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Guidance for Sponsors
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Advances in Imaging of Non-Small Cell Lung Cancer (NSCLC)

By Amit Mehta, M.D., Executive Vice President and Chief Medical Officer · Updated for 2026 by Intrinsic Imaging

Non-small cell lung cancer has become the model for precision oncology. Targeted therapies against EGFR, ALK and KRAS, and immunotherapy given before and after surgery, have transformed outcomes for patients who once had few options. Each advance places new demands on imaging. Tumors treated with targeted agents and immunotherapy do not always shrink in the way RECIST expects, measurement variability can rival the treatment effect, and functional and volumetric techniques are maturing as candidate biomarkers. This issue reviews how imaging assessment of NSCLC is evolving and what sponsors must get right.

Lung Cancer

Lung cancer is the leading cause of cancer death worldwide, accounting for nearly 2.5 million new cases and 1.8 million deaths in 2022.[1] In the United States, an estimated 229,410 people will be diagnosed in 2026 and 124,990 will die of the disease, one in five of all cancer deaths.[2] Five-year relative survival has improved to 28%, and reaches 65% for localized disease.[1] Non-small cell lung cancer accounts for about 85% of cases. Surgery can be curative in early-stage disease, which is why screening with low-dose CT has drawn so much attention, but many patients still present with advanced disease.

Diagnosis and Therapy

Treatment is now selected by genomic profile. For tumors with EGFR mutations, FDA approved amivantamab with lazertinib as a chemotherapy-free first-line regimen in August 2024, joining a line of tyrosine kinase inhibitors.[3] ALK-rearranged tumors, present in a small percentage of adenocarcinomas and common in never-smokers, respond to successive generations of ALK inhibitors. KRAS, long considered undruggable, yielded in May 2021, when sotorasib received accelerated approval as the first therapy for KRAS G12C-mutated NSCLC.[4] Immunotherapy has moved into early-stage disease: in October 2023, FDA approved pembrolizumab with chemotherapy before surgery, continued as a single agent afterward, for resectable NSCLC.[5]

Tumor Assessment

Response assessment on CT has long relied on manual single-plane measurement under the WHO criteria and RECIST, now version 1.1.[6] These methods are standardized and widely accepted, but they depend on size alone. Same-day repeat CT studies have shown that measurement variability in NSCLC can be large enough to mimic response or progression,[7] and studies comparing criteria have found RECIST 1.1 to perform better than its predecessor in tumors treated with targeted therapy.[8]

Limits of Size-Based Criteria

Targeted and immune therapies expose two limitations. First, some tumors respond slowly or continue to grow while remaining sensitive to treatment. In EGFR-mutated disease, patients are often treated beyond RECIST progression, and tumors may

show an initial response followed by slow growth over many months. Second, tumors seldom grow as spheres, and size criteria ignore physiological signs of response such as central necrosis or cavitation. Immunotherapy adds pseudoprogression, which iRECIST addresses with confirmation scans.[9]

PET Imaging

Integrated FDG-PET/CT outperforms PET or CT alone for staging and is instrumental in distinguishing benign from malignant nodules. PERCIST provides a standardized framework for metabolic response.[10] Novel tracers, including radiolabeled targeted agents, are being developed to study drug delivery and target engagement in tumors and lymph nodes.

Volumetric Measurement

Multidetector CT with isotropic voxels allows accurate tumor volumes to be measured. Volumetry is more reproducible than one- or two-dimensional measurement and reduces variance between readers and over time,[11] and early work suggested that volume change during targeted therapy could distinguish tumors with and without EGFR mutations.[12] Volume is not yet a validated response biomarker, but it is increasingly captured as an exploratory endpoint.

CT Perfusion and Diffusion-Weighted MRI

Perfusion CT and MRI measure contrast uptake over time and estimate blood flow, blood volume and permeability. In advanced NSCLC, higher baseline blood flow and blood volume have been associated with partial response,[13] but software packages still disagree too widely for perfusion to serve as a validated biomarker. Diffusion-weighted MRI, which maps water motion within tissue, has been investigated as a predictor of progression-free and overall survival; it offers insight into tumor biology, though its role in formal response assessment remains investigational.

Guidance for Sponsors

Imaging an NSCLC trial

- **Standardize acquisition.** Fix slice thickness, reconstruction kernel and contrast timing in the imaging charter.[14]
- **Match criteria to mechanism.** Use RECIST 1.1 for primary endpoints, with iRECIST for immunotherapy.[6,9]
- **Plan for treatment beyond progression.** Define in the protocol how imaging after RECIST progression will be read.
- **Capture exploratory biomarkers.** Acquire volumetric and PET data in a way that allows later analysis.[10,11]
- **Read centrally.** Use blinded independent central review with adjudication.[14]

Summary

Genomically targeted therapy and immunotherapy have opened a new window on a disease once defined by late diagnosis. The imaging community has met the challenge with refined criteria and new quantitative tools. Applying the wrong biomarker or imaging strategy can wrongly declare a therapy a failure and cost patients a valuable option, so these trials demand an imaging partner with deep expertise in thoracic oncology.

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