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Staging and monitoring in the treatment of lymphomas

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Abstract Lymphoma staging systematically includes a CT scan of the cervical, thoracic and abdominopelvic regions. PET is indicated in diffuse large B cell lymphomas (DLBCL) and Hodgkin’s disease. Evaluation of the response to treatment is based on Cheson’s 1999 morphological criteria, which have been replaced by the 2007 IWC criteria, which combine morphological and metabolic responses. CT and FDG-PET are complementary in characterizing residual masses: if negative, a PET scan indicates the absence of residual disease, if positive; it directs a CT-guided biopsy to obtain the histological evidence. Monitoring clinical features and laboratory values is primordial following treatment. Imaging is performed as a second intention for investigating a relapse, if necessary associated with a PET scan. Multimodal imaging implies multidisciplinary consultation between haematologists, imaging specialists and histopathologists.

A lymphocyte may evolve towards a tumoral process at any stage in its differentiation thus inducing a lymphoma with characteristics directly related to the degree of its differentiation. The great diversity in the stages of lymphopoiesis (B and T-cell) explains the wide range of lymphomas, de facto with clinical and therapeutic diversity. The WHO classification of lymphomas is based on this connection between the tumour cell and its normal equivalent, which necessitates characterization of malignant lymphocytes — morphological, histological, phenotypic, cytogenetic and molecular — that is as complete as possible. Since diagnosis and therapeutic management depend on this stage characterizing the malignant cell, it is essential, for the most complete exploitation possible, which must be performed by a competent histopathology team, to have a biopsy

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sample of optimal quality right from the time of diagnosis. In France, the "lymphopath" network provides this expertise throughout the country.

Given the obvious diverse nature of lymphomas, it is important to remember a few major facts. Lymphomas can be divided into two large groups with Hodgkin’s lymphomas (HL) (or Hodgkin’s disease) on one hand, and malignant non-Hodgkin’s lymphomas (NHL) on the other. In the second group, 85% of proliferations arise from the B line (B lymphomas) against only 15% from the T line (T lymphomas). B and T lymphomas can then be subdivided into various entities depending on the degree of differentiation of the lymphocyte.

We often speak of aggressive lymphomas and indolent lymphomas. This is a purely clinical view, which has no anatomical or pathological basis. It can be said that aggressive lymphomas, diffuse large cell lymphomas (DLBCL) or Burkitt’s lymphoma for example, are generally very chemosensitive and present unfrequently a long term relapse. In contrast, indolent lymphomas present more frequently relapses despite a relative chemosensitivity. This is a rather "caricatural" view of lymphomas but is based on clinical observations. The therapeutic progress of recent years has shown that a cure is a realistic objective in the large majority of lymphomas: Hodgkin’s disease, DLBCL, Burkitt’s lymphoma.

Staging a lymphomatous disease consists of standard laboratory examinations with the addition of imaging. The latter systematically includes a thoraco-abdominopelvic CT scan, and if necessary a cervical scan, with injection of an iodinated contrast agent. Positron emission tomography (PET) is not substituted for a CT scan, but is combined with CT in just two histological types of lymphomas with high avidity for FDG: DLBCL and Hodgkin’s disease [1]. Apart from these two conditions, the systematic use of PET in staging is not based on any international recommendation. However, PET may be discussed case by case, particularly when an aggressive transformation is suspected. Transformed areas usually have greater avidity for FDG than untransformed areas. A PET scan can also be suggested in the initial staging of follicular lymphoma for which radiotherapy may be an alternative treatment.

The emergence over the past few years of metabolic imaging techniques has thus modified the relationship between haematology and imaging, but conventional radiology retains an essential role in the care of the patient, from initial diagnosis to monitoring. CT and FDG-PET are complementary [2] particularly in characterizing lesions, because metabolic imaging can direct CT-guided biopsy, by identifying residual masses or by authenticating the transformation of an indolent lymphoma into a high-grade lymphoma (Fig. 1). These decisions concerning invasive diagnostic procedures are taken during multidisciplinary meetings between haematologists, histopathologists, radiotherapists and radiologists [3,4]. It is essential for the imaging specialist to understand the therapeutic issues when discussing with the haematologist who will adapt and evaluate the treatment depending on the images and on the clinical criteria and laboratory values, with the objective of providing curative treatment in aggressive lymphomas [5].

**Evaluation of response of the tumour to treatment**

Evaluation of the response to treatment relies very largely on the CT evaluation measuring the reduction in target lesions defined in the diagnosis.

Sometimes undertaking intermediate examinations may be discussed to assess the response after only a few courses of chemotherapy. Such examinations including a CT scan and/or ultrasonography are above all relevant for the most aggressive lymphomas (DLBCL, Hodgkin’s disease, mantle cell lymphomas, etc.). The point of an intermediate examination is more questionable in indolent lymphomas, which are usually chemosensitive. On the other hand, PET is being used more and more in intermediate examinations although its most documented indication in the literature is limited to Hodgkin’s disease or DLBCL. Moreover, the present trend is to increasingly perform intermediate PET scans to allow early adaptation of treatment, either for increasing treatment in slow responders or for decreasing it in the most responsive patients. The question of intermediate examinations using PET scans is still being studied.

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**Figure 1.** Grade II follicular lymphoma, systematic monitoring. a: CT scan: appearance of a pelvic mass; b: CT-guided biopsy: histopathological confirmation of transformation into diffuse large B cell lymphoma.
At the initial stage of the disease, therapeutic management is based on the Ann Arbor classification, which itself is largely based on the CT/FDG-PET combination, an essential step in carrying out a precise evaluation of the tumour response, combining imaging with clinical and laboratory data — IPI and FLIPI scores [6]. The standardised international criteria for the morphological response of lymphomas refer to Cheson’s classification with two-dimensional measurements from the thoraco-abdominopelvic CT scan, and differ from the single-dimension criteria of the RECIST 1.1 solid tumour classification.

Evaluation of the response of lymphomas to treatment has evolved over two periods, determined by the arrival of FDG-PET. The Cheson 1999 morphological criteria [7], established from a CT scan, which used to be the only imaging procedure for initial staging and evaluation, were modified and updated between 2005 and 2007 [8,9] to take PET into account, providing not only objective response criteria but also prognostic value for the disease. Since then they have consisted therefore of evaluation combining a CT scan with injection and PET, even though in most centres these are two examinations performed separately, one by the radiologist, the other by a nuclear medicine specialist. Synthesis of the results forms the standardised evaluation according to the international criteria established by Juweid and Cheson in 2005 then 2007.

Some lymphomas, however, are inconsistent in their uptake of FDG thus limiting the usefulness of PET in certain patients with T-cell lymphoma or indolent non-follicular lymphoma (MALT, mantle cell, lymphocytic). The CT scan remains the initial technique for diagnosis and during evolution under treatment, until these lymphomas are transformed into high-grade tumours, when they become eligible for PET [10].

At present, CT is therefore the essential feature of the end of treatment examination. It should be remembered that the indication for a PET scan at the end of treatment currently only concerns Hodgkin’s disease and DLBCLs. For all other lymphopathies, CT remains the reference technique. While PET undeniably makes a major contribution in lymphomas, the risk of false positives must also be taken into account, resulting in the CT scan being maintained in the end of treatment examination. Like the CT scan of the initial examination, the end of treatment CT scan should include an exhaustive description of residual masses, which must be compared with the initial masses and associated with numerical measurement of tumour reduction. The two largest dimensions of the tumours should be measured and multiplied together. The percentage reduction in this area is then established, between monitoring scans.

**IWC Cheson 1999 criteria [7]**

The morphological response in the end of treatment CT established by Cheson in 1999 corresponds to the recommendations of the international group that depends on the anatomical definition of the response with a ”normalised” lymph node dimension of 1.5 cm in its greatest transverse diameter. Initially on diagnosis, however, a lymph node the greatest transverse diameter of which is more than 1 cm is considered as possibly indicating lymphomatous invasion. Regression of the tumour mass of the lymph node following treatment is accompanied by fibrosis, necrosis or inflammation resulting in persistent enlargement of the lymph nodes even though they are histologically free of any viable tumour cells. It should be noted that unlike the criteria for solid tumours (RECIST), lymphomatous lymph node sizes are evaluated on their largest transverse diameter for defining return to normal.

Initial and post-treatment measurements, always in two dimensions, are made on axial slices on two perpendiculars starting from the largest transverse diameter.

The clinical, laboratory and histopathological parameters of the bone marrow, taken into account by the haematologist to assess the overall response are added to the morphological response criteria.

**Complete response**

This is the disappearance of all measurable lymph node or extranodal lesions (Fig. 2). All nodal masses must have regressed to less or equal to 1.5 cm in their greatest

![Image](image_url)

**Figure 2.** Burkitt’s lymphoma in a 3-year-old child. a: initial CT scan: centro-hepatic and hepatic pedicle lymphomatous infiltration, with coeliac and retroperitoneal lymphadenopathies; b: end of treatment CT scan: complete response with disappearance of the hepatic and lymph node lesions.
transverse axis for lymph nodes initially greater than 1.5 cm before treatment. Lymph nodes with a greatest diameter of between 1.1 and 1.5 cm before treatment must have decreased to less than 1 cm in their greatest transverse diameter or by more than 75% of the sum of the products of the greatest diameters (SPD). No measurable nodule must be detectable in the other organs affected by the lymphoma (the spleen, liver, kidneys, adrenal glands, lungs etc.).

Unconfirmed complete response
This is a response in the 1999 CT criteria, now deleted since FDG-PET inclusion (Fig. 3). It corresponded to patients with complete response criteria but with persistence of a residual mass, regression of which was more than 75% of the SPD, with normal or undetermined bone marrow.

Partial response
This is a reduction in the SPD greater or equal to 50% in the six initially most voluminous lymph nodes in the supra and/or sub-diaphragmatic regions affected. Hepatic and splenic nodules must regress by at least 50% of the SPD, with no new site of disease.

Stable disease
This is defined as no partial response or disease progression or recurrence.
Relapse of the disease, after complete response (Fig. 4). This is the appearance of any new lesion or increase greater or equal to 50% in the initial targets.

Figure 3. Mantle cell lymphoma, initial CT scan and a monitoring scan 9 months after treatment: unconfirmed complete response. Mesenteric mass (a) Bilateral external iliac lymphadenopathies (b) CT scan after treatment: regression of initial targets evaluated at 95% according to the Cheson criteria (c, d).

Figure 4. Thoracic CT scan: pulmonary relapse in the left inferior lobe after a complete response in a 29-year-old man. Biopsy provided histopathological diagnosis of recurrence of Hodgkin’s disease.
Disease progression
This occurs when any initially identified lesion in non-responding patients or patients who had a partial response increases again by greater or equal to 50% of the SPD from the nadir, whether or not accompanied by the appearance of new lesions during or at the end of treatment.

Response criteria integrating PET: IWC 2007 criteria [9]
The limits of the 1999 IWC are due to the incapacity of the CT scan to differentiate between viable tumour tissue and necrosis and/or fibrosis in residual masses. On the other hand, FDG-PET metabolic imaging is capable of characterizing a viable tumour (or its absence) in residual masses with diagnostic accuracy of 80 to 90%. Consequently, FDG-PET better reflects tumour response in lymphomas despite the poorer spatial resolution, and is more sensitive than CT in detecting small volume tumours, including in lymph nodes of normal size in a CT scan (i.e. < 1 cm). This is because of better contrast due to intense uptake by certain pathological lymph nodes relative to adjacent normal tissues. In addition, the fusion of images with a CT scan allows better location of hyperfixing lymph nodes by avoiding partial volume effects. These two imaging methods are complementary and for this reason the new IWC 2007 criteria combine the morphological data of the CT scan with the metabolic data of FDG-PET (Table 1) based on the work of Juweid et al. in 2005 [8].

Standardisation of response criteria is necessary for interpreting and comparing clinical trials, for modifying therapeutic strategy during evolution of the disease and for validating the efficacy of new therapeutic agents. These new 2007 recommendations include not only morphological and metabolic imaging but also immuno-histochemistry and flow cytometry, to define response in non-Hodgkin’s and Hodgkin’s lymphomas. Clinical and laboratory criteria of the bone marrow (bone marrow biopsy if necessary) are still taken into account by the haematologist, while associating imaging criteria.

Table 1 Response to treatment criteria – International Workshop Criteria (IWC).

<table>
<thead>
<tr>
<th>Type of response</th>
<th>IWC 1999 CT scan</th>
<th>IWC 2007 CT and PET scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Normal</td>
<td>PET scan becoming negative (if PET0+) and CT scan normal (if PET0-)</td>
</tr>
<tr>
<td>Unconfirmed complete response</td>
<td>Reduction &gt; 75%</td>
<td>Reduction ≥ 50% (CT scan) and PET+ (if PET0+)</td>
</tr>
<tr>
<td>Partial response</td>
<td>Reduction &gt; 50%</td>
<td>Reduction &lt; 50% (CT scan) and PET+ (if PET0+)</td>
</tr>
<tr>
<td>Stability</td>
<td>Reduction &lt; 50%</td>
<td>New lesion &gt; 1.5 cm or increase in initial lesion ≥ 50%</td>
</tr>
<tr>
<td>Progression/Relapse</td>
<td>New lesion &gt; 1.5 cm or increase in initial lesion ≥ 50%</td>
<td></td>
</tr>
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PET0: PET scan performed at the time of diagnosis.

Patients who had a positive PET image before treatment, and in those who did not have a PET scan before treatment (Figs. 5 and 6).

If the PET scan was negative before treatment or if FDG fixation is uncertain at the end of treatment, the Cheson 1999 criteria apply with complete regression of all initial tumour masses (normal lymph nodes less or equal to 1.5 cm).

It should be noted that lymph nodes with a long axis measuring between 1.1 and 1.5 cm before treatment must decrease to less or equal to 1 cm in their short axis following treatment.

Hepatosplenomegaly and all splenic or hepatic nodules have disappeared: bearing in mind that splenic involvement is not solely related to size, as a normal size spleen can be invaded by the lymphoma.

Cheson’s 1999 unconfirmed complete response has disappeared from the response evaluation: a negative PET result is enough to confirm complete response even when a residual mass is present.

Partial response
This is defined as a positive PET scan at the end of treatment in at least one initial site, in patients where the PET scan was positive before the treatment (or in patients who did not have a PET scan before treatment), with a reduction greater or equal to 50% in the SPD of initial lymph node masses (not more than six targets) and absence of any new site (Figs. 7 and 8). The other morphological criteria of a Cheson 1999 partial response remain the same (non-target lesions, hepatosplenic nodules).

PET is negative before treatment but with uncertain FDG fixation at the end of treatment: the CT scan criteria then define the partial response, identical to Cheson 1999.

Stable disease
PET is positive at the end of treatment on the initial sites with no new sites in the CT or PET scan, meeting neither the partial response criteria nor those of disease progression.

Relapse and disease progression
This is defined as the appearance of any new lesion greater than 1.5 cm during or at the end of treatment even if other lesions are decreasing in size. FDG uptake in a site initially
Figure 5. Hodgkin's disease: bulky mediastinal mass for which the histopathological diagnosis was made after CT-guided biopsy. a, b: CT scan: voluminous mediastinal mass measuring 14 × 9.5 cm; c: initial PET scan: hypermetabolism confirming supradiaphragmatic lymph node involvement; d, e: end of treatment CT scan: residual mass measuring 4.2 × 5.2 cm corresponding to an 84% reduction according to the Cheson criteria, i.e. an unconfirmed complete response; f: end of treatment PET scan: considered as a complete response.
unaffected can only be determined as relapse or progression after confirmation by a CT scan. New pulmonary nodules on the CT scan without any initial lymphomatous pulmonary lesion are usually benign. No therapeutic decision should be taken based solely on a PET positive result without histological confirmation.

There must be an increase greater or equal to 50% from the nadir in the SPD of lymph node and/or extranodal lesions.

Non-measurable lesions (effusions, bone involvement) are recorded as present or absent. When an FDG-PET scan has not been performed (certain indolent lymphomas), evaluation of the response will be made solely from the CT scan on the classic 1999 criteria but residual masses are considered as a partial response. The unconfirmed response status has definitively been removed.

Imaging residual masses and transformation into high-grade lymphoma

The presence of residual masses (Fig. 9) after chemotherapy and/or radiotherapy does not necessarily indicate persistence of the lymphomatous condition [11,12]. This is a major problem in interpreting response to treatment, in particular in the 30 to 50% of patients who have a high tumour mass at the initial diagnosis (e.g. bulky mass > 10 cm). In reality, residual disease is only present in 20 to 30% of these patients [13]. The contribution of PET is primordial in evaluating residual masses: a negative PET scan means the absence of residual disease; a positive PET scan indicates the sites of residual disease. A bulky mass is common in Hodgkin’s disease and its complete disappearance is unusual. Detection of a viable tumour in sometimes calcified residual lesions is impossible with a CT scan, hence the decisive contribution of metabolic imaging. When there is a dissociated response, biopsy to confirm the diagnosis histologically must be discussed: it may be the same type of lymphoma, but chemoresistant, a transformation or, more rarely, an associated cancer explaining the focalised non-response, e.g. the persistence of a single mediastinal mass related to concomitant bronchial cancer, while all the other lymph node or extranodal sites have regressed. A residual mass, which is positive in a PET scan, may not be a tumour but may be granulomatosis, fibrosis, or an infectious focus. In all cases, however, PET can direct the CT-guided

Figure 6. Lymphoma with sub-diaphragmatic involvement. a, b: initial CT scan: voluminous retroperitoneal mass surrounding the ureters with dilatation of the left renal cavities, combined with left internal iliac lymph node involvement; c, d: end of treatment CT scan after six courses of chemotherapy: very good response with retroperitoneal residual mass measuring 32 × 15 mm and disappearance of the left internal iliac lymph node involvement, i.e. a reduction of 96% according to the Cheson criteria, but considered as a complete response with PET.
biopsy. Histological evidence of the progression or relapse of any intercurrent lesion is essential before beginning salvage treatment.

A low grade non-Hodgkin’s lymphoma being monitored clinically through laboratory values and via CT scans, which is suspected of transforming into an aggressive lymphoma, will become positive in a PET scan at a specific site. It has been demonstrated that a PET scan can effectively guide a biopsy to obtain histological evidence of transformation into Richter’s syndrome by measuring the standardised uptake volume (SUV), a semi-quantitative parameter, considered to be a tumour grade biomarker capable of determining the response to treatment or transformation with a PPV of 100% and a NPV of 67.3% for an SUV greater than 17 [14].

The CT-guided biopsy must be performed under optimal conditions: this means CT guidance with precise pinpointing on the PET scan by fusing the images, several good quality samples collected in a tube of formol, and also a fresh sample for cryopreservation sent immediately to the laboratory to obtain a complete analysis. This will include its immunohistochemistry and molecular biology, to type the lymphoma precisely and determine the appropriate treatment, which will be decided in a multidisciplinary meeting.

Post-treatment monitoring of lymphomas and estimate of the cumulative radiation dose

Post-treatment follow-up differs depending on whether clinical trials or standardised clinical practice protocols are concerned. It depends on whether the initial objective of the treatment is curative or palliative. Monitoring by clinical examination and minimum laboratory tests by the haematologist is primordial: in 80% of cases it allows a relapse to be diagnosed (a palpable mass, alteration in the general condition, deterioration of laboratory values) without the assistance of imaging, which may be performed as a second intention for staging the relapse, with a PET scan if needed to direct CT-guided biopsy.

In clinical trial protocols, CT scan monitoring, once every 3 months for 2 years, then every 6 months for 3 years, and finally annually for 5 years, is recommended to assess progression-free survival, event-free survival or other criteria assessing survival (Hodgkin’s cells or lymphoma). On the other hand, clinical monitoring must be prolonged for
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Figure 8. Stage IV Hodgkin’s disease with bone involvement in the PET scan. a, b: CT scan: anterior and middle mediastinal mass; c,d: CT scan after four courses of treatment: poorly responding patient with a reduction of 63% of the initial mass and persistence of hypermetabolism in the PET scan thus considered as a partial response, leading to a change in chemotherapy for salvage then an autologous bone marrow transplant.

Figure 9. Residual mass 2 years after the end of treatment of a diffuse large B cell lymphoma. a: initial CT scan: mediastinal mass of 9 × 8 cm; b: control CT scan after 2 years with a confirmed complete response and a non-evolving residual mass of 2 cm considered to be inactive.

... follicular or other indolent lymphomas. Imaging will depend on the clinical evolution [15,16].

Finally, the diversity of lymphomas explains why the risks of relapse are so variable from one type of lymphoma to another. It is therefore difficult to establish general rules for monitoring applicable to all lymphomas. Apart from in clinical trials, for the most aggressive lymphomas (DLBCL, MCL, Burkitt’s lymphoma), an imaging examination at 3 or 6 months then 1 year after the end of treatment is the scheme most often suggested. For the more indolent forms, an imaging examination may be performed at 6 months and 1 year. Beyond the first year after the end of treatment, a 6-monthly examination may be suggested. In some types of lymphoma, particularly the most indolent, it is possible to alternate an ultrasound examination and a CT scan. In contrast, late relapse of some aggressive lymphomas such...
as DLBCL is uncommon. Wider spacing of examinations may therefore be discussed in some cases. The frequency of and the imaging examinations to request thus depend on the nature of the type of lymphoma. In current practice, despite poor efficiency for screening relapses, monitoring with a CT scan is performed every 6 months for the first 2 years, then annually. It also screens for late complications of the chemotherapy and radiotherapy.

Although widely used for per and post-chemotherapy evaluation, PET however has no place (yet?) in monitoring lymphomas.

Nievelstein et al. [17] recently quantified the exposure to ionising radiation and the risk of mortality secondary to CT scans and PET in patients with non-Hodgkin’s lymphoma and Hodgkin’s lymphoma. In children with Hodgkin’s disease, the cumulative effective dose secondary to medical imaging examinations varied from 66 Sv to 113 mSv. In adults with non-Hodgkin’s lymphoma it was a mean of 97 mSv. Mean imaging-related radio-induced mortality was estimated [18] in children with Hodgkin’s disease as 0.4% for boys and 0.7% for girls and in adults with non-Hodgkin’s lymphoma as 0.07% for men and 0.09% for women.

These results confirm the necessity to reduce CT and PET scans in children depending on the therapeutic protocols [19]. Nevertheless, the authors temper the results considering the justification for imaging procedures, for which the risk of radio-induced mortality is real but modest in patients whose overall survival has considerably lengthened over the last decades, with a risk of mortality linked to the disease very much higher than the risk of radio-induced mortality. In this study, low-dose CT scans were not taken into account; their protocolling use could contribute to decreasing the risk of diagnostic medical irradiation.

The recent development of whole body MRI in evaluating malignant lymphoma is still in the research stage and although promising, the application of MRI on a routine clinical basis cannot yet be envisaged as an alternative to FDG-PET, which remains the reference examination [10] for the initial or therapeutic evaluation of lymphomas. Concordance between MRI and PET is moderate (with a mean of 75%), with a risk of over-staging by whole body diffusion-weighted MRI compared with a PET scan [20]. Morphological and functional MRI and metabolic PET are complementary: it is likely that the next technological advances combining MRI and PET will produce a major change in paediatric oncology procedures, in particular in staging, re-staging and monitoring the treatment of malignant lymphomas.

The role of imaging in the therapeutic strategy for lymphomas

For the most indolent lymphomas with no clinical repercussions or effect on laboratory values, such as some follicular lymphomas, some marginal zone lymphomas, or Waldenström’s disease, it is possible to offer simple therapeutic abstention with monitoring. On the other hand, for more aggressive lymphomas, such as diffuse large B cell lymphomas, T-phenotype lymph node lymphomas, or mantle cell lymphomas, it is essential to propose chemotherapy. The most common lymphomas require diverse treatment options [21].

As far as follicular lymphoma (FL) is concerned, the choice of treatment strategy is based on evaluation of prognostic factors, including the number of lymph node sites involved (>4 or not), the stage (I or II versus III or IV), or the size of the tumour masses. To assess these parameters, a CT scan is essential. Depending on these parameters, therapeutic abstention with monitoring or chemotherapy with monoclonal antibodies may be chosen. For the latter option, six CHOP courses are often proposed followed by maintenance treatment with rituximab spread over 2 years. Throughout the monitoring period, CT control scans are performed possibly alternating with ultrasound examinations. Very often, relapses or progression in FL remain asymptomatic clinically or in terms of laboratory values, and it is then imaging that identifies the evolution and reactivation of the disease. It should be noted that PET is not formally indicated in this type of lymphoma. As for the choice of first line treatment, the choice of relapse treatment will be based, among other things, on the imaging examination, the length of time since the end of the previous course of treatment, the age of the patient, the clinical presentation and laboratory values, and comorbidities. All therapeutic options can be discussed, from simply monitoring to returning to chemotherapy, and even intensification with an autologous transplant. It must be remembered that FL is still an incurable lymphoma and is therefore quick to relapse; hence the importance of monitoring.

As regards diffuse large B cell lymphomas, treatment is also based on the combination of immunotherapy (anti-CD20 antibodies, rituximab) and chemotherapy, and the reference protocol is also R-CHOP. Depending on the staging (CT and PET scans), the laboratory test results and the age of the patient, four or eight courses of R-CHOP chemotherapy (or variants such as R-ACVBP) are given, delivered every 14 or 21 days. The place for an autologous transplant as first line treatment in diffuse large B cell lymphomas can be discussed, but the current trend is to reserve autologous transplantation for relapses or for patients found to be slow responders on intermediate examination (by CT and PET scan). Autologous transplantation is based on the collection of a haemopoietic stem cell transplant, usually from a venous sample. More intense chemotherapy is then given causing prolonged aplasia of about ten days. The period of recovery from aplasia is reduced by re-injecting the transplant, normally 48h after the end of chemotherapy. This is a treatment based on the administration of chemotherapy over a short period of time and the autologous transplant is only a support to reduce the duration of aplasia and therefore the risk of infection. Unlike in FL, relapses are usually early with this type of lymphoma and become rarer once beyond the first year after the end of treatment. A CT scan is the standard examination for monitoring.

As far as mantle cell lymphomas are concerned, the situation is different. An autologous transplant is given as a first line of treatment to patients less than 65 years old following reduction in the tumour mass by chemotherapy plus immunotherapy. In older patients, again R-CHOP chemotherapy is preferred, and is followed by maintenance treatment with rituximab. As in FL, it is an incurable condition with late relapses occurring sometimes more than 5 years after
the end of treatment. A CT scan is the standard examination for staging, for the end of treatment examination and for monitoring.

As regards Hodgkin’s lymphoma, a CT scan combined with a PET scan is essential and allows a decision to be made concerning therapeutic options. The choice of chemotherapy (most often ABVD or BEACOPP), the number of courses to administer and additional irradiation depend on the results of this examination. CT and PET scans also allow intermediate response and the end of treatment response to be evaluated. Only CT scans will be used for monitoring, not PET.

These four cases of lymphoma illustrate the importance of having:
• a good histological diagnosis so that suitable treatment can be proposed (the role of the biopsy);
• complete staging (the role of CT scans, but also PET just for certain lymphomas);
• a complete end of treatment examination (CT and PET scans) and then of organising suitable monitoring (CT scans and ultrasound examinations).

Conclusion

Computed tomography, like all conventional imaging (ultrasoundography, thoracic X-rays) is involved in all the stages of managing lymphomas, from the diagnosis through to staging to follow-up monitoring. The growing emergence of metabolic imaging may lead to the belief that CT and ultrasonography have been relegated to second place. Attentive reading of the most recent literature rapidly refutes this impression. It appears, above all, that wise and optimal use of multimodal imaging techniques implies multidisciplinary consultation and constant dialogue between radiologists, specialists in nuclear medicine and haematologists.

TAKE-HOME MESSAGES
• The diagnosis and therapeutic management of lymphomas require a surgical or CT-guided biopsy of optimal quality.
• The examination systematically comprises a CT scan of the cervical, thoracic and abdominopelvic regions, with injection of a contrast agent; according to the international recommendations, PET is indicated for staging lymphomas that have high avidity for FDG: diffuse large B cell lymphomas (DLBCL) and Hodgkin’s disease.
• For characterizing lesions, CT and PET scans are complementary, with the metabolic imaging directing a CT-guided biopsy by identifying residual masses or for authenticating the transformation of an indolent into a high-grade lymphoma.
• The Cheson 1999 criteria have been replaced by the IWG 2007 criteria integrating the CT scan’s morphological criteria and FDG-PET’s metabolic response. The presence of residual masses following chemotherapy and/or radiotherapy does not necessarily indicate persistence of the lymphomatosus disease: a negative PET scan means the absence of residual disease.
• Aggressive lymphomas — DLBCL, Burkitt’s lymphoma, etc. — are very chemosensitive and rarely relapse later, whereas indolent lymphomas (follicular lymphoma, etc.) are usually chemosensitive but have a tendency to relapse in the more or less long term, hence the importance of monitoring haematological and laboratory values, and clinical evolution. This will help assess the appropriateness of a CT scan or ultrasound examination some time after the end of treatment.
• Low dose CT scans should allow the secondary cumulative effective dose to be reduced, particularly in children.
• Wise and optimal use of multimodal imaging implies multidisciplinary consultation and constant dialogue between radiologists, specialists in nuclear medicine and haematologists.

Clinical case

In a 60-year-old patient with a pleural effusion, cells were discovered corresponding, on cytological analysis of the biopsy liquid, to follicular lymphoma (Figs. 10 – 12).

Questions
1. What initial staging would you recommend?
2. A PET scan confirmed supra or sub-diaphragmatic lymph node involvement and a semi-quantitative study of SUV.max found a more hypermetabolic lesion in the left external iliac area, with an SUV.max of 40.6. What does this value suggest to you?
3. A biopsy is recommended. Which mass would you biopsy?
4. What diagnostic evolution would you suspect in this patient?

Answers
1. Staging systematically includes a CT scan of the cervical, thoracic and abdominopelvic regions following injection of a contrast agent. Except in particular therapeutic protocols, PET is not indicated as a first course of action in follicular lymphoma. However, this patient was included in a protocol requiring an initial PET evaluation.
2. This high SUV.max value of 40.6 leads to aggressive transformation of the lymphoma being suspected in the left external iliac area.
3. The left iliac mass, which is the most hypermetabolic in the PET scan, should therefore be biopsied, but also the posterior mediastinal lesion, to confirm the initial diagnosis of follicular lymphoma.
4. Histopathological examination of the left iliac lymphadenopathy showed a grade 3a follicular lymphoma (the number of centroblasts is very high within the nodules) but with a few centrocytic cells persisting it is prevented from being classed as grade 3b. Histopathological examination of
Figure 10. Axial contrast-enhanced CT shows left pleural effusion and left iliac lymph node.

Figure 11. a,b: PET/CT: FDG-avid mediastinal and left iliac masses.

Figure 12. a,b: PET/CT: FDG-avid mediastinal and left iliac masses.
the right posterior mediastinal lymphadenopathy showed a grade 2/3a follicular lymphoma. Consequently it was not a transformation into a diffuse large B cell lymphoma, but despite everything — because of the suspected left iliac aggressive component in the PET scan and the aggressive clinical presentation for a follicular lymphoma — the chemotherapy was intensified to R-CHOP (though stopped short of autologous transplantation as there was no histological evidence). That also meant that the method of evaluating the response of this follicular lymphoma to treatment was modified, with an intermediate PET scan and a PET and CT scan at the end of treatment. This observation illustrates the importance of histological evidence, which is essential to confirm the transformation of a lymphoma before envisaging treating it. It also highlights the influence of PET scans on the treatment and monitoring method.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References