Response criteria for lymphoma

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Learning objectives

Lymphoma is a condition with high prevalence that has given rise to the development of many therapies. The International Working Group (IWG) has developed a set of criteria that defines the response of lymphoma to treatment, in order to be able to compare the effectiveness between different treatments.

The objective of this study is to know about the standard guide that assesses the response to the treatment of lymphomas.
Background

Having a standard for response criteria provides common objectives for clinical trials, which in turn makes it possible to compare between different studies and facilitates the identification of more effective therapies and their approval by regulatory organisms\(^1\).
Introduction

Before 1999, there was a considerable variety between groups of clinical trials with regard to the size of a normal lymph node, the frequency of assessment, the time needed in order to assess the effectiveness of the response, the method used in order to assess the response, the assessment of the response (either prospectively or retrospectively), the percentage of increase necessary to determine that there is progression of the disease, and many other factors\(^2\).

In 1999, the IWG, which was composed of clinical doctors, radiologists and pathologists with experience in the assessment and management of patients with non-Hodgkin's lymphoma, published a guideline with criteria for the assessment of response and measures\(^2\). Several points in the guideline were misinterpreted, particularly the term "complete remission/unconfirmed", as well as the recommendations not to include extranodal disease in the response criteria. Also, the use of PET is currently widespread in the diagnosis and monitoring of lymphomas. For this reason, a reevaluation of the criteria described by IWG was necessary, and it was undertaken by the International Harmonization Project (IHP), which has been divided into subcommittees for response criteria, objectives of clinical trials, imaging, clinical medicine and pathology\(^3\).

Modifications of the IWG criteria

**PET**

PET-FDG offers a functional image of the disease, and it is used in the staging, restaging and assessment of the response to treatment\(^1\). However, there are some recommendations for the use of PET, depending on the type of lymphoma and its FDG avidity, as well as on the objectives of the clinical trial\(^4\).

1. PET is recommended before treatment in order to establish the extension of the disease in potentially curable lymphomas with high FDG avidity, such as diffuse B-cell lymphoma and Hodgkin's lymphoma. On the other hand, it is not recommended for lymphomas that present FDG avidity but are not curable or present an aggressive histology, such as follicular lymphoma or mantle cell lymphoma. It is also not recommended for lymphomas with low FDG avidity.
With regard to the objectives of clinical trials, PET before treatment is only recommended when the objective is to determine the response rate.

2. Some studies have shown that a PET scan after one or two cycles of chemotherapy predicts the therapeutic result. However, there are no data that reveal better results if the treatment is changed based on this information. Therefore, a PET scan in the middle of treatment should only be performed in clinical trials.

3. After treatment, PET is recommended in order to assess diffuse B-cell lymphoma and Hodgkin’s lymphoma. It is only recommended in other lymphomas if a PET had already been performed before treatment and the results were positive. In clinical trials, it is only recommended when the objective is to assess the response rate. We must take into account the fact that inflammatory changes after treatment last for 2 weeks if chemotherapy has been applied or 2-3 months if the therapy included radiation or a combination of radiotherapy and chemotherapy. For this reason, the PET scan should be delayed until at least 3 weeks after treatment, although it is recommended to wait between 6 and 8 weeks.

4. PET scans are not recommended for monitoring after treatment.

**Assessment of the bone marrow**

The reassessment of the bone marrow after treatment is used in order to assess the therapeutic response. This determination is carried out together with the morphological study of the medullary biopsy. Other techniques, such as immunohistochemistry, flow cytometry and polymerase chain reaction have been proven to detect a hidden disease, but there are no protocols for their use.

The characteristics of a bone marrow that has responded to treatment are a normal histologic profile with a small clonal B cell population (<2%) that is detected with flow cytometry.

Immunohistochemistry makes it possible to detect a hidden disease in morphologically normal bone marrow, because it uses specific antibodies (CD5, cyclin, D1, CD23, CD10, DBA44 and kappa and lambda light chains).

These more sensitive diagnostic methods must be incorporated into the clinical trials in order to determine their usefulness in the orientation of the therapy.
However, in clinical practice decisions should not be based only on them, without other data that confirm them with a morphological analysis\(^1\).

**Measures of lymph nodes**

All lymph nodes with a large axis of more than 1.5 cm are considered pathological, regardless of the size of the small axis\(^1\).

If a lymph node has a large axis between 1.1 and 1.5 cm, the node is considered pathological if the small axis is larger than 1 cm\(^1\).

All lymph nodes with large and small axes smaller than or equal to 1 cm are considered normal\(^1\).

**Extranodal disease**

The assessment of a measurable extranodal disease must be undertaken with the same approach as with the nodal disease. For example, measures of long and short axes shall be provided in splenic lesions\(^1\).

Diseases that can only be assessed, such as pleural effusion, ascites or bone lesion, shall be registered as «present» or «absent». If these findings persist after treatment, a negative result shall be confirmed with a histological analysis\(^1\).

**Response criteria** Table 1 on page

**Complete response** Fig. 1 on page 11

All the following criteria must be met\(^1\):

1.- Complete disappearance of all clinical evidences of detectable disease and of the symptoms related to the disease that was present before the treatment.

2a.- Lymphomas with typical FDG avidity: In patients who had not undergone a PET scan before treatment or with a PET with positive results before treatment, there may be a residual mass after the treatment, of any size, as long as the results of the PET scan after treatment are negative.
2b.- Lymphomas with variable or unknown FDG avidity: In patients who had not undergone a PET scan before treatment or with a PET with negative results before treatment, all the lymph nodes and nodal masses must recover their normal size as seen in the CT scan (# 1.5 cm in the large axis for those that were > 1.5 cm before treatment). Lymph nodes that had been previously affected and that had a size between 1.1 and 1.5 cm in the large axis and >1 cm in the short axis before treatment must have a small axis #1 cm after treatment.

3.- Spleen and liver: If they were marked as enlarged before treatment, either via a physical exploration or a CT scan, they should not be palpable after treatment and they will have a normal size confirmed by imaging techniques. Nodules associated with the lymphoma must disappear after treatment.

However, the determination of splenic involvement is not always possible because a normal-sized spleen may still present lymphoma, whereas an enlarged spleen may be due to an anatomical variation, blood volume, use of hematopoietic growth factors or other causes that are not related to the lymphoma.

4.- Disappearance of the bone marrow infiltrate after treatment and biopsy. The sample for the biopsy must have an adequate quality (unilateral sample of more than 20 mm). If the result of the morphologic study does not produce conclusive results, then the immunohistochemical techniques shall produce a negative result.

A sample with a negative result in the immunohistochemical tests but with the presence of a small clonal lymphocyte population shown by flow cytometry will be considered a complete response.

**Partial response Fig. 2 on page 12**

All the following criteria must be met:\[1:\]

1.- Decrease by at least 50% of the sum of the product of the diameters of up to six dominant lymph nodes or node masses.

These nodes or masses will be selected according to the following criteria: being measurable in at least 2 perpendicular dimensions; if possible, they should be from different areas of the body; and they must include those located on the retroperitoneal and mediastinal areas whenever these areas are involved.
2.- There must not be an increase in the size of other nodes, the liver or the spleen.

3.- Splenic or hepatic nodes must decrease #50% in size (considering the sum of the product of their diameters). In the case of a single node, its large transverse axis must be reduced by #50%.

4.- With the exception of splenic or hepatic nodes, the involvement of other organs must be assessed, and no measurable disease can be found.

5.- The assessment of the bone marrow is not relevant to the determination of a partial response if it was positive before treatment. However, in this case, the cell type should be specified.

Patient who reach complete clinical remission with these last criteria but with persistence of morphological involvement in the bone marrow are considered to be in partial response. If the bone marrow was infiltrated before treatment and there is a complete clinical remission but the bone marrow is not reassessed after treatment, patients are considered to be in a situation of partial remission.

6.- No evidence of new disease sites.

7.- Lymphomas with FDG avidity: In patients who did not undergo a PET scan before treatment or with positive PET results before treatment, the results after treatment shall be positive in at least one of the previously affected sites.

8.- Lymphomas with variable or unknown FDG avidity: In patients who did not undergo a PET scan before treatment or with negative PET results, CT scan criteria will be applied.

In patients with follicular lymphoma or mantle cell lymphoma, PET scan is only recommended if there are one or at most two residual lesions that have been reduced by more than 50% according to the CT scan; and those patients will rarely present negative PET results and must be included into the partial response group.

Stable disease Fig. 3 on page 13

It is defined by the following criteria:\(^1\):
1.- Any condition that does not meet the criteria for complete or partial remission, but it also does not meet the criteria for progressive disease.

2.- Lymphomas with typical FDG avidity: Positive PET results in previously involved locations but without the appearance of new disease areas.

3.- Lymphomas with variable or unknown FDG avidity: In patients who did not undergo a PET scan before treatment or with negative PET results, there shall be no changes in the size of the initial lesions as seen by the CT scan after treatment.

Relapse or progressive disease Fig. 4 on page 14

They are defined by the following criteria\(^1\):

1.- Appearance of any new lesion with any axis > 1.5 cm during or after treatment, even if other lesions have reduced their size.

The increase in FDG uptake in a previously unaffected location is only considered a relapse or progressive disease after it is confirmed with a different technique.

In patients without a personal record of lymphoma infiltration in the lungs, the appearance of new pulmonary nodes in the CT scan suggests that they are generally benign. Therefore, the treatment decision must not be taken based only on the PET scan without further histological confirmation.

2.- Increase of the sum of the diameters of the nodes, or increase of the size a single node or other lesions, by at least 50%.

In order to classify the disease as progressive, a lymph node with a small axis < 1 cm shall increase by \#50\% and reach a size of 1.5 x 1.5 cm or > 1.5 cm in its large axis.

3.- Increase of the large axis of any previously identified single node that had a small axis > 1 cm by at least 50%.

4.- PET scan results must be positive for lymphomas with typical FDG avidity or for lesions that had already been PET-positive before treatment, unless the lesion is too small to be detected (<1.5 cm in its large axis according to the CT scan).
<table>
<thead>
<tr>
<th>Response</th>
<th>Definition</th>
<th>Nodal masses</th>
<th>Spleen, Liver</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Disappearance of all evidence of disease</td>
<td>a) FDG-avid or PET+ prior to therapy: mass of any size if PET-</td>
<td>Not palpable</td>
<td>Normal morphology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Variably FDG-avid or PET-: regression to normal size on CT</td>
<td>Nodules disappeared</td>
<td>If indeterminate by morphology the IHQ should be -</td>
</tr>
<tr>
<td>Partial response</td>
<td>Regression of measurable disease and no new sites</td>
<td>≥50% decrease in SPD of up to 6 largest dominant masses, no increase in size of other nodes</td>
<td>≥50% decrease in SPD</td>
<td>Irrelevant if + prior therapy, but cell type should be specified</td>
</tr>
<tr>
<td></td>
<td></td>
<td>a) FDG-avid or PET+ prior to therapy: ≥1 PET+ at previously involved site</td>
<td>No increase in size of liver or spleen</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Variably FDG-avid or PET-: regression on CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>Failure to attain complete or partial response or progressive disease</td>
<td>a) FDG-avid or PET+ prior to therapy: PET+ at prior sites of disease and no new sites on CT or PET</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) Variably FDG-avid or PET-: no change in size of previous lesions on CT</td>
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</tr>
<tr>
<td>Relapse or progressive disease</td>
<td>Any new lesion or increase ≥50% of the SPD</td>
<td>New lesion(s) &gt;1,5 cm in any axis</td>
<td>≥50% increase in SPD</td>
<td>New involvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50% increase in longest diameter of a previously identified node &gt;1 cm in short axis</td>
<td>Lesions PET+ if FDG-avid lymphoma or PET+ prior to therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥50% increase in SPD</td>
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</tr>
</tbody>
</table>

**Table 1: Response criteria**

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**Fig. 1:** 76-year-old woman with a complete response of a low grade no Hodgkin's follicular lymphoma. In the first row there are axial CT images after contrast administration that show cervical, preaortic and inguinal lymph nodes. The second row shows the control CT scan where there isn't any of the previous nodes.

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Fig. 2: 51-year-old man with partial response of a grade 3 no Hodgkin's follicular lymphoma. The first row is the diagnostic CT scan that show a heterogeneous abdominal mass with ascitis, thickening of the omentum and diafragmatic lymph nodes. In the posttreatment CT control the ascitis, the omental thickening and the lymph nodes are disappeared, and the mass has decreased more than 50% of its size.

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**Fig. 3:** 17-year-old woman with stable disease of a treatment Hodgkin's lymphoma with positive PET. The first row with axial CT images show an anterior mediastinum mass with calcifications, calcified lymph node in the right pulmonary hilium, a focal hepatic lesion and retroperitoneal lymph nodes. The second row is the posttreatment CT that show a decrease less than 50% of the sum of the product of the lymph nodes and the persistence of the focal hepatic lesion.

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**Fig. 4:** 58-year-old woman with a progressive disease of a large cell lymphoma. The first row with the diagnostic CT images shows a left axillary mass. Posttreatment CT shows an increase higher than 50% in the size of this mass, and new prevascular and retroperitoneal lymph nodes, and pleural effusion.

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Conclusion

It is important to carry out a correct and standard assessment of the therapeutic response of patients with lymphoma, and it must be included in the daily practice of radiologists.

Complete response is defined as the disappearance of all clinical evidence of the disease and its symptoms. Partial response is the decrease of the sum of all adenopathies by at least 50%. A stable disease is defined whenever the criteria for remission or progression are not met. A progressive disease is defined when a new lesion > 1.5 cm appears, or when the sum of the adenopathies or any other node with a small axis > 1 cm increases by at least 50%.
References


