dissected and the number of patients upstaged from N0 to pathologic N1 or N2. They identified no survival differences between the two groups at 3 years, but expressed concern regarding the adequacy of lymph node dissection during VATS lobectomy [9].

A single-institution, propensity-matched study of VATS and open procedure for patients undergoing lobectomy for NSCLC demonstrated more nodes (14.3 versus 11.3; \( p = 0.001 \) and more nodal stations (3.8 versus 3.1; \( p < 0.001 \)) removed by open techniques compared with VATS. More than 90% of patients had clinical stage I disease. Although VATS was not inferior to open procedures with respect to overall and disease-free survival, the researchers recommended that open procedures may be more appropriate for patients with more advanced clinical disease [10].

In another single-institution study for clinical stage I patients, VATS approaches had fewer total number of lymph nodes dissected compared with open lobectomy, and fewer N2 nodes as well. Although no survival difference was identified between the two groups, the investigators recommended “more focused lymph node sampling with VATS lobectomy” [11].

A broader evaluation of lymph node dissection was examined from The Society of Thoracic Surgeons general thoracic surgery database of more than 11,500 clinical stage I NSCLC patients undergoing operation [12]. Patients undergoing an open approach were identified as having more occult nodal metastases than patients undergoing VATS. Patients with an open approach had a statistically significant N1 nodal upstaging, but no significant difference in upstaging from N0 to N2 metastasis, suggesting more variability in hilar and peribronchial dissection with a VATS approach.

Data from the National Comprehensive Cancer Network’s NSCLC database were analyzed for 388 patients who underwent lobectomy (199 VATS and 189 open). It was found that open and VATS approaches were generally similar in the percentage of patients who had at least three N2 stations examined, the number of N2 LN stations, and the total number of N1+ N2 lymph nodes (although the median number was only four in both groups) [13].

Even with clinical early stage NSCLC, a SND facilitates pathologic staging, and may have a clinical benefit by reducing the variability of pathologic staging. Analysis of surgically treated NSCLC patients from the National Cancer Database found that pStage I NSCLC patients were best treated when a minimum of 10 lymph nodes were resected at the time of any lung resection [14]. Patients with fewer than 10 lymph nodes removed had poorer survival (hazard ratio 1.21, 95% confidence interval: 1.18 to 1.25) compared with patients who had 10 or more lymph nodes removed. Of interest is that 35% of patients had only four or fewer lymph nodes removed. Based on these data, the Commission on Cancer is evaluating the following quality measure: “A total of at least 10 lymph nodes are removed and pathologically examined for resected NSCLC (pathologic stage IA, IB, IIA, and IIB).”

The ACOSOG Z0030 trial (“Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 [less than hilar] non-small cell carcinoma”) prospectively evaluated the therapeutic advantage of lymph node dissection (LND) compared with lymph node sampling (LNS) in patients with early stage disease. The study showed resection was safe [15], and demonstrated no difference in survival for patients with clinical early stage NSCLC with LND, compared with patients who underwent LNS [16]. The rate of occult N2 disease was 4% for patients with a negative LNS, and who were randomly assigned to LND. The ACOSOG Z0030 study had a structured protocol for clinical staging, LNS, and LND. Despite no therapeutic survival advantage in the LND group, the researchers emphasized the value of LND to optimize pathologic staging in a patient with lung cancer. The choice of approach, either open or VATS, does not change the need for LND even in patients with early stage NSCLC. Both open and VATS procedures were effective in achieving the fundamentals of the operation, including complete local control and lymph node dissection. These investigators observed that a median of 6 or more lymph nodes were obtained from at least three separate mediastinal stations in 99% of patients [17]. They recommended that mediastinal lymphadenectomy should include stations 2R, 4R, 7, 8, and 9 for right-sided cancers; and stations 4L, 5, 6, 7, 8, and 9 for left-sided cancers [17]. Future prospective clinical trials to evaluate anatomic staging and its relationship to procedure outcome, and patient survival, may be a lower priority than therapeutic trials, particularly with the explosion of molecular characterization of individual lung cancers. Larger population studies to compare the outcomes of patients with SNB by open and VATS techniques are needed.

The quality and extent of lymph node dissection is at the discretion of the surgeon. A systematic process for examination and dissection of specific ipsilateral nodal stations is expected. The determination of number of lymph nodes versus number of lymph node fragments will be at the discretion of the pathologist. The volume (or weight) of lymph nodes resected has not been clearly associated with the veracity of pathologic staging. It is incumbent upon the surgeon to optimize intrathoracic staging by a structured dissection of the hilar and mediastinal nodal stations and removal of all accessible nodal tissues.

In summary, patients with NSCLC should undergo a structured preoperative clinical staging evaluation including surgical evaluation of the mediastinum where indicated to ensure optimal initial treatment
recommendations, and complete resection of the tumor and a systematic node dissection to ensure the most accurate pathologic stage [18]. Guidelines from the National Comprehensive Cancer Network [19], the ESTS [20], and the American College of Chest Physicians [1] are pragmatic and outline a systematic approach to staging for the thoracic surgeon. Although the incidence of occult N2 is low (4% to 5.5%) in recent studies, complete resection in patients with clinical N0 and subsequently pathologic occult N2 is associated with better than expected survival. Is this related to a therapeutic effect from the SND or from improved pathologic staging? I cannot completely answer these questions from this manuscript—however, these patients were optimally selected, had the most limited N2 disease burden possible, and had a structured approach to both clinical staging and intraoperative lymph node dissection. Surgeons should not hesitate to proceed with resection to achieve optimal local control in these patients. A systematic lymph node dissection is a fundamental component of these procedures.

References