# RESPONSE ASSESSMENT IN LYMPHOMA

# THE LUGANO CLASSIFICATION AND BEYOND

## Imaging Endpoints – Connecting Imaging to the Cure

The Lugano Classification, published in 2014 (also referred to as Cheson 2014) updated and replaced the previously utilized 2007 IWG-NHL guidelines (Cheson 2007). The primary goals of the Lugano Classification were to improve the radiologic assessments of lymphoma patients during clinical trial reads, eliminate ambiguity in the assessment of response status, and provide a universally applicable approach to facilitate the comparison of patients and data for clinical trials and regulatory purposes. Since then, several new radiologic criteria have been developed to address therapeutic efficacy using novel therapies such as immunotherapy and cellular therapy. Here we discuss the key features of the lymphoma response criteria and recommendations on the use of diagnostic CT/MRI with the evaluation of FDG-PET and a methodology to operationalize these criteria in a clinical trial.

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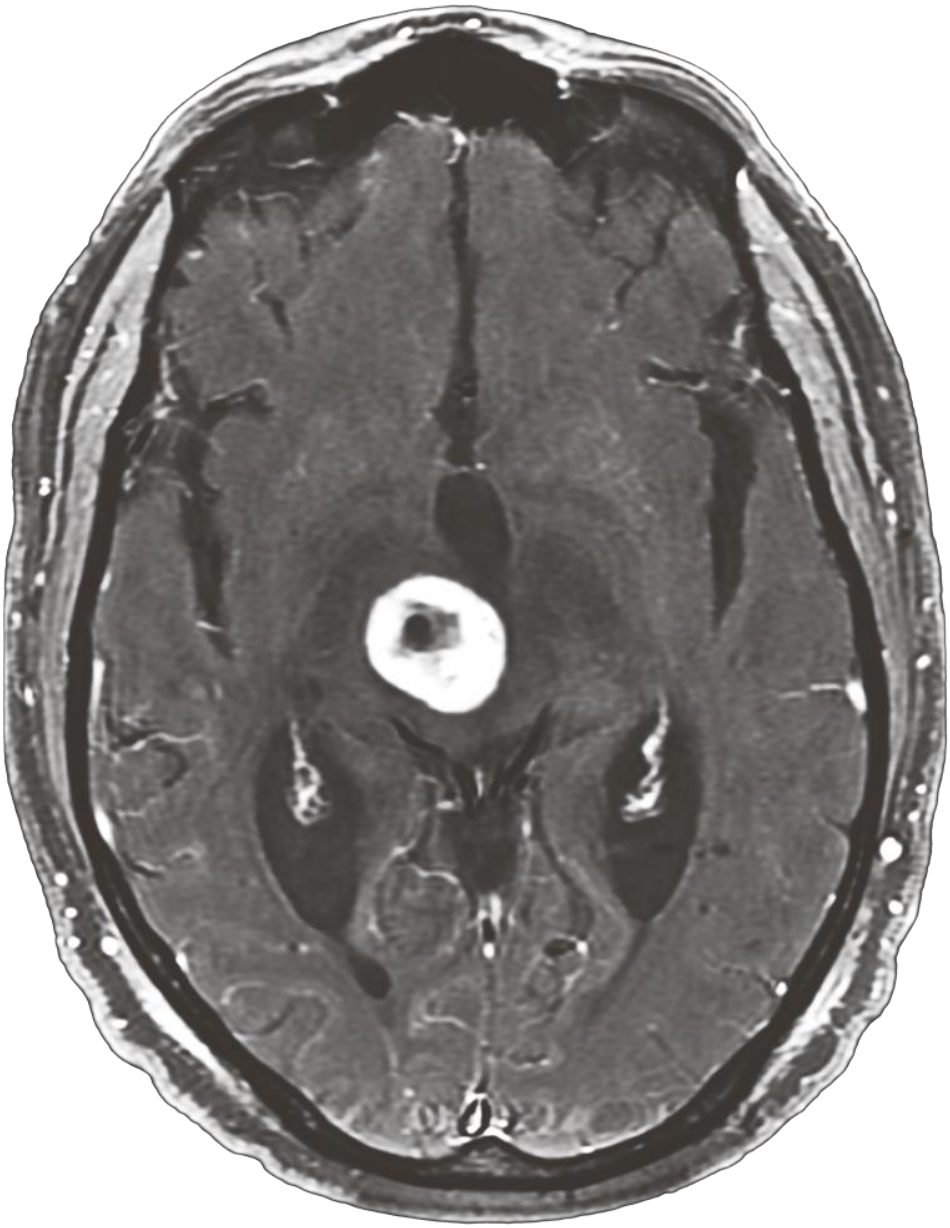


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# USING CHESON 2014 - THE LUGANO CLASSIFICATION

## STANDARDIZING THE EVALUATION OF LYMPHOMA

**Introduction**

According to the American Cancer Society, approximately 74,690 adults and children in the United States will be diagnosed with non-Hodgkin lymphoma (NHL), about 8,500 with Hodgkin lymphoma (HL), and more than 600,000 Americans will be living with lymphoma. Since 1997, the death rates for NHL have decreased by 3 percent annually in men and by 3.7 percent annually in women. Currently, lymphoma comprises more than 67 subtypes of NHL or HD. Thanks to the development of a new arsenal of treatments involving chemotherapy, or targeted therapy, the outlook for a cure is improving.

The foundation for measuring success of any new treatment begins with clinical trials which evaluate the safety, tolerability, and efficacy of a particular therapy under carefully controlled conditions. Since the determination of treatment efficacy is one of the most important goals of any clinical trial, the role of conventional imaging with $^{18}$F-FDG PET, CT, and MRI becomes paramount for assessing response to therapy in solid tumors and hematologic malignancies. This is especially true in lymphoma since many of the subtypes exhibit robust glucose metabolism via the Warburg effect. This makes the acquisition and interpretation of $^{18}$F-FDG PET scans one of the most critical aspects of assessing treatment response.

Since 1999, there has been an evolution in defining radiologic-based treatment response criteria, driven by the desire to standardize the use of $^{18}$F-FDG PET in clinical trials (and clinical practice). The goal of many of these criteria has been to incorporate both anatomic (i.e., CT or MRI) and metabolic (i.e., $^{18}$F-FDG PET) imaging into a composite endpoint of overall response. A brief overview of the advancement of these guidelines, their key features and how we can help to make your trial successful will be the focus of this white paper. At Imaging Endpoints, we continue to set the iCRO standards for lymphoma trials and have been honored to support the most notable clinical trials in the industry, leading to regulatory approval and helping to save patients' lives.

**Historical Overview[1,2,3]**

The initial criteria for assessment for lymphoma evaluation in clinical trials included the 1999 IWG-NHL guidelines, also referred to as Cheson 1999. Cheson 1999 relied on the use of diagnostic CT (or MRI) performed at each time point. At that time, $^{18}$F FDG-PET was not routinely utilized in the assessment of lymphoma due to the lack of widespread availability and limited experience with this modality. The Cheson 1999 criteria also included a now-historical category of response, Complete Response Unconfirmed (CRu). CRu was used to capture a Complete Response (CR) in the presence of nodes that decreased in size but remained above the size threshold for normal.

By 2007, there was a growing recognition of the importance of the use of PET in the response evaluation of FDG avid tumors (e.g., Diffuse Large B Cell Lymphoma or DLBCL and HL) which resulted in an update to the Chesson criteria. In this 2007 update, both diagnostic CT along with $^{18}$F-FDG-PET/CT performed at designated intervals were considered important for determining a complete response as well as to substantiate any progression observed on CT. Cheson 2007 helped to establish the use of $^{18}$F FDG-PET for PET-avid lymphoma trials and to assist the radiologist in identifying target lesions at baseline (target lesions were to be FDG-avid while non-target lesions were considered FDG negative). FDG-PET also contributed to the overall response assessment at follow-up time points to evaluate for complete response (i.e., complete remission). In this process of integrating $^{18}$F-FDG PET with CT, there was a recognition that residual tumor may be present on CT but may not have any FDG uptake. In which case, the patient may be considered to have achieved a response despite residual disease on CT. On the other hand, if a CR was met on CT (i.e., normalization of lymph nodes by size criteria), but the PET remained positive, the CR would be downgraded to a Partial Response (PR). New lesions were required to meet minimum size criteria on CT and be PET-positive for FDG Avid malignancies.

Although Cheson 2007 criteria made significant improvements over the original 1999 publication, there were assorted unresolved issues and challenges along with wide-ranging interpretations. This led to difficulties in comparing clinical trial outcomes. Some of the most challenging issues revolved around the manner of evaluating sites of disease involvement. Specifically, should measurable disease include both nodal and extra-nodal sites and, if so, how many total sites of disease should be followed? Since lymphomas can often involve solid organs, such as the spleen, leading to splenomegaly (and, at that time, a belief that it could also result in diffuse, non-focal liver enlargement), how should organ size be evaluated (e.g., visually, by volume, or by length) and what would constitute a threshold measurement for enlargement? There also remained uncertainty on how to evaluate bone marrow involvement (e.g., bone marrow biopsy vs. on $^{18}$F FDG PET uptake)

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1 Cheson BD, Horning SJ, Coiffier B, et al. (1999). Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's lymphomas: NCI Sponsored International Working Group. *J Clin Oncol, 17,* 1244-1253.

2 Cheson BD, Pfistner B, Juweid ME, et al. (2007). Revised Response Criteria for Malignant Lymphoma. J Clin Oncol, 25, 579-586.

3 Cheson BD, Fisher RI, Barrington SF, et al. (2014). Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. Journal of Clinical Oncology 32:3059-3067

and a requirement to consider clinical symptoms (e.g., B-Symptoms) in the outcome measurements. Finally, the evaluation of progression in Cheson 2007 was also widely interpreted in clinical trials. For example, progression could be met by an increase in the sum of perpendicular diameters (SPD) of all measured lesions, an increase in diameter of a single lesion, or by an increase in the product of the perpendicular diameters (PPD) of a single lesion. To address these ambiguities, the Cheson 2007 criteria was updated in 2014 following several consensus meetings in Lugano, France, and was cumulated in a final opinion paper for the 2014 updates.

**The Lugano Classification**

The Lugano Classification sought to remediate several past issues with the Cheson 2007 guidelines. The key features of Lugano that distinguish this criterion from the previously published guidelines included:

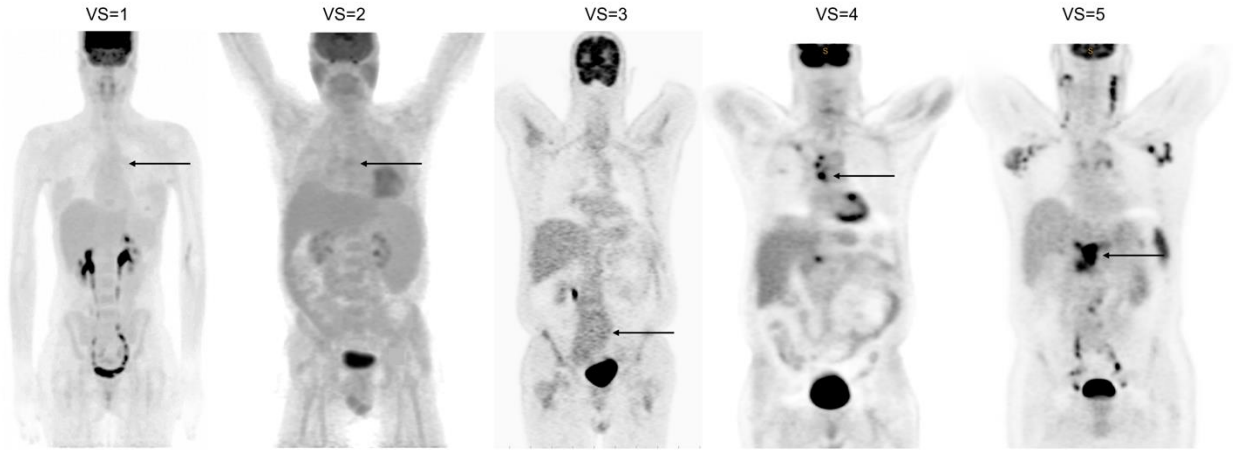
- Standardizing the staging of FDG-avid lymphomas
- Moving response by $^{18}$F FDG-PET for FDG-avid histologies away from a binary assessment of either presence/absence to a more robust 5-point visual scale based upon normal uptake in the liver and mediastinal blood pool activity as reference organs in which to rate $^{18}$F FDG uptake (Figure 1)
- Bone marrow biopsy were no longer indicated for the routine staging of HL and most DLBC. FDG-PET should be used instead for the assessment.
- Providing guidance on quantifying organ enlargement: spleen is considered enlarged on CT when vertical (cranial to caudal) length >13cm, and removing liver size as an organ of interest
- Providing clear guidelines that single lesion progression was consistent with Progressive Disease (PD) in which the Product of Perpendicular Diameter or PPD progression of single site clarified, and SPD progression no longer warranted
- Minimizing unnecessary scanning, thus avoiding undue radiation exposure

Implementing Lugano 2014 has been a step forward for the clinical trial community seeking to apply this criterion in new protocols or on-going programs as it has placed the use of $^{18}$F FDG PET front and center in determining response. Despite the relative importance of $^{18}$F FDG PET over CT in determining response and progression for FDG-avid histologies, this may not necessarily apply to non-avid histologies or unknown FDG-avid lymphomas where CT assessments are essential for overall time point responses.

**Evaluation of the Lugano Classification**

Lugano essentially provides a dual modality approach to the evaluation of response: an assessment on CT (or MRI) scan based on size criteria and an assessment on PET/CT for metabolic response. While Cheson 2007 utilized a binary PET positive/negative approach, the Lugano Classification relies on a more robust visual evaluation utilizing a five-point scale (5-PS) to evaluate the PET score at a time point (Figure 1).

**Figure 1: 5-Point Scale for Evaluating FDG Uptake in Lymphoma**




This figure shows representative examples of the visual score (VS) adopted in the Lugano 2014 guidance criteria for treatment response in FDG Avid Lymphomas (see Table 1 for details of PET scoring system). Arrows point to the lesion with the highest FDG uptake from which the VS is derived.

The tables below provide information regarding the visual PET scoring system and Lugano criteria responses.

**Table 1: 18F FDG PET Visual Score**

| Visual Score | Evaluation Criteria |
|---|---|
| **1** | No uptake above background |
| **2** | Hottest area of uptake ≤ mediastinum |
| **3** | Hottest area of uptake > mediastinum but ≤ liver |
| **4** | Hottest area of uptake moderately > liver |
| **5** | Hottest area of uptake markedly > liver and/or new lesions present |

**Table 2 . Criteria for Response Assessment**

| Modality | Complete Response | Partial Response | Stable Disease | Progressive Disease |
|---|---|---|---|---|
| **CT** | Lymph nodes ≤ 1.5 cm in LDi<br><br>Complete disappearance of radiologic evidence of disease | Single lesion: ↓ ≥ 50% in PPD<br><br>Multiple lesions: ↓≥ 50% in SPD of up to six lymph nodes or extranodal sites | ↓ ≤ 50% in SPD of up to 6 lymph nodes or extranodal sites (no criteria for progressive disease are met) | At least 1 of the following:<br>1) New lymphadenopathy or ↑; single node must be abnormal with:<br>a. LDi > 1.5 cm and<br>b. ↑ ≥ 50% from PPD nadir and<br>c. LDi or SDi ↑ 0.5 cm if ≤ 2.0 cm and ↑ 1.0 cm if > 2.0 cm<br>2) ↑ splenic volume:<br>a. with prior splenomegaly: ↑ > 50% of its prior ↑ beyond baseline<br>b. Without prior splenomegaly: ↑ > 2.0 cm<br>c. New or recurrent splenomegaly<br>d. New or larger nonmeasured lesions<br><br>3) Recurrent previously resolved lesions<br><br>4) New extranodal lesion > 1.0 cm in any axis (new lesions < 1.0 cm in any axis are included if attributable to lymphoma)<br><br>5) A new node >1.5 cm in any axis |
| **FDG PET-CT** | Scores 1,2,3 in nodal or extranodal sites with or without a residual mass | Scores 4 or 5 with ↓uptake compared with baseline<br><br>and<br><br>residual mass(es) | Scores 4 or 5 with no obvious change in FDG uptake | Scores or 5 in any lesion with ↑ uptake from baseline<br><br>and/or<br><br>New FDG-avid foci |

LDi = longest transverse diameter; SDi = shortest transverse diameter ; PPD = product of perpendicular diameters; SPD = sum of the product of the perpendicular diameters of multiple lesions; ↑ = increase; ↓ = decrease

While the use of FDG-PET using a 5-PS visual assessment score is a qualitative assessment, there is no clear consensus on how to use quantitative measurements such as Standard Update Values (SUVs) to determine response or progression. There are two major concerns over using quantitative assessments with SUV measurements: (1) the possible inherent bias for deriving a response based on a SUV score and (2) the high degree of variability in SUV measurements between scan visits. For example, SUV measurements can be very sensitive to patient preparation, fasting glucose levels, injected dose, uptake period prior to scanning, scanner acquisition, reconstruction parameters, and patient-related artifacts. As a result, the reliance on SUVs cannot generally be trusted across a

clinical trial population using multiple sites, different scanners, or between patient time points, unless there is phantom harmonization across sites and/or strict attention to details of image acquisition. Each of these conditions can affect SUV measurements. As a result, a lesion SUV of 5.0 may be similar to liver (5-PS score of 3) uptake at one imaging time point, but greater than liver uptake on the following time point (5-PS score of 4). Based on SUV measurements, in this case there would be no change in FDG activity, but there would be a change in VS leading to an assessment of disease progression. Consequently, Imaging Endpoints recommends that while SUVs may be utilized in the evaluation of $^{18}$F FDG PET scans for lymphoma response, they should not be used as a sole driver for determining Lugano outcomes. The PET imaging program overseen at Imaging Endpoints has been instrumental in performing site/scanner standardization and harmonization using phantom programs so that quantitative assessments can be successfully conducted in many multi-institutional clinical trials.

**Assessment of Solid Organ Involvement: Spleen Measurements**

The spleen is a very important organ of the lymphatic system that can become involved with disease, causing either focal tumor nodules (which can be selected as target lesions) or diffuse lymphomatous infiltration, leading to splenomegaly. The latter type of splenic involvement is generally assessed by measuring splenic length. The upper limits of normal for spleen length has been established by Lugano 2014 to be 13.0 cm. Any measurement beyond 13.0 cm is considered to be related to lymphoma. There have been several attempts to standardize splenic length assessments. A recent consensus panel led by Imaging Endpoints and including lymphoma experts, academia, and industry key opinion leaders has recommended the use of axial CT slices from a diagnostic CT scan to determine spleen length. In this approach, the anatomic landmark locations (known as slice levels) that span the full length of the spleen are used to determine the most consistent estimate of spleen size. For example, if the topmost part of the spleen is present on axial slice location +100.0mm and the bottom most part of the spleen is present on axial slice location +190.0 mm, then the splenic length is 90 mm (190.0 mm – 100.0 mm) or 9.0 cm. This approach is better than trying to estimate spleen size on coronal views (due to off-axis placement of the measurement), or directly from the $^{18}$F FDG PET scans (since FDG PET can misrepresent organ size).

**Implementing the Lugano Classification: Uncertainty Remains**

Although the Lugano criteria provides additional instructions on its implementation during clinical trials, there can be challenging scenarios that may occur during the trial that can affect the results, whether due to differences in findings between FDG-PET and diagnostic CT, image quality challenges between time points, or areas that are not clearly specified in the criteria. As an example, which lymph nodes should be included as target lesions assessments (largest, most FDG avid, etc.) is not clearly defined. How should the spleen be measured for the most accurate and consistent assessment of splenic involvement? Should bone marrow uptake on $^{18}$F FDG PET scans alone be considered as a marker of marrow involvement, and if so, what is the role of a bone marrow biopsy? How does the reader account for $^{18}$F FDG PET ambiguities in image assessments during study review (e.g., potential false positive and false negative imaging findings)? What is the frequency of acquiring diagnostic CT and $^{18}$F FDG PET imaging? What is the most appropriate read paradigm for clinical trials? Should an independent oncology review be included in your trials?

Addressing these topics prospectively is critically important to successfully using the Lugano

Classification in your clinical trials, particularly for Phase III and/or registration studies. Imaging Endpoints understands these complexities and nuances, and our experience in implementing Lugano will help you at every step of the way to make your clinical trial a success.

**PRoLog Consensus Initiative[8]**

Despite recent advances and clarification of Lugano 2014, additional challenges and clarifications not addressed by this updated response assessment can arise during blinded centralized reviews of imaging in a clinical trial setting. Given Imaging Endpoints' success in obtaining regulatory approval for lymphoma treatments and our recognition of the key technical and operational challenges that required prospective attention to achieve these approvals, Imaging Endpoints was selected to spearhead a consensus effort of key opinion leaders from the International Working Group (IWG), academia, and industry to address several concerns that have surfaced when using Lugano 2014. Through the auspices of PINTaD[4], the PRoLoG Committee ( PINTaD Response Criteria in Lymphoma Working Group) was established to provide best-practice consensus guidance for applying Lugano criteria in clinical trials.

In this working group, several issues were addressed with specific recommendation offered, including:

- The use and frequency of performing $^{18}$F FDG PET-CT
- The use of a diagnostic CT with contrast injection (should be based on lymphoma histology and stage, FDG-avidity, and efficacy endpoints)
- The importance of both $^{18}$F FDG PET-CT and a diagnostic CT with contrast at baseline
- The importance of $^{18}$F FDG PET over CT in FDG-avid lesions at baseline and for treatment response
- The need for patients without FDG-avid lesions at baseline to be followed by diagnostic CT (unless transformation is suspected)
- How to measure the spleen and integrate this organ in overall response assessments
- The need to consider the technical aspects and potential artifacts of $^{18}$F FDG PET in image interpretation

These topics and other recommendations are being published to help standardize the implementation of Lugano 2014.

4 Pharma Imaging Network for Therapeutics and Diagnostics

### Refinement of Lugano Classification in the Era of Immunotherapy (LYRIC 2016 [5])

The use of immunotherapy and cellular therapy has uncovered an interesting pattern of tumor growth followed by response. This pattern of progression followed by response has been coined "pseudo-progression" and is thought to be related to tumor swelling and new lesion growth, either because of delayed activation of the immune system or directly related to immune cell infiltration of tumor lesions. In recognition of this phenomenon, Lugano 2014 has been modified to allow for a period of disease progression before the onset of response, provided that the patient is clinically stable. To account for pseudo-progression during real-time assessment of response, the term "Indeterminate Response" has been added to the response criteria as a way to address such changes in lesion size and tumor burden until confirmed as being true progression. In patients categorized as having any indeterminate response (IR), a repeat imaging after 12 weeks is required. Several ongoing trials at Imaging Endpoints are now using the LYRIC criteria in the setting of immune therapy. These guidelines have yet to be validated by the agency for use as the primary criteria for assessing lymphoma responses, but the use of LYRIC can nonetheless be valuable for secondary and exploratory imaging endpoint.

**Table 4. Comparison of the Overall Assessment by LYRIC vs. Lugano criteria**

| LYRIC Criteria | CR | PR | PD |
|---|---|---|---|
| | Same as Lugano | Same as Lugano | As with Lugano with following exceptions<br><br>IR1: ≥50% increase in SPD in **first 12 weeks**<br><br>IR2: <50% increase in SPD with new lesion or ≥50% increase in PPD of one or more lesion at **any time** during treatment<br><br>IR3: Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD at **any time** during treatment |

### International Working Group Consensus Response Evaluation Criteria in Lymphoma (RECIL 2017)

Recognizing the success of implementing RECIST 1.1 by performing unidimensional lesion measurements compared to bidimensional measurements, the International Working Group has defined a new set of criteria for measuring disease in lymphoma patients on CT. Known as the RECIL

5 Cheson BD, Ansell S, Schwartz L, et al: Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood 128:2489-2496, 2016

Working Group, they hypothesized that single-dimension measurement of a maximum of three target lesions rather than bidimensional measurements of a maximum of six lesions (suggested by Lugano 2014) could be accurately used to assess therapeutic responses in lymphoma patients, similar to Lugano 2014. The RECIL criteria are more aligned with RECIST and are applicable for both adult and pediatric patients with lymphoma.[6] This criterion also provides some guidance on specific thresholds to integrate more quantitative $^{18}$F FDG uptake into an overall response assessment. RECIL may also be very useful in non-FDG Avid Lymphomas. A head-to-head comparison of this criteria compared to Lugano 2014 in active clinical trials is underway and Imaging Endpoints has incorporated both Lugano and RECIL in current studies. A table comparing RECIST, Lugano 2014, and RECIL 2017 is shown below.

**Table 3. Comparison of RECIST 1.1, Lugano and RECIL 2017 criteria**

| | RECIST 1.1 | Lugano 2014 | RECIL 2017 |
|---|---|---|---|
| Number of Target Lesions | Up to 5 | Up to 6 | Up to 3 |
| Measured methods | Uni-dimensional: long diameter of non-nodal lesions, short diameter of lymph nodes | Bi-dimensional: perpendicular diameters | Uni-dimensional: long diameter of any target lesion |
| Incorporates PET results to describe CR | May be considered to confirm CR and/or to declare PD based on detecting new lesions | Yes | Yes |
| CR | Complete disappearance of all target lesions and all nodes with long axis <10mm<br><br>No New Lesions | Complete disappearance of all target and all nodes with long axis <10mm*<br><br>Normalization of $^{18}$F FDG (VS 1-3) and no new lesions<br><br>Spleen size is normal<br><br>No bone marrow involvement | Complete disappearance of all target lesions and all nodes with long axis <10mm.<br><br>≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET<br><br>Spleen size is normal<br>No bone marrow involvement |
| PR | 30% or more reduction in target lesions, stable to improved non-target lesions, no new lesions | CT: 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. Spleen must have regressed by 50% in length beyond | CT: ≥30% decrease in the sum of longest diameters of target lesions but not a CR<br><br>FDG PET: Visual Score 4 |

6 Younes A, Hilden P, Coiffier B, et al. (2017). International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Annals of Oncology 28: 1436–1447.

| | | | |
|---|---|---|---|
| | | normal. No New lesions<br><br>FDG PET: Visual Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size. Bone marrow residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed) | or 5 with reduced uptake compared with baseline and residual mass(es) of any size. Bone marrow residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed) |
| Minor response | No | No | Yes, reduction in sum of long diameters between ≥10% and <30% |
| Stable disease | Not CR, PR or PD | Not CR, PR, PD | Not CR, PR, MR or PD |
| PD | Increase in sum of diameters by 20% | Increase in the sum of products of perpendicular diameters by>50%, or any single lesion by>50% | Increase in sum of the longest diameters by 20%. For relapse from CR, at least one lesion should measure 2 cm in the long axis with or without PET activity |

CR, complete response; PD, progression of disease; PET, positron emission tomography.

* In certain circumstances, residual anatomic lesions without FDG uptake in FDG Avid lymphomas may be considered a CR.

**Evolving Landscape of Lymphoma Assessments: Metabolic Tumor Volumes**

Since the publication of Lugano 2014 with the use of the 5-point scoring system, there has been growing interest in more quantitative assessments of FDG uptake. Although qualitative visual assessment of $^{18}$F FDG Uptake remains the mainstay of measuring treatment response, several studies have indicated that measuring the "metabolic" tumor volume (MTV) of the entire lymphoma tumor burden rather than SUV measurements of a subset of lesions may be a more robust method for predicting response and adverse events. In MTV analysis, the volume of disease is estimated by detecting the volume of pixels that contain FDG signal above a certain threshold (e.g., 41% or greater of SUVmax). The resultant measurement of MTV (with units of cubic centimeters) can then be followed longitudinally to determine the change in the extent of disease.

Although these new trends in lymphoma assessments are gaining more interest, many have yet to be tested in the regulatory approval environment. Nevertheless, Imaging Endpoints has been involved in incorporating these more recent methods of analysis in lymphoma trials (especially as secondary and exploratory endpoints) as well as using novel PET tracers in lymphoma subjects. At Imaging Endpoints, we are pioneering new methods for automatically detecting abnormal FDG PET lesions and quantitating MTV. These examples show you the many ways that Imaging Endpoints helps to "connect imaging to the cure."

**Radiologist Readers and Evaluation of Lymphoma**

Imaging Endpoints strongly recommends that reviewers of the CT and $^{18}$F FDG PET images have appropriate knowledge, experience, and expertise in both imaging modalities. Imaging Endpoints has best-in-class imaging and oncology experts and has specific recommendations to improve the evaluation of lymphoma by any of the criteria discussed in this white paper in a central review setting. Most critically, we provide the radiologist with testing and training cases of unique situations to assist in robust reader rules for applying criteria in clinical trials. We monitor all read results to ensure a high-quality review.

**Imaging Endpoints Experience and Expertise in PET**

Imaging Endpoints has maintained a leadership role in PET imaging services and analysis for the clinical trial industry for many years. This is due in part to our extensive team of physicians, scientists, and technologists who are engaged in all aspects of PET imaging and have eagerly contributed to PET science and technology. Moreover, our dedicated in-house and expert PET-trained radiologists can not only offer content expertise, but are amongst the key opinion leaders in the field today. Our readers and key opinion leaders have contributed significantly to lymphoma clinical trials through regulatory approvals and key publications. Please visit our website for additional information at www.imagingendpoints.com.

**Imaging Endpoints: Exceptional Scientific Guidance**

As a leader in PET imaging and with study teams that have extensive expertise in lymphoma clinical trials, Imaging Endpoints is poised to successfully implement the most relevant read paradigms for lymphoma evaluation to meet your study needs. We excel in dedicating expert and nimble project teams that adapt to meeting the changing demands of your trials. We routinely work with our

sponsors to not only design their central review plan but to assist in protocol development, case report form development, and assessment criteria utilization, ensuring a robust final data set. We will assist you by providing guidance, expertise, and planning of your product pipeline to ensure that every aspect of radiology science has been fully utilized. As your partner, we will take the lead in developing imaging protocols/techniques that will take advantage of the latest imaging discoveries in oncology and immunology to successfully integrate them into the multicenter environment that will focus on the needs of your clinical trial.

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## NEW ERA OF DRUG DEVELOPMENT USING IMAGING ENDPOINTS' iCRO EXPERTISE

A new era for exploiting the power of medical imaging beyond standard criterion is upon us. The industry demands that more customized and sophisticated approaches be incorporated into clinical trials to help evaluate eligibility and efficacy, or to determine optimal dose. Our scientific and regulatory experts customize, optimize, and standardize the imaging analysis criteria for each unique trial based on the specific demands of the drug, protocol and trial objectives. We also deploy advanced imaging technologies to maximize trial data, and our international experts support regulatory submissions and approvals across the globe. These are just some of the reasons that Imaging Endpoints has emerged as the largest, most respected Imaging CRO in oncology. Please contact us if you would like to learn more about the leading technologies, expertise, and services that we offer.

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