Practical Implications Of The New Lung Cancer Staging System

Rodolfo E. Bordoni, MD

Definition of stage for any type of cancer is essential for treatment recommendations. The standard staging system for cancer in general has three components, called TNM. T refers to tumor size and extension; N to the extent of regional lymph node involvement and M describes the extent of spread to distant sites. In lung cancer, clinical stage is determined by the use of multiple diagnostic test including chest XR, CT scans, PET scan and MRI, and pathological stage by invasive procedures including biopsies (obtained by bronchoscopy, mediastinoscopy, or trans-thoracic needle biopsy) and surgery (thoracotomy or more recently, video-assisted thoracic surgery (VATS). The method of staging, clinical or pathological, has major implications in treatment and prognosis.

The initial TNM staging system for lung cancer, based heavily on intuition, only 2,155 patients, all from one institution, and treated almost exclusively with surgery, was first adopted by the American Joint Commission on Cancer (AJCC) in 1973 and by the Union Internationale Contre le Cancer (UICC) in 1974. The staging system was first revised in 1997, also based on a limited number of patients (5,319), from a single institution, and treated over a long period of time. The new 2009 staging revision is the product of an extensive initiative by the International Association for the Study of Lung Cancer (IASLC), involving a database of 100,869 patients (81,015 included in the final data set), spanned a short time frame (1990 to 2000), included patients from very different backgrounds (Europe 58%, USA 21%, Asia 14%, Australia 7%), and backed by careful patient outcome validation and statistical analysis. Most of the cases accounted for non-small cell lung cancer (NSCLC) (84%) and only 16% were identified as small cell type (SCLC). Only the NSCLC cases were used for the new lung cancer staging system. Treatment involved surgery, radiotherapy, chemotherapy, or a combination of the above, making this new staging system much more comprehensive than the prior two. The new system based its recommendations on patient survival, based on best stage. The revisions were internally and externally validated (against the Surveillance, Epidemiology and End Results (SEER) database), matching the data by time period, histology, gender, age, and region.

T descriptor: For T (tumor size and extension), both classifications separate tumors in T1, T2, T3 and T4. In the old system, T1 tumors were defined as ≤ 3 cm. The new staging system separates lesions in T1a (≤ 2 cm) and T1b (>2 to 3 cm). This sub-division of T1 tumors is based in significant survival difference between sub-groups (5-y survival 53% and 77% for cT1a and pT1a, respectively, and 47% and 71% for cT1b and pT1b, respectively); however**, this change in T1 tumors nomenclature does not imply any difference in treatment, compared with the old system. All T1 tumors are staged as stage IA and are treated with surgery only**, except if the patient is not fitted to tolerate optimal surgery, in which case most of these patients are offered definitive radiation therapy, in the form of external beam or stereotactic body radiation therapy *(CyberKnife).* In the old system, T2 tumors were defined as > 3 cm, or involving main bronchus, ≥ 2 cm distal to the

carina, or invading visceral pleura. In the new system, tumors > 3 cm and up to 5 cm are classified as T2a, while tumors > 5 cm and up to 7 cm are called T2b. As before, the distinction is based on significant survival differences (5-y survival 43% and 58% for cT2a and pT2a, respectively, and 36% and 49% for cT2b and pT2b, respectively). **Tumors > 3 cm and up to 5 cm (T2a) are staged as stage IB, and treated as per the old system with surgery alone, except if evidence of poor prognostic indicators** (> 4 cm in size, poorly differentiated histology or angio-lymphatic invasion), in which case patients in good PS are offered four cycles of cisplatinum-based adjuvant chemotherapy. For patients with tumor size > 5 cm and up to 7cm (T2b) the stage changes from IB in the old system to IIA in the new classification, reflecting the impact on survival of tumor size, ignored by the old staging system. **As in the old classification, all patients with stage IIA (T2b disease) are offered surgery followed by adjuvant cisplatinum-based chemotherapy.** T3 tumors were not defined by size in the old system, but by their extension: direct invasion of the chest wall, diaphragm, or pericardium, or involving the main bronchus, < 2 cm distal to the carina. In the new system, a T3 tumor is still defined by its extension but also includes a size definition (> 7 cm). In the old system, a tumor > 7 cm was called T2 and staged as IB, while now is called T3 and staged as IIB. **This change is stage in the new classification, does not imply a different treatment approach; as in the past, tumors > 7 cm in size are treated with surgery, if resectable and operable, followed by adjuvant cisplatinum-based chemotherapy.** In addition, T3 tumors are now classified as $T3_{Inv}$ or $T3_{Centr}$, just to help understand their anatomic characteristics ($T3_{Inv}$ (by invasion): directly invading chest wall, diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium, and $T3_{Centr}$ (central location): tumor in the main bronchus <2 cm distal to the carina, or atelectasis/obstructive pneumonitis of entire lung). The new addition to the T3 "family" is the so-called $T3_{Satell}$ (additional nodule in the same lobe), called T4 in the old system. Patients with $T3_{Satell}$ are now staged as stage IIB, as opposed to stage IIIB in the old system. The change in nomenclature is based on significant better survival than thought for patients diagnosed with an additional nodule in the same lobe (5-y survival 29% and 28% for $cT3_{Satell}$ and $pT3_{Satell}$, respectively) than T4 disease, as defined in the new classification (5-y survival 14-25% and 22% for cT4 and pT4, respectively). **The practical implication of the new staging system is that patients with stage IIB disease, defined by the presence of $T3_{Satell}$, may now be offered surgery (lobectomy) with curative attempt, if the disease is considered resectable and the patient operable, followed by adjuvant cisplatinum-based chemotherapy.** T4 was defined in the old staging as invasion of the mediatinum, heart, great vessels, trachea, esophagus, vertebral bodies, carina, or separate tumor nodules in the same lung lobe, or tumor with malignant pleural effusion. In the new classification, the first part of the above definition applies to the current sub-type $T4_{Inv}$ (by invasion), with no therapeutic implications; most of these patients will have stage III disease and will be offered definitive, combined modality, concurrent chemotherapy and radiation. Separate tumor nodule/s in the same lung lobe are now called $T3_{Satell}$ and staged as stage IIB, as opposed to stage IIIB in the old system, with therapeutic implications as explained above. On the other end of the spectrum, patients with malignant pleural effusion, classified as T4 in the past, are now called M1a, again based on survival more consistent with metastatic disease (see below). Finally, a new sub-group called $T4_{Ipsi\ Nod}$ (additional nodule in a different ipsilateral lobe) was created. This is a departure from the old nomenclature that called additional nodules in different lobes M1 or metastatic disease. The new nomenclature better describes the patient's condition and separate groups with different prognosis (5-y survival 14% for $cT4_{Inv}$ and 22% for $cT4_{Ipsil\ Nod}$). **The new staging**

have therapeutic implications for patients with excellent clinical and pulmonary status, that may be considered for at front surgery (pneumonectomy) with curative intent, if $T4_{Ipsi\ Nod}$. Interestingly, if these patients are offered surgery, their prognosis equalizes (5-y survival for $pT4_{Inv}$ and $pT4_{Ipsi\ Nod}$ is 22%). In contrast, clinically staged patients with malignant pleural effusion, considered as T4 in the old staging system, are considered now as M1a, due to the statistically worse survival than T4 disease (5-y survival 2%) and comparable with metastatic disease (5-y survival 1% if distant metastasis and 2% if contralateral nodule). **This stage migration does not have therapeutic implications; these patients are all offered systemic therapy, if in good general conditions and good organ function.**

N descriptor: For N (extent of regional lymph node involvement) both classifications separate nodes in N0 thru N3. Analysis of the prognostic influence of the N descriptor supported the old categorization of N0, N1, N2, and N3, as recognized in the past by the old, 1997 staging system. Therefore, no changes were made in the in the N descriptor as defined by the old classification.

M descriptor: For M (extent of spread to distant sites), the old staging system recognizes two categories: Mo or no distant metastasis and M1 to characterize the presence of distant metastasis. The new classification separates M1 disease into M1a to define separate tumor nodules in a contralateral lobe, from M1b, which is the equivalent of M1 disease (distant metastasis) in the old classification. This distinction is based on a significant survival difference ($p<0.0001$) between M1a (contralateral nodule) and M1b (distant metastasis) with a 5-y survival of 3% and 1%, respectively. **Other than the prognostic significance, the distinction between M1a and M1b does not have, in general, any treatment implication. Patients with stage IV disease, M1a or M1b, are offered systemic therapy (chemotherapy, targeted therapy or a combination of both), if in good performance status.** Surgery or radiation therapy still applies to cases of oligo-metastatic disease or as palliation of symptoms, respectively.

In summary, the main implications of the new staging system are prognostic (e.g.; distinction of T1 tumors into T1a and T1b –all patients are offered surgery alone; distinction of T2 tumors into T2a and T2b, and stage "migration" of T2b disease up into stage IIA, as opposed to IB –all patients are offered surgery and only those with poor prognostic factors are followed with chemotherapy; upstaging of tumors > 7 cm from T2 into T3 and from stage IB to stage IIB –all patients are offered surgery, if resectable and operable, and adjuvant chemotherapy; presence of malignant pleural effusion, classified as T4 in the past, is now called M1a –all patients are considered for systemic therapy, if in good PS). However, in a few instances the new system may have therapeutic implications, including:

1. **$T3_{Satell}$** is now staged as stage IIB, as opposed to stage IIIB, and these patients may now be offered surgery (lobectomy) with curative attempt, if the disease is considered resectable and the patient operable
2. **$T4_{Ipsi\ Nod}$** is now staged as stage IIIA, as opposed to stage IV, and selected patients with excellent clinical and pulmonary status may now be offered at front surgery (pneumonectomy) with curative attempt.

Rodolfo E. Bordoni, MD

Chairman, Research and Therapeutics

Georgia Cancer Specialists

Chairman, Department of Medicine

WellStar Kennestone Hospital

Atlanta, Georgia

Rodolfo E. Bordoni, MD serves as chairman of the Research and Therapeutics Committee for Georgia Cancer Specialists. Dr Bordoni received his medical degree from the National University of Rosario in Argentina. He then completed his medical residency in internal medicine at the British Hospital and Medical Center in Rosario, Argentina followed by a clinical fellowship in hematology and oncology at Emory University in Atlanta. Dr Bordoni serves as an advisor for professional education at the Georgia Cancer Foundation, founder and chairman of the Annual Atlanta Lung Cancer Symposium, and host of the Georgia Cancer Foundation Monthly Professional Education Program "Meet the Professor." Dr Bordoni is a member of the board of directors for Georgia Center for Oncology Research and Education and chairman of the Georgia Lung Cancer Working Group. In addition, he is a member of the Cobb County Medical Society, the American College of Physicians, the Georgia Society of Clinical Oncology, the Medical Association of Georgia, and the American Federation for Clinical Research. Dr Bordoni has published numerous peer-reviewed research articles and has lectured nationally and internationally.