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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 adjuvant chemotherapy treatment for Stage IB (T2a, N0) non-small cell lung adenocarcinoma.

Surgical resection remains the standard treatment for fit patients with early stage NSCLC. Controversy remains as to which patients should receive adjuvant postoperative chemotherapy. NCCN Guidelines Version 7.2015 NSCLC states, "Consider adjuvant chemotherapy for high-risk, margin negative (R0) stages IB-IIA[o]", with prognostic factors such as tumor size, visceral pleural involvement, poor differentiation, and vascular invasion defining "high risk". The current high risk factors, while informative, are largely qualitative, subjective, and can be highly variable in routine clinical practice. 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 patients with early stage disease. 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.[1]

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 7.2015; non-small cell lung cancer, footnote o).

Rationale: Guidelines state that adjuvant chemotherapy should be considered for surgical margin negative (R0) stage IB (T2a, N0) and Stage IIA (T2b, N0) patients presenting with high-risk factors. The Guidelines define 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, though semi-quantitative, has failed to prove a reliable predictive measure. Two published studies assessed the prognostic and adjuvant chemotherapy predictive utility of tumor size cutoffs in patients with IB disease; subset analyses resulted in discordant tumor size limits for high-risk designation and potential benefit from adjuvant chemotherapy. CALGB 9633, which failed to reach its primary endpoint, derived a 4 cm cutoff from a post-hoc subgroup analysis,[2,3] and a retrospective analysis of a small patient cohort (n=119) found significance (p=0.043) at a different value, 3.2 cm.[4] Further confounding are the results of a recent National Cancer Data Base (NCDB) analysis showing that patients with a tumor size $\geq$ 3 cm derive a statistically significant survival advantage from adjuvant chemotherapy.[5] While tumor size captures the extent of cancer progression at resection, progression rate cannot be prospectively derived from size, and therefore consideration of tumor aggressiveness by gene expression analysis can provide better risk assessment.

In several independent, published studies[6-9] multivariate analysis revealed that RNA expression-based prognostic signatures were highly-predictive of mortality, while tumor size was not. In addition, these studies identify a large proportion of patients with IB staging who actually have high risk disease, and for whom chemotherapy would rarely be considered based on tumor size alone. For example, a validated RNA expression-based measure, termed the "cell cycle progression score", was used to assess mortality risk in a cohort of stage IB patients. Though tumor size was not a significant prognostic factor [HR = 0.56 (95% CI = 0.28–1.29; p = 0.16)], the RNA-based measure of tumor aggressiveness did add prognostic discrimination [HR = 1.53 (95% CI = 1.01–2.33; p = 0.044)].[7] Furthermore, in a recent prospective study, molecular and NCCN risk assessment differed in 14 of 23 patients with stage IA to IIA disease (61%). Importantly, postoperative recurrences occurred only in molecular high-risk patients whereas both NCCN high- and low-risk patients recurred, suggesting that the molecular assay more accurately identifies high-risk patients.[10] Thus, patients with IB disease 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 cutoff 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.[6-9, 11-13] These assays provide reproducible and quantitative measures of tumor aggressiveness, an important data point in addition to the existing risk factors that may help tailor treatment decisions in patients with early stage disease.

Sincerely,

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References:

1. Bunn PA, Kim, E: Improving the care of with stage IB non-small-cell lung cancer: role of prognostic signatures and use of cell cycle progression biomarkers. *Clinical Lung Cancer* 16(4):245-251, 2015
2. Strauss GM, Herndon JE, 2nd, Maddaus MA, et al: Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *J Clin Oncol* 26:5043-5051, 2008
3. Katz A, Saad ED: CALGB 9633: an underpowered trial with a methodologically questionable conclusion. *J Clin Oncol* 27:2300-2301; author reply 2301-2302, 2009
4. Park SY, Lee JG, Kim J, et al: Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. *J Cardiothoracic Surg* 151:1-8, 2013
5. Speicher PJ, Gu L, Wang X, et al: Adjuvant chemotherpay after lobectomy for T1-2N0 non-small-cell lung cancer: are the guidelines supported? *J Natl Compr Canc Netw* 13:755-761, 2015.
6. Wistuba, II, Behrens C, Lombardi F, et al: Validation of a proliferation-based expression signature as prognostic marker in early stage lung adenocarcinoma. *Clin Cancer Res* 19:6261-6271, 2013.
7. Bueno R, Hughes E, Wagner S, et al: Validation of a Molecular and Pathological Model for Five-Year Mortality Risk in Patients with Early Stage Lung Adenocarcinoma. *J. Thorac Oncol*, 10(1):67-73, 2015
8. Kratz JR, He J, Van Den Eeden SK, et al: A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. *Lancet* 379:823-832, 2012.
9. Kratz JR, Van Den Eeden, SK, He J, et al: A prognostic assay to identify patients at high risk of mortality despite small, node-negative lung tumors. *J Am Med Assoc,* 308: 1629-1631, 2012.
10. Woodward GA, Gubens MA, Jahan TM, et al: Prognostic molecular assay might improve identification of patients at risk for recurrence in early-stage non-small-cell lung cancer. *Clinical Lung Cancer* 15(6):426-32, 2014.
11. Der SD, Sykes J, Pintilie M, et al: Validation of a histology-independent prognostic gene signature for early-stage, non–small-cell lung cancer including stage IA patients. *J Thorac Oncol* 9:59–64, 2014.
12. Zhu, CQ, Ding, K, Strumf, D, et al: Prognostic and Predictive Gene Signature for Adjuvant Chemotherapy in Resected Non-Small-Cell Lung Cancer *J Clin Oncol* 28:4417-4424, 2010.
13. Shedden K, Taylor JM, Enkemann SA, et al: Gene expression-based survival prediction in lung adenocarcinoma: a multi-site, blinded validation study. *Nat Med* 14:822-827, 2008