uncertain, given the current status of this field. However, the efforts by Ma and colleagues will certainly contribute to a growing body of literature that will eventually guide management of this disease.

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Commentary: Every detail matters—Understanding the impact of KRAS mutations

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Despite surgical resection, 30% to 60% of patients with early-stage non-small cell lung cancer (NSCLC) develop recurrent disease.^{1,2} Adjuvant chemotherapy has shown survival benefit in stages Ib and II NSCLC, but several genetic mutations have been identified in the pathogenesis of lung cancer that affect both prognosis and response to treatment.^{2,3} Moreover, some of these genetic modifications serve as potential targets for therapy in certain patients. Thus, genetic mutation mapping has the potential to guide the staging and treatment of lung cancer. As such, some centers perform mapping on all

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CENTRAL MESSAGE

The presence of certain *KRAS* mutations in early-stage lung adenocarcinoma may portend a worse clinical prognosis.

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adenocarcinomas and in up to three-quarters of patients with early-stage disease.¹

Two of the most clinically significant markers identified in NSCLC, specifically adenocarcinomas, are the *p53* tumor suppressor gene and the Kirsten rat sarcoma viral (*KRAS*) oncogene. These genes regulate cell growth, differentiation, and death.^{1,2,4,5} Overexpression of *p53*, but not a mutation in *p53*, is a known prognostic marker of poor outcome, and studies have shown that these patients benefit from adjuvant chemotherapy. On the other hand, *KRAS* mutations, which are found in approximately

30% of lung adenocarcinomas,^{4,5} have not been identified as a poor prognostic marker despite extensive analyses. This is likely due to heterogeneity among patient cohorts and tumor type. Consistent evidence does show that patients with *KRAS* mutation do not benefit from adjuvant chemotherapy, but some recent studies have reported variable responses depending on the mutation subtype.^{2,3}

In this issue of the *Journal*, Ma and colleagues⁶ looked to further elucidate the prognostic value of varying *KRAS* mutations among patients with resected lung adenocarcinoma. As shown in previous studies, the authors found that *KRAS* mutations were more common in males, smokers (current and former), and patients with solid tumors. Although *KRAS* mutation was not identified as a prognostic factor for recurrence-free survival or overall survival in the entire cohort, multivariate analyses showed that *KRAS* mutation was independently associated with shorter recurrence-free and overall survival in part-solid tumors and stage I disease. Survival analysis showed a higher cumulative recurrence rate and worse overall survival in patients with *KRAS* mutation. Furthermore, mutations in the G12 codon, the most common site of mutation, including those with hydrophobic subgroups G12C and G12V, were associated with worse overall survival compared with non-G12 mutations. This supports the notion that clinical outcomes in patients with *KRAS* mutation differ depending on codon subtype. While

analysis of the cohort as a whole was consistent with previous research, this study shows that the clinical outcomes in patients with *KRAS* mutation differ depending on codon subtype, among other factors.

Although the application of targeted therapies for *KRAS* mutations has been largely unsuccessful so far, this type of careful subset analysis of genetic mutation analysis provides valuable information about prognosis for individual patients and may yet lead to alterations in treatment pathways.

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