

Genetic profile of treatment-resistant lung cancer more variable than previously thought

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The genetic mutations underlying treatment resistance in non-small cell lung cancer (NSCLC) are more complex and dynamic than previously thought. Analysis of 355 biopsied tumors from patients who acquired resistance to EGFR inhibitors, the most common form of targeted therapy for NSCLC, found that mutations frequently varied between biopsies and that nearly one in five patients harbored more than one type of genetic resistance to treatment. Findings will be presented today at the [2017 Multidisciplinary Thoracic Cancers Symposium](#)".

Between 10 and 30 percent of NSCLC cases are driven by mutations in the epidermal growth factor receptor (EGFR) gene. These [patients](#) typically are treated with drugs that inhibit activation of the gene, but nearly all tumors eventually develop resistance to these therapeutic agents. Currently, many patients who acquire resistance to EGFR-targeted therapy undergo a tumor [biopsy](#) and are designated as either positive or negative for specific secondary mutations. This prognosis guides decisions for subsequent courses of targeted therapy, and further biopsies are not routinely obtained, given the invasive nature of rebiopsy in the lungs. Recent studies have indicated, however, that resistance in EGFR-mutant NSCLC can vary and that a permanent designation based on a single biopsy may be insufficient.

"In the past, [resistance mechanisms](#) were usually thought of as static. Our study demonstrates, conversely, that a binary designation of resistance may oversimplify cancer's true biology. These [genetic mutations](#) can fluctuate over time, and some patients can harbor more

than one mutation," said Zofia Piotrowska, MD, lead author of the study and a thoracic oncologist at the Massachusetts General Hospital Cancer Center in Boston.

"In an era where cancer treatment is increasingly personalized to the biology of each individual patient, our findings highlight the importance of molecular testing and the need for improved, noninvasive methods for serial testing."

To better understand the biological diversity of EGFR-resistant NSCLC, researchers retrospectively analyzed 355 biopsies of NSCLC tumors obtained from 221 patients after they acquired resistance to first-line EGFR inhibitor therapy. All patients were seen at a single institution between April 2008 and May 2016. The median patient age was 59 years (range 28-88), and 69 percent of patients were female. Researchers examined tumor samples for various genetic causes of EGFR resistance, including T790M, the most common secondary mutation.

All patients received at least one biopsy at first resistance to EGFR inhibitors. Nearly one in five (19%) of these 221 biopsies demonstrated more than one resistance mechanism simultaneously. The overall distribution of resistance mechanisms was consistent with previous research. The T790M mutation was found in 61 percent of patients, and the proportions of other mutations were as expected. Specifically, 18 percent of patients had EGFR amplification, 2 percent acquired PIK3CA mutations, 5 percent had amplification of the MET gene, 3 percent transformed non-small cell to small cell disease and 1 percent acquired BRAF mutations.

Eighty-three patients (37%) underwent two biopsies during post-resistance treatment. For half of these patients (49%), resistance mechanisms varied between biopsies, including both "gain" and "loss" of the T790M mutation (20% and 11% of two-biopsy patients,

respectively). Three of the 17 patients who "lost" T790M demonstrated a new resistance mechanism on the second biopsy.

Researchers also sought to determine whether serial biopsies were safe and feasible for NSCLC patients. Two of the 307 biopsies (0.7%) resulted in clinically significant complications, and 13 percent of patients (n = 28) underwent three or more post-resistance biopsies.

"As much as half of the time, the dominant resistance mechanisms observed on one biopsy may no longer be relevant on a second biopsy, and that second biopsy may uncover a new, potentially targetable, resistance mechanism," said Dr. Piotrowska. "We hope that these findings will prompt clinicians to consider rebiopsy when selecting a new therapy. While we observed that biopsies were generally safe and feasible, noninvasive testing methods, such as liquid biopsies that analyze tumor DNA circulating in the patient's blood, may provide another method to more easily characterize [resistance](#) over time."

Provided by American Society for Radiation Oncology

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