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NCCN Guidelines Panel: Non-small Cell Lung Cancer

Myriad Genetic Laboratories thanks the committee for the opportunity to submit information regarding high-risk factors considered when determining treatment with adjuvant chemotherapy for stage IB non-small cell adenocarcinoma.

The process for treatment determination in early-stage NSCLC patients is less than ideal. If operable, surgical resection is the standard treatment. However, in some patients, high risk factors such as tumor size and visceral-pleural involvement indicate consideration of more aggressive treatment. Version 4.2014 of the NCCN guidelines states, "Consider adjuvant chemotherapy for high-risk stages IB-II[l]". With the exception of tumor size, these high risk factors, while informative, are largely qualitative. Furthermore, their measurement is subjective, making standardization across locations difficult. RNA expression assays developed and validated in large patient cohorts now offer a quantitative, reproducible measure of lung cancer-specific and overall mortality risk in early-stage patients. The inclusion of such measures of tumor aggressiveness among the NCCN high-risk factors would improve risk assessment for these patients and thus aid treatment decisions for physicians.

Specific Changes: Recommend the Lung Cancer Guidelines Committee add results from molecular testing for tumor aggressiveness using independently validated RNA expression-based prognostic signatures to the list of high risk factors cited for consideration when determining treatment options for patients with stage IB lung adenocarcinoma (NCCN Guidelines Version 4.2014; non-small cell lung cancer, footnote l).

Rationale: Current guidelines state that adjuvant chemotherapy should be considered for stage IB (peripheral T2a, N0), stage I (central T1ab-T2a, N0), stage II (T1ab-2ab, N1; T2b, N0), and stage IIB (T3, N0) patients presenting with high-risk factors. The guidelines identify six high-risk factors as follows:

- poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors])
- vascular invasion
- wedge resection
- tumors >4 cm
- visceral pleural involvement

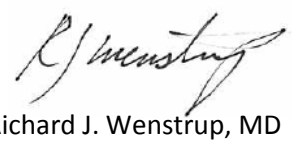
- incomplete lymph node sampling (Nx)

Tumor size, while quantitative, has failed to prove a reliable prognostic measure. Two studies that looked at the prognostic power of tumor size in IB patients disagree on the appropriate cut-off for high-risk designation. CALGB 9633, which failed to reach its primary endpoint, derived a 4 cm cutoff from a posthoc subgroup analysis.[1,2] The second study found significance (p=0.043) at a different value, 3.2 cm, in only a small cohort (n=119) of patients.[3] While size indicates cancer progression at the time of tumor resection, speed of cancer progression cannot be derived from size. This distinction may explain why tumor size is not highly prognostic, and why consideration of tumor aggressiveness provides better risk assessment.

In several independent, published studies[4-7] multivariate analysis revealed that RNA expression-based prognostic signatures were highly-predictive of mortality, while tumor size was not. In addition, these studies point to a large proportion of high-risk IB patients for whom chemotherapy would never be considered based on their tumor size alone. As an example, in one study,[5] a validated mathematical combination of an RNA expression-based measure with TNM stage, termed the "prognostic score", was used to assess mortality risk in IB patients (Appendix A). Prognostic score risk overlapped significantly in patients with large and small tumors, ranging from 21 to 43% and 17 to 43% for tumors above and below the 4cm cut-off, respectively. Thus, IB patients may presently be over or under treated and a molecular assay of tumor aggressiveness may greatly improve risk stratification among these patients.

In light of the subjective nature of some high-risk factors and the conflicting data on the cut-off for tumor size, physicians need additional means to assess risk and treatment options in this early stage patient population. New RNA expression-based prognostic signatures have been developed and validated in large patient cohorts and are significantly, and independently, associated with risk of lung cancer death and outcomes as demonstrated by multivariate statistical analyses.[4-10] These assays provide reproducible and quantitative measures of tumor aggressiveness, an important data point in addition to the existing risk factors that may help differentiate treatment decisions in early stage patients.

Sincerely,



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Appendix A

Figure 1. Overlapping Prognostic Scores (PS) for IB patients with tumors ≥4 cm and < 4 cm. PS = 20 x (0.33 x CCP score + 0.52 x Stage) + 15. Stage, treated as a numerical variable (1=IA, 2=IB, 3=IIA, 4=IIB), is effectively constant for this stage IB analysis. Ref. 5; data on file.