Background: Somatic gain-of-function mutations in EGFR (exons 19 and 21) and KRAS, (exon 2) are found in some lung adenocarcinomas. In patients with metastatic disease, these mutations have predictive and prognostic significance: 1) EGFR mutations are associated with sensitivity to the tyrosine kinase inhibitors, gefitinib and erlotinib, 2) KRAS mutations are associated with primary resistance to these drugs, and 3) patients with EGFR mutant tumors may have a longer overall survival (OS) versus patients with EGFR wildtype tumors. Whether EGFR and KRAS mutations also have an impact on survival, when compared to one another, in patients who undergo lung resection for curative intent in the absence of targeted therapy has not been established.

Methods: We analyzed the clinical characteristics and outcomes data for 300 patients who underwent resection at our institution for Stage I-III lung adenocarcinoma. Tumors from all patients were assessed for both EGFR and KRAS mutations by direct dideoxynucleotide sequencing by the Genome Sequencing Center at Washington University St. Louis, and/or PCR based methods at Memorial Sloan-Kettering Cancer Center. Survival distributions were estimated using Kaplan-Meier curves and compared using the log-rank test.

Results: We found EGFR and KRAS mutations in tumors from 40 and 50 patients, respectively. No tumor had both mutations. None of the patients with mutations received induction or adjuvant therapy with erlotinib or gefitinib. With a median time to follow-up of 22.3 months, patients with EGFR mutant tumors had a longer overall survival on univariate analysis versus patients with KRAS mutant tumors (p=0.015, see Figure 1) and a trend towards longer survival versus patients with tumors wildtype for both genes (p=0.070). After adjustment for pathologic stage, patients with EGFR mutations displayed a trend towards longer survival when compared to patients with KRAS mutations (p=0.166). The median OS for patients with EGFR mutant or wildtype tumors was not reached, while for the patients with KRAS mutations should be considered as prognostic factors in studies of adjuvant therapy.

Conclusions: In the absence of treatment with EGFR-targeted therapy, EGFR and KRAS mutations are positive and negative molecular predictors, respectively, of survival in resected lung adenocarcinoma. These data suggest further that EGFR and KRAS mutations define clinically distinct molecular subsets of lung adenocarcinoma. Mutational status should be routinely performed on resected specimens, and EGFR and KRAS mutations should be considered as prognostic factors in studies of adjuvant therapy.

Figure 1. Kaplan-Meier survival curves from 300 patients with resected lung adenocarcinoma. Median survival was not reached for patients with EGFR mutant or wildtype tumors, while it was 42 months for those with KRAS mutant tumors.