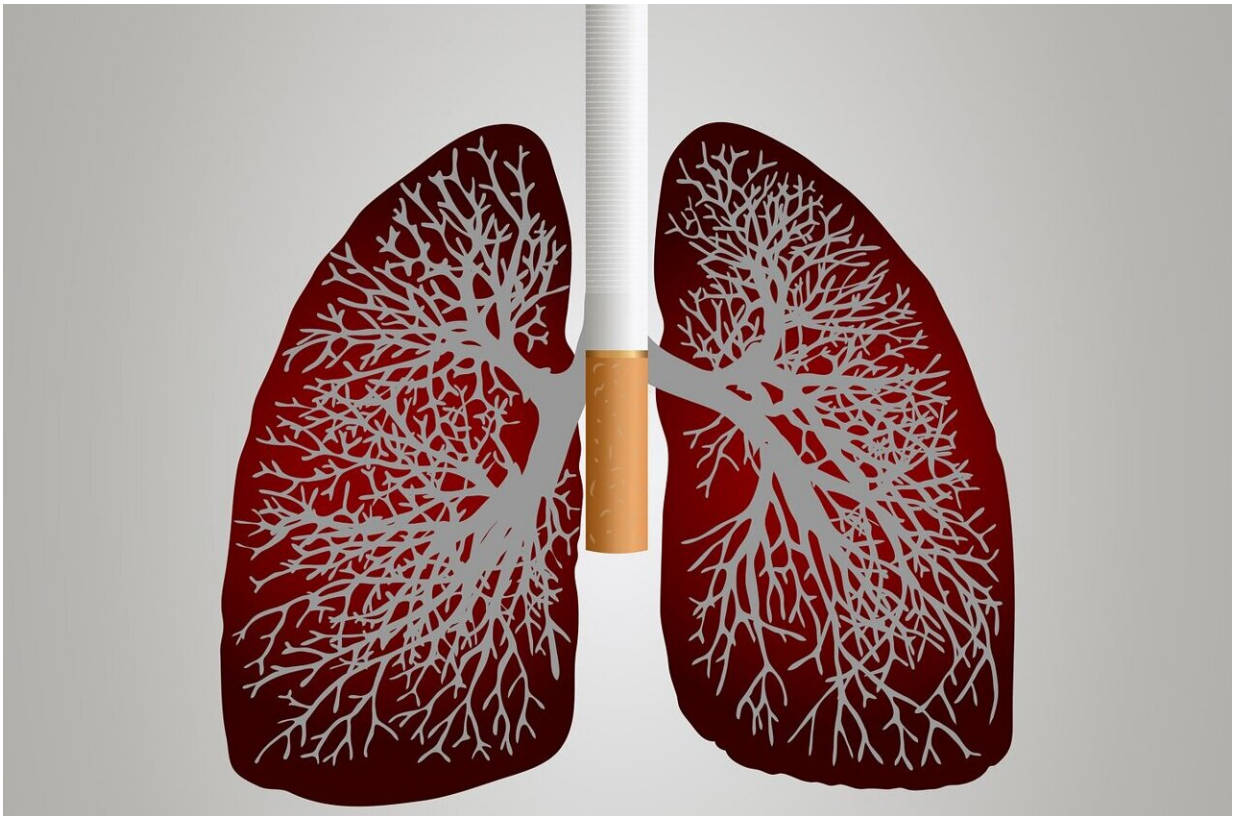# A model to predict non-small cell lung cancer patient outcomes to immunotherapy

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Immunotherapy agents that inhibit the molecules PD1, PD-L1 or CTLA-4 have become widely used in clinical practice to treat non-small cell lung cancer, or NSCLC. Approximately 20% to 50% of advanced

NSCLC patients have strong responses to immunotherapy and show prolonged survival, but the remaining patients often have poor responses. There is an urgent need to identify biomarkers that can predict which patients will not respond to therapy to avoid unnecessary treatment and administer potential beneficial drugs instead.

PD-L1 expression measured in a patient's tumor is a common biomarker that is often used to determine patients who should be treated with anti-PD1/PD-L1 therapy. However, several studies have shown that patients may be responsive to these agents even with low expression of PD-L1. Other similar tissue-based biomarkers may be cost-prohibitive or require an adequate quality and quantity of tissue that may be limited in supply.

In a new article published in *JNCI Cancer Spectrum*, Moffitt Cancer Center researchers describe a prediction model they have created that includes information calculated from computed tomography images that can identify patients who are not likely to respond to immunotherapy.

Rather than analyzing common tissue-based biomarkers, such as protein expression patterns, the Moffitt research team assessed the potential of using characteristics from pre-treatment CT scans combined with clinical data to identify markers associated with outcomes to immunotherapy.

"Quantitative image-based features, or radiomics, reflect the underlying pathophysiology and tumor heterogeneity and have advantages over tissue-based biomarkers as they can be rapidly extracted using standard-of-care medical images and capture data from the entire tumor rather than a small portion of the tumor that is biopsied and assayed," said Matthew Schabath, Ph.D., associate member of the Department of Cancer Epidemiology at Moffitt.

The researchers analyzed clinical characteristics and radiomics features

of 180 NSCLC patients treated with anti-PD1/PD-L1 with or without anti-CTLA-4 therapy. "Our goal was to create a parsimonious model, known as a simple model with the fewest variables and the greatest predictive power possible," said Bob Gillies, Ph.D., senior member and chair of the Department of Cancer Physiology.

They found that among 16 clinical features considered, the levels of serum albumin and the number of metastatic sites a patient had were significantly associated with overall survival. Among 213 radiomic features, gray level cooccurrence matrix (GLCM) inverse difference was associated with overall survival. Statistical analysis and data modeling revealed that these characteristics were appropriate parameters for inclusion within the model, which resulted in four groups divided according to risk of death following immunotherapy: low risk, moderate risk, high risk and very high risk.

The researchers validated their model in two additional patient populations and confirmed that the very high risk group had an extremely poor overall survival after immunotherapy, with a three-year overall survival of 0%, while the low risk group had a three-year overall survival of approximately 40%. They also discovered that the radiomic feature GLCM inverse difference was associated with expression of the gene CAIX that is involved in tumor hypoxia and regulates tumor growth and metastasis, which provides biological support for GLCM inverse difference as a potential biomarker. Considering hypoxia, or low oxygen in your tissues, has important implications for all types of cancer development, these results suggest that GLCM inverse difference may be a possible predictor for patient responses to other anti-cancer drugs.

"These results suggest very high-risk patients should either avoid immunotherapy altogether or utilize upfront combination treatments that may yield an improved response," said Schabath. "We hope with further study this model can be used to change clinical practice and allow

patients to avoid drugs they may not have a response to."

  More information: Ilke Tunali et al, Hypoxia-Related Radiomics and Immunotherapy Response: A Multicohort Study of Non-Small Cell Lung Cancer, *JNCI Cancer Spectrum* (2021). DOI: 10.1093/jncics/pkab048

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