Editorial Commentary

Lung cancer staging: accuracy is critical

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Complete and accurate staging for patients diagnosed with lung cancer to assess the extent of disease is of critical importance so that appropriate treatment recommendations may be provided (1). An incorrect clinical staging classification can lead to wrong decisions on withholding potentially curative resection as well as inappropriate nonsurgical definitive therapy and palliative treatment options. In their study, Navani and colleagues analyzed the accuracy of clinical staging for stage I–IIIa non-small cell lung cancer (NSCLC) (2).

Navani and coworkers employed individual participant data from a meta-analysis of randomized, controlled trials comparing preoperative chemotherapy (± radiotherapy) to surgery alone in NSCLC (2). They evaluated the concordance between the clinical TNM (cTNM) stage at randomization and pathologic TNM (pTNM) stage following surgery for patients in the surgery only group (control group). Nine studies were included in the analysis with the study accrual periods ranging from 1987 to 2005. There was a low amount of agreement between cTNM and pTNM staging at 52% (weighted Cohen's κ =0.35). Clinical understaging occurred in 34% of cases and in clinical overstaging occurred in 14% of cases. Clinical staging failed to detect nodal involvement in 19% of cases while 12% of patients were erroneously concluded to have node-positive disease. Survival varied with the accuracy of cTNM staging. A worse survival was noted in clinically understaged patients as compared to patients that were correctly staged or clinically overstaged. However, this result was driven by the underlying pTNM stage; 44% of patients classified as cTNM stage I were found on pathologic staging to be stage II–IV, and 33% of patients classified as cTNM stage II were found on pathologic staging to be stage III–IV, thus accounting for their lower survival.

While the study by Navani and colleagues was well done, the results are not surprising and do not provide additional information to the understanding of the current performance of NSCLC staging methodologies. Of the 9 included studies in their analysis, one study used chest radiography (3), one study used chest computed tomography (CT) and positron emission tomography (PET) imaging (4), and 2 studies used chest CT plus abdominal ultrasound (5,6) while the other studies used chest CT alone as the imaging modalities for staging (7-11). In the study that did use PET imaging, PET scanning was not routinely used during the study period and only 67 of the 261 patients underwent PET scan as a part of their staging (2). Navani and coworkers note that two of the included trials in the analysis used mediastinoscopy as part of the staging protocol. In the study by Gilligan and colleagues, however, the authors note that most patients were staged by bronchoscopy and chest CT since mediastinoscopy and PET scan were not standard practice in the United Kingdom at the time of the trials' inception (4). The study by Splinter and coworkers is reported in abstract form so it is unknown how systematically mediastinoscopy was performed (8). In the studies by Gilligan (4), Wu (5), and Yang (6), bronchoscopy was used as part of the staging process however the type of bronchoscopic staging was not specified in these studies and all of these studies predated

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the use of endobronchial ultrasound.

Thus, the methods used by the studies included in the analysis by Navani and colleagues overall do not reflect current NSCLC staging guidelines and practices. In the section on methods for staging NSCLC, as part of the third edition of the American College of Chest Physicians (ACCP) lung cancer guidelines, the summary median positive predictive value (PPV) for mediastinal staging by chest CT was for all studies was noted to be 58% and the median negative predictive value (NPV) was noted to be 83% (12). Chest CT, therefore, is clearly not an ideal means to stage the mediastinum. As mentioned, it is unclear what type of bronchoscopy was performed in the three studies included in the analysis. One could assume that bronchoscopy with standard blind transbronchial needle aspiration (TBNA) was performed as part of the bronchoscopic staging. Blind TBNA was noted to have an overall median sensitivity of 78% and NPV of 77% in the third edition ACCP lung cancer guidelines. Bronchoscopy with blind TBNA has a significant false negative rate. As a consequence, the vast majority of patients in the included studies were staged with modalities that have significant false positives and false negatives. That a significant number of patients were overstaged and understaged in the analysis by Navani and coworkers is therefore not surprising.

PET-CT is now routinely recommended in the staging of NSCLC (1,12). PET and PET-CT does better than chest CT in staging the mediastinum with a median PPV of 75% and a median NPV of 91% for PET and a median PPV of 63% and a median NPV of 90% for PET-CT noted in the third edition ACCP lung cancer guidelines (12). PET scanning also offers information with regards to extrathoracic staging. Overall, in randomized, controlled trials of PET scanning, distant or N2,3 nodal metastases are correctly detected in about 20% more patients compared with conventional staging (13-15). Two randomized controlled trials of PET scanning found a reduction in the number of noncurative resections, defined as the presence of benign disease, unsuspected N2 involvement, unresectable disease, recurrence, or death from any cause within 1 year, from approximately 40% to 20% (14,15). No difference in the thoracotomy rates or the development of metastatic disease was noted in one study, but the majority of patients in this study had stage I disease and there were very few patients with N2,3 or distant metastases in either arm (13). Confirmation of PET scan findings is important, however, because of the risk of incorrectly upstaging a patient PET and denying the patient a potentially curative resection. In the randomized, controlled trials involving PET scans, this scenario could have happened in 5% to 42% of patients, however, the requirement for a definitive validation of a suspicious PET scan finding in these studies prevented this (12).

For patients with discrete mediastinal lymph node enlargement, with or without PET uptake, that do not have distant metastases, invasive staging of the mediastinum is recommended over staging by imaging alone per ACCP, European Society of Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) guidelines (1,12,16). Invasive mediastinal staging is also recommended for patients with PET activity in mediastinal lymph nodes but normal appearing nodes by CT and no distant metastases. In patients with a central tumor or N1 lymph node enlargement, who are at increased risk of N2,3 nodal involvement, but have a normal mediastinum by CT and PET scans and no evidence of distant metastases, invasive staging of the mediastinum is recommended over staging by imaging alone (12,16). For invasive mediastinal staging, patients may undergo EBUS, endoscopic ultrasound (EUS), combined EBUS-EUS, or mediastinoscopy. In the third edition of the ACCP lung cancer guidelines, the median NPV for EBUS-TBNA and mediastinoscopy were observed to be very similar so a needle biopsy technique such as EBUS, EUS, or combined EBUS-EUS was recommended as the initial invasive mediastinal staging procedure (12). The ESMO guidelines recommend EBUS/EUS if lymph nodes are abnormal on imaging and, if lymph nodes are normal on imaging but patient is at risk for N2,3 involvement, either EBUS/EUS or video-assisted mediastinoscopy depending on local expertise (16).

The correct staging of lung cancer is of critical importance. Determination of the proper stage leads to the correct treatment for the patient and the correct expected prognosis. As was seen in this study by Navani and colleagues, clinical understaging leads to an overestimate of survival. Patients that are overstaged may potentially be denied curative intent therapies. It is critical that physicians who are involved in the care of patients with lung cancer adhere to lung cancer staging guidelines and that, in general, imaging alone should not be used for mediastinal staging. Suspicious extrathoracic findings on PET scan without clear evidence of metastatic disease should be further evaluated in patients who are otherwise candidates for surgical resection.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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