Prognosis and "granularity": Building on staging foundations?

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Harvey I. Pass, MD, a searcher of granules.

Central Message

The Lung Cancer Staging System is improved and validated, but the future may belong to those elements in addition to the usual TNM descriptors, including pathologic and molecular "granularity."

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Frank Detterbeck's Expert Opinion regarding[1] the changes and implementation of the 8th edition of the International Association for the Study of Lung Cancers (IASLC) Staging Classification is must reading for every thoracic surgeon. It is a wonderful overview of the difficulties, even with huge numbers of patients, of breaking up a seemingly homogeneous disease into defined heterogeneous categories, and the proof is in the pudding that you can take these homogeneous yet still heterogeneous amalgams and validate the results. Even with these validations, do we actually know that these prognostic characteristics are gratifyingly sensitive and specific or are they just averaging outcomes over a given cohort of patients?

One of the confounding, but futuristically "hopeful" elements that he mentions in his overview is the idea of "granularity" or how deep can you go with the discovery of independent, unrelated factors, all of which could be combined in a statistical model to predict outcome. Could nonstandard TNM "granules" add accuracy to prognostication? The present "granularity" of lung cancer staging, although much improved from the 1970s, is probably at the "Model T level," and we are just starting to realize, as did Giuliano and colleagues[2] for breast cancer, that lung cancer complexity is not just a forest, but a whole bunch of individual trees of different species. TNM histologic granularity has already been recognized by the IASLC adenocarcinoma classification system,[3] but further pathologic granularity will involve concerted recording of the size of the *solid* component within these adenocarcinomas. Which is more powerful: the size of solid or type of adenocarcinoma? "N" heterogeneity also needs to be addressed with regard to the influence of the number of N1 and N2 lymph nodes resected and prognosis, and this starts not only in the operating room but also at the pathology bench.[4]

However, lung cancer therapists, PhDs, pathologists, epidemiologists, molecular biologists, and informatics gurus are now confronted with so much potential "granularity" in lung cancer from the literature that it may be no longer acceptable to just rely on our old friends' TNM. Just take the individual histologic subtypes, for example. Beginning in 2012[5] and expanded with The Cancer Genome Atlas (TCGA),[6] lung adenocarcinoma could be reclassified by 3 transcriptional subtypes (terminal respiratory unit, proximal inflammatory, and proximal proliferative), 3 methylation subtypes (CpG island methylator phenotype: high, medium, or low), histologic subtype (solid, acinar, lepidic, papillary/micropapillary, mucinous, and other), or 6 integrated subtypes consisting of quantitative difference by copy number, DNA methylation, and messenger RNA expression. For squamous cell carcinoma, TCGA describes 4 molecular subtypes (classic, basal, secretory, and primitive), 4 methylation clusters, and 3 distinct integrative clusters.[7] To make it even more "granular," other investigators have combined the TCGA squamous and adenocarcinoma data to define 9 separate genomic subtypes for non–small cell lung cancer,[8] and others have been able to define prognosis solely on the basis of 25 immune-related genes.[9]

My head spins trying to "grade" these examples of granularity for clinical relevance right now…and so do the heads of the IASLC investigators who are in fact prospectively designing a prospective integrated clinical demographic, molecular, and histologic registry to supplement ongoing editions of the Lung Cancer Staging System. Nevertheless, staging moves forward to a day of integrated granules with the highest accuracy to forecast how our patients will do and treat them appropriately.

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