Tracking the Evolution of Non-Small-Cell Lung Cancer

Background Among patients with non-small-cell lung cancer (NSCLC), data on intratumor heterogeneity and cancer genome evolution have been limited to small retrospective cohorts. We wanted to prospectively investigate intratumor heterogeneity in relation to clinical outcome and to determine the clonal nature of driver events and evolutionary processes in early-stage NSCLC. Methods In this prospective cohort study, we performed multiregion whole-exome sequencing on 100 early-stage NSCLC tumors that had been resected before systemic therapy. We sequenced and analyzed 327 tumor regions to define evolutionary histories, obtain a census of clonal and subclonal events, and assess the relationship between intratumor heterogeneity and recurrence-free survival. Results We observed widespread intratumor heterogeneity for both somatic copy-number alterations and mutations. Driver mutations in EGFR, MET, BRAF, and TP53 were almost always clonal. However, heterogeneous driver alterations that occurred later in evolution were found in more than 75% of the tumors and were common in PIK3CA and NF1 and in genes that are involved in chromatin modification and DNA damage response and repair. Genome doubling and ongoing dynamic chromosomal instability were associated with intratumor heterogeneity and resulted in parallel evolution of driver somatic copy-number alterations, including amplifications in CDK4, FOXA1, and BCL11A. Elevated copy-number heterogeneity was associated with an increased risk of recurrence or death (hazard ratio, 4.9; P=4.4×10−4), which remained significant in multivariate analysis. Conclusions Intratumor heterogeneity mediated through chromosome instability was associated with an increased risk of recurrence or death, a finding that supports the potential value of chromosome instability as a prognostic predictor. (Funded by Cancer Research UK and others; TRACERx ClinicalTrials.gov number, NCT01888601.)

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