

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.

About the Author

Dr. Amit Mehta, Executive Vice President, Chief Medical Officer and Co-founder of Intrinsic Imaging, wrote the original edition of this issue. He completed his diagnostic radiology residency and a fellowship in minimally invasive image-guided surgery at Harvard Medical School's Massachusetts General Hospital, and he is double board-certified in diagnostic and vascular interventional radiology in Canada and the United States. He has co-authored three medical textbooks and received the Radiological Society of North America's George Brown Award and the Joseph E. Whitley Award. He is a General Partner at Builders VC and serves as a reviewer of SBIR and STTR grant applications for the National Institutes of Health.

References

1. American Cancer Society. Cancer Facts & Figures 2026. [cancer.org](https://www.cancer.org)
2. National Cancer Institute SEER Program. Cancer stat facts: lung and bronchus cancer. seer.cancer.gov
3. U.S. FDA. FDA approves lazertinib with amivantamab-vmjw for non-small lung cancer. August 19, 2024. [fda.gov](https://www.fda.gov)
4. U.S. FDA. Approval package: Lumakras (sotorasib). May 28, 2021. accessdata.fda.gov
5. U.S. FDA. FDA approves neoadjuvant/adjuvant pembrolizumab for resectable non-small cell lung cancer. October 16, 2023. [fda.gov](https://www.fda.gov)
6. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228–247. recist.eortc.org
7. Zhao B, James LP, Moskowitz CS, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. *Radiology*. 2009;252(1):263–272. pubmed.ncbi.nlm.nih.gov/19561260
8. Nishino M, Jackman DM, Hatabu H, et al. New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. *AJR Am J Roentgenol*. 2010;195(3):W221–W228. pubmed.ncbi.nlm.nih.gov/20729419
9. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol*. 2017;18(3):e143–e152. pubmed.ncbi.nlm.nih.gov/28271869
10. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med*. 2009;50(Suppl 1):1225–150S. pubmed.ncbi.nlm.nih.gov/19403881
11. Zhao B, Schwartz LH, Moskowitz CS, et al. Lung cancer: computerized quantification of tumor response—initial results. *Radiology*. 2006;241(3):892–898. pubmed.ncbi.nlm.nih.gov/17114630
12. Zhao B, Oxnard GR, Moskowitz CS, et al. A pilot study of volume measurement as a method of tumor response evaluation to aid biomarker development. *Clin Cancer Res*. 2010;16(18):4647–4653. pubmed.ncbi.nlm.nih.gov/20534736
13. Wang J, Wu N, Cham MD, Song Y. Tumor response in patients with advanced non-small cell lung cancer: perfusion CT evaluation of chemotherapy and radiation therapy. *AJR Am J Roentgenol*. 2009;193(4):1090–1096. pubmed.ncbi.nlm.nih.gov/19770333
14. U.S. FDA. Clinical trial imaging endpoint process standards: guidance for industry. April 2018. [fda.gov](https://www.fda.gov)

About Intrinsic Imaging, LLC

Headquartered in Bolton, Massachusetts, Intrinsic Imaging is an imaging CRO and core lab supporting Phase I–IV drug trials, medical device studies and AI/CAD validation studies. The company has completed three FDA Bioresearch Monitoring Program inspections, each with zero Form FDA 483 observations, and holds five BSI certifications: ISO 9001, ISO 13485, ISO 22301, ISO/IEC 27001 and ISO/IEC 27018. Its network of more than 1,000 board-certified, fellowship-trained physicians has supported trials at more than 4,000 sites in 64 countries.



Contact

Intrinsic Imaging, LLC
 580 Main Street, Suite 210
 Bolton, MA 01740
 Tel: +1 978-616-4650
Contact@IntrinsicImaging.com
www.IntrinsicImaging.com