Criteria-Based Imaging and Response Evaluation of Lymphoma 20 Years After Cheson: What is New?
A Review of the Current Classifications

Kriterien-basierte Bildgebung und Responsebeurteilung bei Lymphomen 20 Jahre nach Cheson: Was gibt es Neues?
Eine Übersicht zu den aktuellen Klassifikationen

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ABSTRACT
Background The rapid progress in oncology research requires numerous new scientific publications. This article aims to provide an overview of criteria-based imaging and response evaluation of lymphoma according to the current status of knowledge. In fact, common criteria for evaluating data, especially imaging response evaluation, are essential for comparability of studies. While criteria-based classifications of solid tumors have been established for some time, there are now increasing classifications of lymphoma diseases. The purpose of this review is to describe the development of criteria-based evaluation of lymphoma diseases with a special focus on imaging up to current guidelines.

Methods Literature review based on PubMed including the languages English and German was performed. This review article includes the most important criteria-based response evaluations of lymphoma published between January 1999 and July 2019.

Results and Conclusion The two latest classifications of response evaluation of lymphoma are: The Lugano classification, which has been steadily developed over the past 20 years and has been specially adapted to technical progress, as well as the evaluation method RECIL (Response Evaluation Criteria In Lymphoma), which is based on the RECIST (Response Evaluation Criteria in Solid Tumors) classification already established for solid tumors. Significant imaging components of both classifications are the anatomical measurement and measurement of the metabolic response of the manifestation of lymphoma using positron emission tomography (PET/CT).

Key Points:
▪ Standardized criteria-based response evaluations are essential for the objective and comparable analysis of new drugs for the treatment of lymphoma diseases.
▪ The latest classification RECIL has significantly simplified treatment evaluation and has established a better comparability to the therapeutic evaluation of solid tumors according to RECIST.
▪ Further studies will show the most appropriate classifications depending on study settings.

Citation Format

ZUSAMMENFASSUNG
Hintergrund Der schnelle Fortschritt in der onkologischen Forschung bedingt eine Vielzahl neuer wissenschaftlicher Publikationen. Dieser Beitrag möchte daher einen Überblick...
Introduction

Lymphoma treatment is constantly progressing. New treatment approaches utilize antibodies, immunotherapeutics, and antibody-drug conjugates. To be able to provide optimal treatment for every patient, an individualized treatment approach is needed [1]. In addition to clinical parameters, oncological imaging is often decisive for evaluating the effectiveness of new therapeutic agents. The goal of criteria-based evaluation of imaging is to ensure objective, standardized, comparable, and uniform evaluation during and after treatment. This review article describes the development as well as the current state of follow-up of Hodgkin and Non-Hodgkin lymphoma. The integration of standardized morphological imaging with metabolic response (PET/CT) and highly sensitive methods for detecting residual cells in blood and bone marrow (minimal residual disease, MRD) is particularly important. On the whole, there is a trend from purely expert-based consensus criteria to criteria based on study data.

Cheson criteria (IWG criteria) [2]

While there has been a committee-based classification for Hodgkin lymphoma (HL) since 1989 [3], the first generally recognized standardized classification of non-Hodgkin lymphoma (NHL) was the International Working Group (IWG) classification published by Cheson et al. The classification focused on anatomical measurements of the manifestations of lymphoma. [2]

For the total response evaluation, the Cheson classification takes clinical and laboratory criteria as well as bone marrow biopsy results into consideration in addition to the radiological criteria. Computed tomography (CT) is recommended as the imaging modality of choice. Chest, abdominal, and pelvic CT examination is recommended. CT scan of the neck is typically also performed in clinical application although this examination was not required in the original publication. The following parameters are relevant for the radiological evaluation and corresponding classification (Fig. 1):

- Great transverse diameter (GTD): Greatest lesion dimension in the transverse section.
- Short axis diameter (SAD): Shortest lesion dimension in the transverse section, orthogonal to the GTD. A lymph node > 1 cm in the SAD is considered suspicious. [4–8]
- Sum of the product of the diameters (SPD): The product of the GTD and SAD from a maximum of six “dominant” nodal manifestations is calculated. These products are then totaled. The selected lesions should be distributed in the body to the greatest extent possible and at least one lesion from the retroperitoneum and one from the mediastinum should be selected if present. Lesions in other organs outside the liver and spleen can be detected but not measured as a dominant lesion.

The results of every follow-up imaging examination are classified into one of the six response categories. In addition to the SPD and the occurrence of any new lesions, clinical parameters are essential here. For the first Cheson classification, the size of the spleen and liver was characteristically determined only by clinical examination and not imaging. Complete response unconfirmed (CRu) is a special category. The individual response categories of the Cheson classification are provided in Table 1.

Revised Cheson criteria [9]

The Revised Response Criteria for Malignant Lymphoma published in 2007 was a major revision of the Cheson criteria [9]. In particular, technical advancements in the field of hybrid imaging were taken into consideration. The main changes were:

- The treatment of Hodgkin lymphoma is now also evaluated according to the Cheson criteria. The classification according to Lister et al. was previously used [3].
- The “complete response unconfirmed” (CRu) category was eliminated.
- 18F-FDG-PET or PET/CT was integrated in the criteria as a functional-metabolic part of imaging.
However, PET examination should only be performed in the case of lymphoma with sufficient avidity for $^{18}$F-FDG. Known cases of PET-avid lymphoma include diffuse large B-cell lymphoma (DLBCL), Hodgkin lymphoma (HL), follicular lymphoma (FL) and mantle cell lymphoma (MCL), while chronic lymphatic leukemia (CLL), for example, is a lymphoma with only minimal FDG uptake. To date, FDG uptake in other types of Non-Hodgkin lymphoma has been examined in a variable manner or only minimally. The PET scan is categorized qualitatively only a purely visual basis as positive or negative. The PET scan is categorized as positive when the focal or diffuse uptake of $^{18}$F-FDG is higher than the background activity in a location that cannot be explained purely anatomically/physiologically.

In the case of FDG-avid lymphoma, CR is achieved when post-treatment residual lesions are PET negative regardless of their size. In patients without a pretreatment PET/CT examination, the size of the lymph nodes is decisive as in the Cheson criteria. Original lesions with a GTD > 1.5 cm must have a GTD ≤ 1.5 cm after treatment. Lymph nodes with a GTD of 1.1–1.5 cm and an SAD > 1.0 cm must have an SAD ≤ 1.0 cm after treatment. The size of the spleen and liver must be normal (again) and the spleen must not have any lesions. The morphological imaging criteria as well as the bone marrow finding are also taken into consideration in the revised Cheson criteria. As a result, despite radiological classification as CR, the treatment response can still be classified as PR if corresponding morphological changes in the bone marrow finding are seen. The additional categories are summarized in Table 2.

Lugano classification [10, 11]

A further revision of the Cheson criteria was published in 2014 [10]. This is the currently widely used “Lugano” classification of treatment response in lymphoma. The most important changes regarding imaging were:

- Replacement of the dichotomous PET evaluation with the Deauville 5-point scale (5-PS)
- Introduction of the interim PET scan during treatment

### Table 1

<table>
<thead>
<tr>
<th>CR</th>
<th>CRu</th>
<th>PR</th>
<th>SD</th>
<th>RD after CR/CRu</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>general</td>
<td>disappearance of all radiological signs of the disease</td>
<td>no new lesions</td>
<td>reduction &lt; PR, PD criteria not fulfilled</td>
<td>new lesions</td>
<td>new lesions</td>
</tr>
<tr>
<td>lymph node</td>
<td>previously &gt; 1.5 cm to ≤ 1.5 cm GTD</td>
<td>lymph node &gt; 1.5 cm GTD despite reduction of SPD &gt; 75%</td>
<td>reduction of SPD ≥ 50% of the 6 most dominant lymph nodes or nodal masses</td>
<td>increase in the GTD ≥ 50% of an existing lymph node &gt; 1.0 cm SAD or increase in SAD ≤ 50% in multiple lymph nodes/nodal masses</td>
<td>increase in SAD ≥ 50% of the target lesions</td>
</tr>
<tr>
<td>extranodal manifestation</td>
<td>spleen normalized and lesion-free</td>
<td>no increase in the size of the liver, spleen</td>
<td>reduction of SPD ≥ 50% of the lesions in the spleen and liver</td>
<td>reduction of SPD ≥ 50% of the target lesions</td>
<td></td>
</tr>
</tbody>
</table>


![Fig. 1](image) Schematic drawing of the anatomical parameters (in this example, a total of three “dominant” nodal manifestations were chosen to calculate the SPD. This matches with the sum of all green rectangles).
The 5-PS is a purely visual qualitative assessment that allows a more differentiated classification than was possible with the previous method of evaluating FDG uptake. The criteria for the 5-PS are summarized in ▶ Table 3 [12–14].

The interim PET examination makes it possible to adjust treatment earlier in some cases. Therefore, it is possible to respond more quickly in the case of a lack of treatment response so that corresponding treatment escalation can be initiated or, in the case of early treatment response, treatment can be deescalated to minimize toxicity and secondary diseases [15–18]. The German Hodgkin lymphoma study group was recently able to convincingly prove this concept in the HD18 study: treatment de-escalation on the basis of the interim PET resulted in better overall survival due to lower toxicity [19]. In the recently published PETAL study, the prognostic significance of the interim PET scan for diffuse large B-cell lymphoma was also convincingly shown even if an attempt to escalate treatment with a more aggressive protocol for PET-positive patients was not successful [20]. Studies were able to confirm the advantages of 5-PS compared to the previously recommended dichotomous PET evaluation [21–23].

The “product of the perpendicular diameters” (PPD) is introduced in the anatomical evaluation as a new term. It is the product of the orthogonal diameter, i.e., the product of the GTD and the SAD. While the PPD relates to an individual lesion, the SPD is the sum of multiple PPDs. In prior classifications, an increase in the PPD of an individual lesion could be offset in the sum, the SPD, by the absent or smaller increase in size of the other lesions. The PPD is particularly important for the PD classification. An increase in the size of an individual lesion by ≥50 % in the PPD can now result in classification as progressive. For categorization as SD or PR, a change in the SPD is still the decisive parameter.

A maximum of six dominant lesions are still measured. If possible, the measurement should include a retroperitoneal and a mediastinal lesion. The definition of (extra-) nodal lesions was simplified. Nodal lesions with a diameter > 1.5 cm and extranodal lesions > 1.0 cm are now considered measurable regardless of the axis. An SAD > 1.0 cm is no longer a requirement for defining a measurable lesion.

Enlargement of the spleen was defined more precisely. Per definition, spleen involvement is present starting at a vertical diameter > 13.0 cm. The percentage change in the enlargement of the spleen is monitored during and after treatment. A decrease in a vertical spleen diameter over the limit of 13 cm by >50 % is classified as PR. A spleen with a vertical diameter of 18 cm is 5 cm over the normal size (5 cm = absolute spleen enlargement). A decrease in the spleen diameter after treatment to 15 cm thus means a reduction in the spleen enlargement of 60 % (3 cm/5 cm × 100), corresponding to PR. It is important that only a spleen that is enlarged above the limit value of 13 cm needs to be evaluated. A reduction in the size of the spleen only from 18 cm to 16 cm, i.e., a 40 % decrease in the spleen enlargement (2 cm/5 cm × 100), can at best be classified as SD.

### Table 2 Response classification according to the Revised Response Criteria for Malignant Lymphoma (Revised Cheson).

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>• lymph node &gt; 1.5 cm to ≤ 1.5 cm GTD</td>
<td>• reduction of SPD ≥ 50 % of the max. 6 most dominant lymph nodes</td>
<td>• no increase in size of existing lesions</td>
</tr>
<tr>
<td></td>
<td>• lymph node &gt; 1.0 cm and ≤ 1.5 cm GTD and &gt; 1.0 cm SAD to ≤ 1.0 cm SAD spleen/liver:</td>
<td>• no increase in other lesions and no new lesions spleen/liver:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• spleen/liver normal-sized and lesion-free</td>
<td>• reduction of SPD ≥ 50 % in multiple lesions</td>
<td></td>
</tr>
<tr>
<td>PET in FDG-avid or PET(+) lymphomas</td>
<td>• negative without size limitation</td>
<td>• reduction of GTD ≥ 50 % in solitary lesions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• positive existing lesion(s)</td>
<td>• no increase in size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• positive existing lesion(s) and no new lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• positive</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Table 3 Deauville five-point scale (5-PS).

<table>
<thead>
<tr>
<th>score</th>
<th>criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no 18F-FDG uptake</td>
</tr>
<tr>
<td>2</td>
<td>uptake ≤ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>uptake &gt; mediastinum and ≤ liver</td>
</tr>
<tr>
<td>4</td>
<td>uptake moderately above liver level</td>
</tr>
<tr>
<td>5</td>
<td>uptake significantly above liver level and/or new lesion(s)</td>
</tr>
<tr>
<td>X</td>
<td>new uptake region(s), most likely not part of lymphoma</td>
</tr>
</tbody>
</table>

FDG: fluorodeoxyglucose.
Previously measured lymph node conglomerates (bulky disease) that separate over the course of treatment are handled slightly differently. The PPDs of the individual lesions are now calculated. These separated individual lesions are also part of the SPD in the further course even if that means that the maximum number of 6 is exceeded [11]. The response criteria according to Lugano are summarized in ▶ Table 4.

The Lugano classification is primarily used in cases of malignant lymphoma with nodal involvement. However, as a rule, it can be used for all malignant lymphomas, even primary extranodal diffuse large B-cell lymphoma. The Response Criteria for Primary CNS Lymphoma [24] published by Abrey et al. are used for CNS lymphomas, the European Society for Oncology (ESMO) Clinical Practice Guidelines for diagnosis, treatment and follow-up are used for MALT (Mucosa-Associated Lymphoid Tissue) lymphomas [25], and the Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome published by Olsen et al. are used for cutaneous lymphomas [26]. The recently published response criteria for chronic lymphatic leukemia are also based on the Lugano classification [27].

An example of an evaluation according to the Lugano criteria is shown in ▶ Fig. 2. The measurement parameters and the calculated values are shown in ▶ Table 5. If no spleen and liver lesions are present, the anatomical measurements of the target lesions are decisive for the response classification. A decrease in the SPD of 82.3 % results in a treatment response categorization as PR.

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
</table>
| CT: radiological response | all criteria met:  
  - no new lesions  
  - reduction ≤ 1.5 cm GTD of target lesions  
  - no extranodal manifestation  
  spleen/liver:  
  - spleen and liver normal-sized  
  new lesions: None | • reduction of SPD of the max.  
  6 measurable target lesions  
  (nodal/extranodal) ≥ 50 %  
  - lesions that are too small/ 
  not measurable are assigned 
  a size of 0.5 × 0.5 cm  
  - lesions that are not visible 
  are assigned a size of 
  0 × 0 cm  
  spleen/liver:  
  - length reduction > 50 % of the enlarged spleen  
  new lesions: none | • reduction of SPD of the max.  
  6 measurable target lesions  
  (nodal/extranodal) < 50 %  
  - PD criteria not met new lesions: none | at least 1 criterion met:  
  abnormal lymph nodes must meet the following criteria:  
  - GTD > 1.5 cm and  
  - PPD increase ≥ 50 % and  
  - increase of GTD or SAD by  
  - 0.5 cm for ≤ 2.0 cm  
  - 1.0 cm for > 2.0 cm  
  spleen/liver:  
  - in the case of existing splenomegaly: Increase in the size of the spleen > 50 %  
  - in the case of newly occurring splenomegaly: Increase in the length of the spleen ≥ 2.0 cm with respect to baseline  
  new lesions:  
  - recurrence of lesions that had already returned to the normal range  
  or  
  - new nodal lesion > 1.5 cm regardless of the axis  
  or  
  - new extranodal lesions > 1.0 cm regardless of the axis or ≤ 1.0 cm in the case of clear assignment to lymphoma  
  PET/CT: metabolic response | score 1/2/3 according to 5-PS without residual disease  
  new lesions: none | score 4/5 according to 5-PS with reduced ¹⁸F-FDG uptake with respect to baseline  
  and residual lymph nodes of any size  
  new lesions: none | score 4/5 according to 5-PS  
  new lesions: None | score 4/5 according to 5-PS with increase in ¹⁸F-FDG uptake with respect to baseline  
  new lesions: New ¹⁸F-FDG-avid typical lymphoma lesions  


Table 4 Response evaluation according to Lugano.
Fig. 2 Computed tomography of a 40-year-old man with Hodgkin lymphoma. The left side shows the pretherapeutic images (baseline), and the right side shows the images after chemotherapy (follow-up). **a, b** Mediastinal lymph node. **c, d** Right axillary lymph node. **e, f** Retroperitoneal lymph node.
LYRIC (Lymphoma Response to Immunomodulatory Therapy Criteria) modification [28]

Due to the increasing importance of biopharmaceuticals in the treatment of lymphomas, it became necessary to expand the Lugano classification in 2016 [29]. Immune-modulating biopharmaceuticals can have more diverse effects than the classic treatment consisting of chemo-(immuno-)therapy. In particular, an increase both in the size and number of lesions prior to actual treatment response can initially occur (known as pseudoprogression). Moreover, a metabolic flare phenomenon, i.e., increased tracer uptake as part of (good) treatment response, can occur in 18F-FDG-PET. Indeterminate response (IR) is only used in the PD category. If the IR criteria are met in patients in category PD according to Lugano, treatment can initially be continued. Biopsy of the corresponding lesions can be helpful. Over the course of 12 weeks, imaging is performed again to determine whether it is a case of treatment-based transient PD or actual PD [28].

**Table 5** Calculation of the anatomical measurement parameters regarding the patient case in Fig. 2.

<table>
<thead>
<tr>
<th>target lesion</th>
<th>GTD in mm</th>
<th>SAD in mm</th>
<th>PPD in mm²</th>
<th>SPD in mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline/follow-up</td>
<td>baseline</td>
<td>follow-up</td>
<td>baseline</td>
<td>follow-up</td>
</tr>
<tr>
<td>lymph node, axillary right</td>
<td>43</td>
<td>18</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>lymph node, mediastinal</td>
<td>43</td>
<td>26</td>
<td>27</td>
<td>20</td>
</tr>
<tr>
<td>lymph node, retroperitoneal</td>
<td>30</td>
<td>13</td>
<td>24</td>
<td>8</td>
</tr>
<tr>
<td>lymph node, supraclavicular left</td>
<td>57</td>
<td>20</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>lymph node, cervical right</td>
<td>46</td>
<td>14</td>
<td>44</td>
<td>13</td>
</tr>
</tbody>
</table>

GTD: great transverse diameter, SAD: short axis diameter, SPD: sum of the product of the diameters.

Fig. 2. Computed tomography of a 40-year-old man with Hodgkin lymphoma. The left side shows the pretherapeutic images (baseline), and the right side shows the images after chemotherapy (follow-up). **g, h** Left supraclavicular lymph node. **i, j** Right cervical lymph node.
RECL [30]

RECL (Response Evaluation Criteria In Lymphoma) is based on the existing response evaluation for solid tumors RECIST 1.1 (Response Evaluation Criteria In Solid Tumors) [31]. A closely related classification of treatment response both of lymphomas and solid tumors provides the advantage of better comparability of new drugs in phase I and II studies [32]. The primary goal of the RECL classification is to simplify the Lugano classification for lymphomas. For this purpose, a statistical comparison of the new one-dimensional measurement and the old two-dimensional measurement according to the Lugano classification was performed. As a result, only the parameter GTD is included as an anatomical measurement parameter in the response categories according to RECL. It was also shown that the selection of a maximum of 3 target lesions instead of the up to 6 dominant lymph nodes in the Lugano classification results in comparable assignment of patients to identical response categories. The PET/CT result was not taken into consideration in the RECL study. Therefore, it continues to affect the classification the same as in the Lugano version [30]. In RECL target lesions are clearly defined (GTD ≥ 1.5 cm) regardless of their nodal or extranodal position. The minor response category is new. The main differences with respect to the Lugano classification are summarized in Table 6.

The sum of the longest diameters (SLD) of the target lesions is calculated as an important anatomical measurement parameter. Lymph nodes can be selected as the target lesion when the GTD is ≥ 1.5 cm. Particularly small, elongated lymph nodes should not be selected as the target lesion. Extranodal lesions can be selected as the target lesion when they have a soft-tissue component and a GTD ≥ 1.5 cm that can be reproducibly measured.

The conditions for CR were defined more strictly in comparison to the Lugano classification. Therefore, all defined target lesions must have a post-treatment GTD < 1.0 cm, while a reduction of the GTD to ≤ 1.5 cm was previously sufficient according to Lugano.

PET/CT continues to be recommended for FDG-avid lymphomas. The evaluation is still performed according to Deauville-5-PS. Bone marrow biopsy continues to be important for the corresponding lymphomas. The response evaluation is summarized in Table 7.

While the LYRIC modification was added to the Lugano classification to address immunomodulatory therapeutic agents, the RECL classification recommends confirming PD in two consecutive imaging examinations in the interval.

Measured lymph node conglomerates that separate over the course of treatment are treated as described in the Lugano classification. The spleen size is measured in the vertical length according to the Lugano classification with the normal size remaining < 13 cm [30].

As an example, the RECL classification is also performed for the case in Fig. 2. A maximum of 3 target lesions are selected (condition ≥ 1.5 cm). The largest lymph nodes from various anatomical lymph node stations are representatively selected for this purpose: Left supraclavicular lymph node (Fig. 2g, h) with a GTD of 57 mm, right cervical lymph node (Fig. 2i, j) with a GTD of 46 mm and mediastinal lymph node (Fig. 2c, d) with a GTD of 43 mm. The sum of the GTDs at baseline is 146 mm (= SLD). In the follow-up, the SLD is only 60 mm. This is a decrease in the SLD of 58.9 %. Since the criterion for achieving a GTD < 1.0 cm in all target lesions is not met but the SLD reduction is ≥ 30 %, the patient is also classified as PR according to the RECL classification.
While only anatomical measurement parameters were used in the first classification according to Cheson (IWG criteria), functional-metabolic imaging in the form of PET/CT was included in the revised Cheson classification. However, the evaluation was only positive or negative. In the subsequent Lugano classification, the dichotomous PET evaluation was replaced by the Deauville 5-point scale. The addition of the LYRIC modification takes into consideration the use of new therapeutic agents and their possible transient effects, such as pseudoprogression and increased metabolic activity on PET/CT. The addition of the LYRIC modification takes into consideration the use of new therapeutic agents and their possible transient effects, such as pseudoprogression and increased metabolic activity on PET/CT.

In an analysis of patients of the German CLL Study Group, the role of the MRD status was able to be examined more closely. In the case of a negative MRD status, no difference regarding progression-free survival could be shown between CR patients and PR patients with residual splenomegaly. However, MRD-nega...

### Table 8 Comparison of the response classifications according to Lugano and RECIL.

<table>
<thead>
<tr>
<th></th>
<th>Lugano classification</th>
<th>RECIL classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>anatomical measurement</td>
<td>two-dimensional</td>
<td>one-dimensional</td>
</tr>
<tr>
<td>definition of target lesion</td>
<td>nodal: GTD &gt; 1.5 cm</td>
<td>nodal/extranodal: GTD ≥ 1.5 cm</td>
</tr>
<tr>
<td></td>
<td>extranodal: GTD &gt; 1 cm</td>
<td></td>
</tr>
<tr>
<td>number of target lesions</td>
<td>max. 6</td>
<td>max. 3</td>
</tr>
<tr>
<td>number of response categories</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>SD range</td>
<td>−50% to +50% (calculation of area)</td>
<td>−10% to +20% (calculation of diameter)</td>
</tr>
</tbody>
</table>

SD: stable disease; RECIL: Response Evaluation Criteria in Lymphoma; GTD: great transverse diameter.

### Table 9 Response classification according to RECIL.

<table>
<thead>
<tr>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>complete disappearance of all target lesions and lymph nodes with GTD &lt; 1.0 cm</td>
<td>≥ 30% reduction of SLD of the target lesions, but CR criteria not met</td>
<td>≥ 10% reduction of SLD of the target lesions, but PR criteria not met</td>
<td>&lt;10% reduction or ≤20% increase in SLD of target lesions</td>
</tr>
<tr>
<td>PET/CT</td>
<td>≥30% decrease in SLD of target lesions with a score of 1/2/3 according to 5-PS</td>
<td>score 4/5 according to 5-PS</td>
<td>every score</td>
<td>every score</td>
</tr>
</tbody>
</table>

new lesions none none none none none or present


**Discussion**

A central problem regarding the imaging evaluation of lymphomas is the handling of residual disease after treatment. Lymph nodes do not disappear completely even in CR. In addition, fibrosis, inflammation, and necrosis can result in an increase in the size of the original lymph node despite tumor-free status [34]. Moreover, it must be taken into consideration that the response of the tumor stroma is greatly delayed and is thus not yet concluded in the case of an early response evaluation, especially since desmoid segments can often persist. These changes cannot always be clearly differentiated from lymph nodes with vital tumor cells based on morphological imaging data [35]. Therefore, an increasing number of non-morphological imaging parameters are also used for prognosis evaluation. In an analysis of patients of the German CLL Study Group, the role of the MRD status was able to be examined more closely. In the case of a negative MRD status, no difference regarding progression-free survival could be shown between CR patients and PR patients with residual splenomegaly. However, MRD-nega-
active PR patients with residual lymphadenopathy had a shorter progression-free survival [36]. It must be assumed that additional non-morphological imaging parameters will be applied to the response evaluation thereby increasing its accuracy.

Although the use of standardized criteria has many advantages, there are also a number of sources of error. Examinations being performed by different examiners at various times in the course of treatment can cause measurement errors that can result in incorrect categorization. Studies were able to show, for example for RECIST, that the interobserver variability is significantly greater than the intraobserver variability [37]. This means that multiple evaluations by one radiologist have fewer inaccuracies than evaluations performed by various radiologists. As a result of technical progress and particularly better image resolution, measurement differences have decreased [38]. Nonetheless, if possible, one examiner should be assigned to each patient and kept consistent to at least avoid interobserver variability in studies. Studies have since been able to show that semiautomatic measurement was significantly more accurate for response evaluation in lymphoma than the manual measurement method [39, 40].

Even if a return to one-dimensional measurement of lesions is recommended in the latest RECIL classification for simplification, the role of the volumetric measurement of target lesions for lymphomas should also be examined in the future. This is particularly true in light of the increasingly better functioning of automatic volumetry [39, 40]. Volumetric limits have already been calculated for RECIST 1.1. A primary advantage of volumetry is that it is not affected by asymmetry and other shape-related anomalies of target lesions [41].

The steady technical progress has an impact not only on the automated measurement of lesions but also on examination methods. In the recommendations for the Lugano classification, MRI is only mentioned with respect to CNS involvement [10], while in RECIL MRI is mentioned as an alternative examination modality to CT [30]. The importance of the hybrid method PET/MRI is the subject of current studies [42, 43]. The potential of PET/MRI to reduce ionizing radiation and provide better morphological imaging conditions for certain lymphoma entities is increasingly important.

There are also points for discussion on a statistical basis. For example, the classification of response into categories results in a loss of information since the data was originally continuous. Although categories can simplify study results and also contribute to a better representation of data, the thresholds are ultimately not affected by asymmetry and other shape-related anomalies of target lesions [41].

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