Subtypes of Lung Adenocarcinoma Uncovered

Three distinct patterns of gene expression influence clinical phenotype, response to therapy

Lung adenocarcinoma intrinsic molecular subtypes correlate with grossly distinctive genomic alterations and patient response to therapy, according to a new study (*PLoS ONE* 7:e36530. doi:10.1371/journal.pone.0036530).

"The squamoid subtype has the least distinctive patterns in relationship to oncogenes," senior author D. Neil Hayes, MD, MPH, an associate professor of medicine at the University of North Carolina at Chapel Hill, said in an interview.

'This study suggests that even though lung cancer is complex, the number of predominant patterns is relatively small.'

—D. Neil Hayes, MD, MPH

The subtypes—bronchioid, magnoid and squamoid—represent the main naturally occurring patterns of lung adenocarcinoma gene expression, encompassing different functional pathways and patient outcomes, the investigators reported.

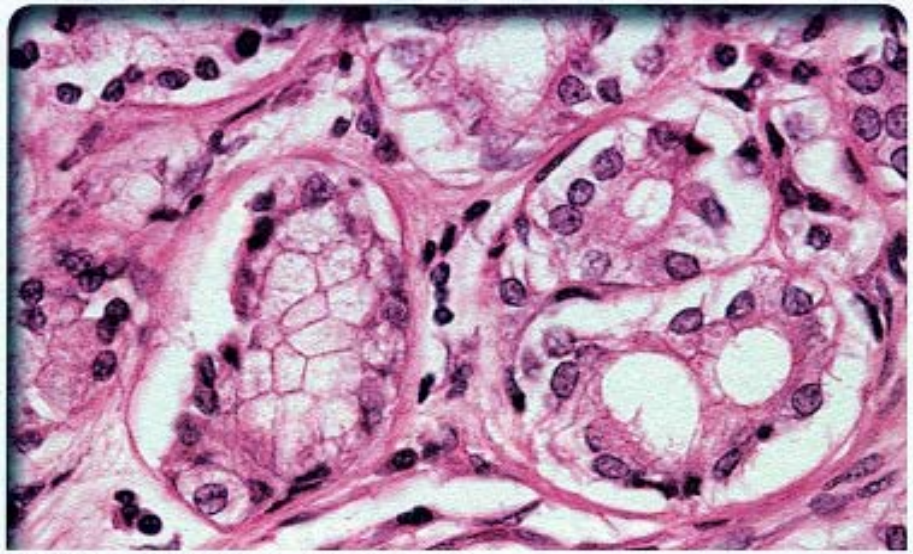
"The study is still preliminary, not practice-changing in an imminent way, but very, very interesting," H. Jack West, MD, the medical director of thoracic oncology at the Swedish Cancer Institute, in Seattle, who was not affiliated with the study, told *Clinical Oncology News*. "It could be an early step toward fundamentally changing how we view and approach lung cancer."

The researchers used published cohorts to detect genomic alterations co-occurring with the molecular subtypes. To provide independent valida-

"We expect to find characteristic mutations of the squamoid subtype."

Clinical phenotypes differed between the subtypes. For example, bronchioid was characterized by patients who were female and nonsmoking and who presented with early-stage cancer. High smoking exposure and late-stage presentation were common in magnoid and squamoid, and magnoid had a high prevalence of male patients.

Patient outcomes also varied between the subtypes. Bronchioid had the best outcome in patient overall survival (Figure), and may have the greatest sensitivity to *EGFR* inhibitors, whereas magnoid cancers responded best to chemotherapy. "A striking result in the paper is that all of the benefit of chemotherapy was limited to the magnoid subtype," said Dr. Hayes.



Lung adenocarcinoma at 40x magnification.

Dr. Hayes suggested that the study had achieved an advance. "Before the current study, the etiology of subtypes was unknown. ... This study suggests that even though lung cancer is complex, the number of predominant patterns is relatively small."

Dr. West said, "Subtypes are like colors. If you jumble them together, you get muddy brown—mediocre results. If you distinguish them and identify and observe the differences between the colors, it has the potential to do a better job of optimizing our results for patients by honing our care for the tumors of individual patients."

—George Ochoa

Dr. West reported no relevant financial disclosures. Dr. Hayes disclosed a patent pending on gene sets related to tumor subtypes.

cohorts to detect genomic alterations co-occurring with the molecular subtypes. To provide independent validation, they assayed the tumors of a novel cohort of patients with lung adenocarcinoma (N=116). They found that the subtypes had significant differences in gene sequence mutations, chromosomal instability, regional DNA copy number, DNA methylation and integrated alterations. For example, bronchioid had the greatest *EGFR* mutation frequency, whereas magnoid had the greatest mutation frequencies in *TP53*, *KRAS* and *STK11*.

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The study findings are not ready for clinical application, Dr. Hayes said. "The subtypes have no clinical diagnostic assay. There may be a theoretical benefit for patients in the future."

Dr. West agreed. "In the next three to five years it could lead to a change in how we practice, but not next week." He added, "I would like to see this replicated in larger settings, and applied prospectively."

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—H. Jack West, MD

AT A GLANCE

Three molecular subtypes represent the naturally occurring gene expression patterns of lung adenocarcinoma

The subtypes produced different clinical phenotypes of disease

There is no clinical assay yet, but the findings could direct treatment within five years

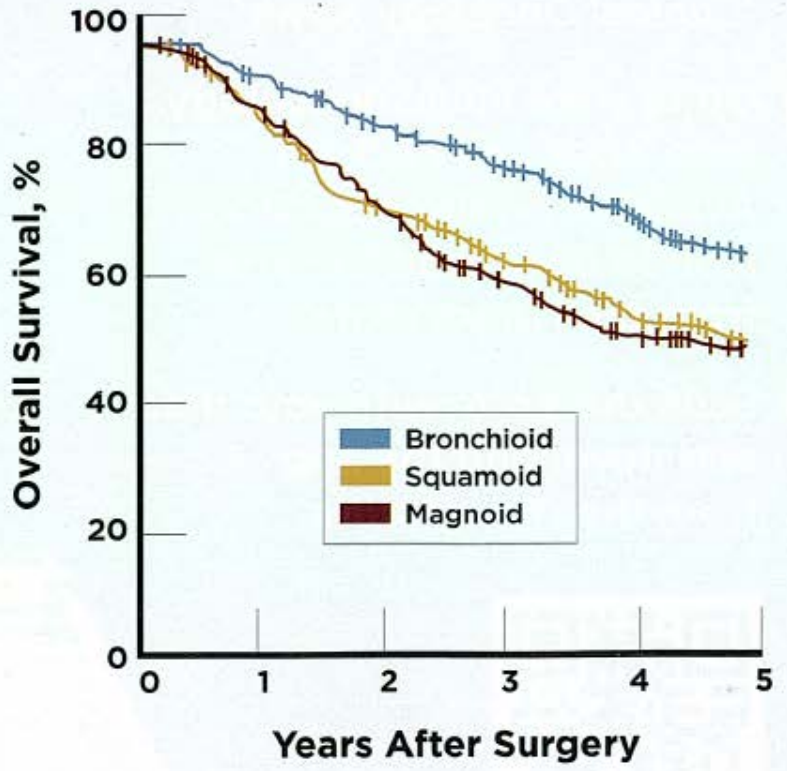

Figure. Overall survival among three primary molecular subtypes of lung adenocarcinoma.[1]

1. Data drawn from five published cohorts assayed for gene expression and including survival follow-up; N = 807.