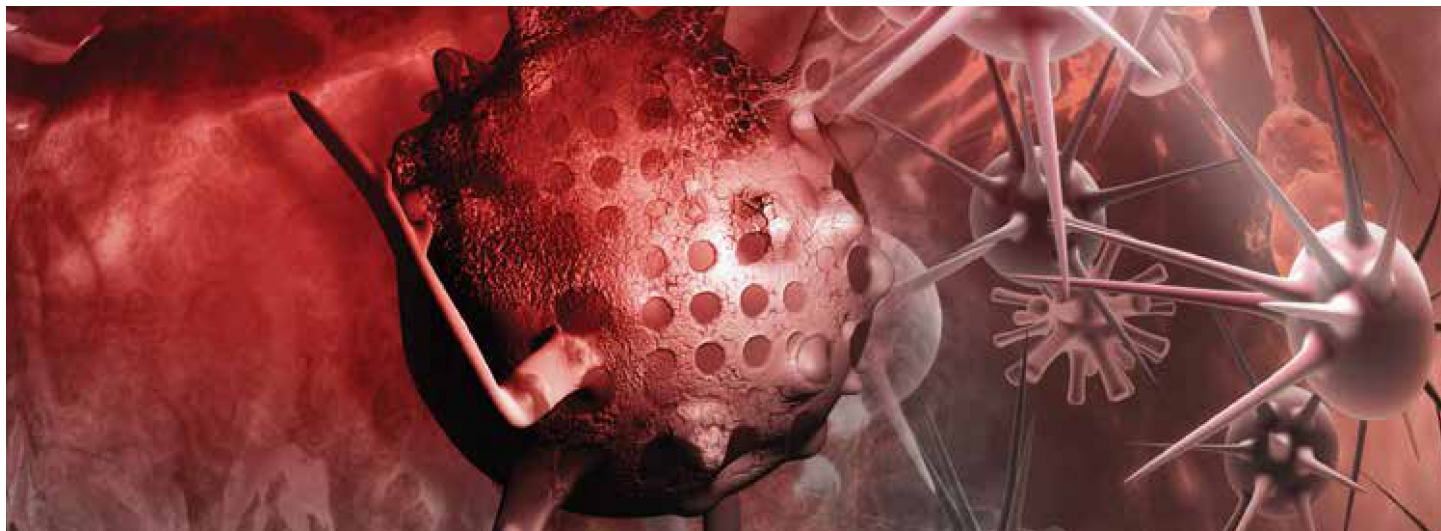


Medical Imaging of Chronic Lymphocytic Leukemia

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



Chronic lymphocytic leukemia has been transformed by targeted therapy. BTK inhibitors, BCL-2 inhibition and cellular therapies have pushed five-year survival above 90%, and in October 2026 FDA approved pirtobrutinib for previously untreated disease. Imaging plays a narrower but critical role in this disease: international guidelines do not require CT in routine practice, yet they consider it desirable in clinical trials, and FDG-PET/CT is the key tool for detecting Richter transformation. This issue sets out where imaging belongs in a CLL trial and how to standardize it.

Introduction

Lymphoid malignancies arise from B cells, T cells and NK cells. The traditional distinction between lymphomas, which present as masses of lymph nodes, and leukemias, which involve the blood and bone marrow, has blurred: many lymphoid malignancies have both tissue masses and circulating cells. Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are now regarded as one disease; the term CLL is used when the disease is primarily in the blood and marrow, SLL when it is primarily nodal.

An estimated 22,760 Americans will be diagnosed with CLL in 2026, and 4,350 will die of it.¹ Five-year relative survival has reached 90.2%.² Many patients are asymptomatic and diagnosed through routine blood work; others present with lymphadenopathy, splenomegaly, hepatomegaly or cytopenias.

Diagnosis and Staging

CLL is usually indolent, and symptoms or evidence of active disease determine the need for treatment. In a minority of patients, the disease undergoes Richter transformation into an aggressive lymphoma with much poorer survival. The Rai and

Binet staging systems remain standard. Both rely on physical examination and blood counts rather than imaging, and enlarged nodes detected only by CT do not change the stage.³

A Transformed Treatment Landscape

Molecular profiling has transformed therapy. High-risk features, including unmutated IGHV, deletion 17p and TP53 mutation, guide treatment selection. Chemoimmunotherapy has largely given way to targeted agents: Bruton tyrosine kinase (BTK) inhibitors, the BCL-2 inhibitor venetoclax and anti-CD20 antibodies. In March 2024, FDA approved lisocabtagene maraleucel, a CAR T-cell therapy, for relapsed or refractory CLL,⁴ and on October 2, 2026, it approved the noncovalent BTK inhibitor pirtobrutinib for previously untreated CLL or SLL without 17p deletion. In the BRUIN CLL-313 trial of 282 patients, pirtobrutinib reduced the risk of progression or death by 80% compared with bendamustine and rituximab (hazard ratio 0.20).⁵

The Role of CT

The 2018 guidelines of the International Workshop on CLL (iw-CLL) state that CT is not generally indicated for initial evalu-

ation or follow-up in routine practice. In clinical trials, however, CT of the neck, chest, abdomen and pelvis is considered desirable at baseline and recommended to evaluate response. One CT should be performed before therapy and a second at the final response assessment if the first was abnormal; for continuous therapies, CT should be performed at the time of maximal clinical response or at a protocol-defined time point.³ Repeated CT monitoring beyond this is usually not clinically relevant and exposes patients to unnecessary radiation.³ Response criteria define the size thresholds that nodes, spleen and liver must meet for complete and partial remission, so consistent measurement across sites is essential.

FDG-PET/CT and Richter Transformation

FDG-PET/CT has a limited role in typical CLL, whose cells are usually only mildly avid, but it is valuable when Richter transformation is suspected. Higher maximum standardized uptake values discriminate transformed disease and guide biopsy toward the most active site.⁶ In a study of patients with progressive CLL, PET/CT detected Richter transformation with a sensitivity of 88.2%, a specificity of 71.2% and a negative predictive value of 94%,⁷ and iwCLL recognizes PET/CT as useful in this setting.³ When transformation is confirmed and treated as aggressive lymphoma, response is assessed with the Lugano classification and the Deauville five-point scale.⁸

Guidance for Sponsors

Imaging a CLL trial

- **Follow iwCLL timing.** Schedule CT at baseline and at final or maximal response, not routinely in between.³
- **Standardize coverage.** Image the neck, chest, abdomen and pelvis with consistent contrast and slice thickness.³
- **Measure consistently.** Define nodal, splenic and hepatic measurement rules in the imaging charter.⁹
- **Plan for transformation.** Specify PET/CT for suspected Richter transformation and Lugano criteria thereafter.^{7,8}
- **Read centrally.** Use blinded, independent central review integrated with clinical and laboratory data.⁹

Summary

Targeted therapies have made CLL a chronic, manageable disease for many patients, and new agents continue to reach approval. Imaging in CLL trials is deliberately focused: CT at defined time points to confirm response, and PET/CT when transformation is suspected. Standardized imaging charters and expert central interpretation ensure that these selective assessments are accurate, consistent and credible.

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.

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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.



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