Inclusion of Lymphangitis as a Descriptor in the New TNM Staging of Lung Cancer

Filling Up the Blank Spaces

To the Editor:

We were excited to read the recent article containing the proposals related to T descriptors for the 8th edition of TNM staging of lung cancer.1 The previous International Association for the Study of Lung Cancer (IASLC) staging project that led to the implementation of the 7th edition has had phenomenal implications for clinical practice, and the same is likely for the 8th edition as well.

Since its first description approximately 200 years ago, lymphangitis carcinomatosis has been realized as a marker of disseminated disease and thus of poor survival.2 The spread of tumor cells to the pulmonary lymphatic system results in thickening of the bronchovascular bundles and septa. The interstitial thickening is also contributed by desmoplastic reaction because of proliferation of neoplastic cells and lymphatic dilation by edema fluid or tumor secretions. Spread of the neoplasm outside the interstitium and lymphatic spaces into the adjacent parenchyma results in a nodular pattern.2

The radiological extent of distribution of nodules (confined to primary tumor lobe [categorized as T3], present in other ipsilateral lobes [categorized as T4], and present in the contralateral lung [categorized as M1a]) has shown to correlate with overall survival.4 Categorization of nodules was one of the prominent changes between the 6th and 7th TNM editions because the IASLC staging project had shown that presence of nodules in the primary tumor lobe and in other nonprimary ipsilateral lobes had survival similar to other T3 and T4 descriptors, respectively, leading these to be downstaged from T4 and M1 in the 6th edition to T3 and T4, respectively, in the 7th edition.

We understand that the extent of lymphangitis was thought to be of prognostic significance, as it was listed as an optional descriptor (cLy) in the 7th TNM with a grading from 0 to 4 (in a way somewhat analogous to presence of nodules).5

The proposed categorization was as follows:

- cLy0: no radiological evidence of lymphangitis
- cLy1: lymphangitis confined to the area around the primary tumor
- cLy2: lymphangitis at a distance from the primary tumor but confined to the lobe of the primary
- cLy3: lymphangitis in other ipsilateral lobes
- cLy4: lymphangitis affecting the contralateral lung

Clinical features and radiological appearance of lymphangitis have been well characterized in general. However, we could not find mention of prognostic implications of lymphangitis carcinomatosis in the recent article containing proposals for the 8th edition. We are not aware whether this is planned to be incorporated in the proposals for M descriptors. Nonetheless, this is a radiological finding that we encounter quite often in clinical practice and is something that needs to be addressed. It would also be interesting to note whether survival data based on above described cLy categorization are comparable with that based on categorization of nodules.

We once again wish to congratulate the IASLC for undertaking the current staging project and sincerely hope that unclassified descriptors such as lymphangitis carcinomatosis and others find mention in subsequent TNM editions backed by robust data analysis as has been the case for other T and M descriptors.

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Reply to “Inclusion of Lymphangitis as a Descriptor in the New TNM Staging of Lung Cancer: Filling Up the Blank Spaces”

In Response:

The Letter to the Editor by Singh et al.1 called our attention to the fact that lymphangitic carcinomatosis had not been mentioned in the recently published article on the revised primary
tumor descriptors of the tumor, node and metastasis (TNM) classification of lung cancer. As the authors explained, before the 7th edition of the TNM classification, there was no specific code to describe lymphangitic carcinomatosis in the lung, which is mainly a situation found at clinical staging. To help register cases in a uniform way, the code cLy was proposed for prospective testing. This code is an optional descriptor that is not integrated in the T or the M components of the classification. Therefore, it has to be registered separately and added to the regular TNM. For example, a right upper lobe tumor invading the chest wall presenting with radiological signs of lymphangitis in the upper and middle lobes, but without nidal disease or distant metastasis, would be classified as cT3N0M0 cLy3.

In the International Association for the Study of Lung Cancer (IASLC) database, data on the cLy descriptor are scarce. This descriptor is available for patients registered prospectively through the electronic data capture system, only, and not for those registered retrospectively. In total, there were 69 patients with non-small-cell lung cancer (NSCLC) with some degree of lymphangitis: cLy1 33 (48%), cLy2 9 (13%), cLy3 14 (20%), and cLy4 13 (19%). Ten additional patients with small-cell lung cancer also presented with lymphangitis. Among patients with NSCLC, lymphangitis was more frequent in larger tumors (29 cT2, 9 cT3, and 27 cT4) than in earlier ones (3 cT1 and 1 cT0). The survival analysis of these patients does not clarify the prognostic impact of this descriptor as the estimated 1-year survival is approximately 41% for patients with cLy1, cLy2, and cLy4, with a paradoxically high 61% estimated 1-year survival for patients with cLy3. So, with these data, solid conclusions cannot be drawn. We certainly need this information on a larger number of patients to fully assess the prognostic relevance of the anatomical extent of lymphangitis. The IASLC database used for the revision of the 7th edition of the TNM classification is predominantly surgical, with 85% of registered patients having been treated surgically, either with surgery alone or in combination with chemotherapy and radiotherapy. This explains why there are so few patients with lung cancer and associated lymphangitis.

We thank Drs. Singh, Baldi, and Behera for their interest in the IASLC Lung Cancer Staging Project and for having pointed out the prognostic implications of lymphangitis. Only with larger and more detailed databases, we will be able to further refine and better understand its prognostic impact.

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Cryotherapy for Lung Metastases
A Justifiable Procedure?

To the Editor:
The report of 1-year results from the nonrandomized study “Evaluating cryoablation of metastatic lung tumors in patients-safety and efficacy: the ECLIPSE trial-interim analysis at 1-year” has shown that this technique is moderately efficacious in terms of local control of disease. But like so many similar reports of techniques for removal or ablation of pulmonary metastases, it is based on the uncertain premise that removing a few asymptomatic “oligometastases” improves patients’ survival.

The oligometastatic state is poorly defined and has no demonstrable basis in cancer biology or biostatistics. The term was first coined in 1995 but citations only began to increase in the 2000s. Writing in 2014 an interdisciplinary group of authors, including Weichselbaum, one of the originators of the term, suggested that there might be more wishful thinking than evidence. Although de Baere et al. believe that metastasectomy is “the standard of care,” the only evidence they cite is a registry of surgeons’ self-reported results from the 1945 to 1995. The recent literature on surgical metastasectomy is considerably more circumspect. There are no known randomized trials or other controlled studies to prove effectiveness. This is the reason for running the Pulmonary Metastasectomy in Colorectal Cancer (PulMiCC) randomized controlled trial now open internationally.

The practice of lung metastasectomy is very highly selective and targets those with one or very few metastases and longer intervals between primary resection and lung metastasectomy. These are inherently the longest living patients at the tail end of the survival distribution of metastatic cancer. Some are alive for 5 years with or without treatment. These patients, destined to survive without metastasectomy, are greatly over represented in the groups selected for surgery creating the illusion of effectiveness. In ECLIPSE, 75% of the patients had had a variety of prior treatments for metastases. By 12 months, 40% had developed new metastases, with a mean time to developing them of 10.7 months, but none had died of cancer. This suggests that these patients had widespread but slow growing subclinical metastatic disease and raises questions about the justification...