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# Imaging of Non-Hodgkin Lymphomas: Diagnosis and Response-Adapted Strategies

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## Abstract

Optimal lymphoma management requires accurate pretreatment staging and reliable assessment of response, both during and after therapy. Positron emission tomography with computerized tomography (PET/CT) combines functional and anatomical imaging and provides the most sensitive and accurate methods for lymphoma imaging. New guidelines for lymphoma imaging and recently revised criteria for lymphoma staging and response assessment recommend PET/CT staging, treatment monitoring, and response evaluation in all FDG-avid lymphomas, while CT remains the method of choice for non-FDG-avid histologies. Since interim PET imaging has high prognostic value in lymphoma, a number of trials investigate PET-based, response-adapted therapy for non-Hodgkin lymphomas (NHL). PET response is the main determinant of response according to the new response criteria, but PET/CT has little or no role in routine surveillance imaging, the value which is itself questionable. This review presents from a clinical point of view the evidence for the use of imaging and primarily PET/CT in NHL before, during, and after therapy. The reader is given an overview of the current PET-based interventional NHL trials and an insight into possible future developments in the field, including new PET tracers.

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## Keywords

Imaging · PET/CT · Lymphoma · Non-Hodgkin · Staging · Response

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## Contents

1	Introduction .....	126
2	Staging .....	127
2.1	PET/CT for Staging in Non-Hodgkin Lymphomas .....	127
2.2	PET/CT Staging in Indolent Non-Hodgkin Lymphomas .....	127
2.3	PET/CT Staging in Staging of Aggressive Non-Hodgkin Lymphomas.....	128
3	PET and PET/CT for Early Treatment Monitoring and Response-Adapted Therapy .....	130
3.1	Interim PET in Indolent NHL .....	131
3.2	Interim PET in Aggressive NHL .....	131
4	PET/CT for Post-therapy Response Evaluation of Lymphomas .....	133
5	Disease Surveillance After First Remission .....	135
5.1	Aggressive Non-Hodgkin Lymphomas .....	135
5.2	Indolent Non-Hodgkin Lymphomas.....	137
6	Response Prediction with FDG-PET Before High-Dose Salvage Therapy .....	137
7	Other Imaging Methods than FDG-PET and CT .....	137
7.1	Newer PET Tracers .....	137
7.2	Magnetic Resonance Imaging .....	138
8	Conclusions and Recommendations .....	138
	References .....	139

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## 1 Introduction

Over the last 2–3 decades, we have seen substantial improvements in the prognosis of patients with non-Hodgkin lymphomas (NHL) [1]. These improvements can be attributed to the following factors:

1. Better understanding of the biology of the diseases and advances in molecular pathology, leading to better disease characterization and identification of valuable prognostic markers as well as therapeutic targets.
2. Better imaging methods, most importantly computerized tomography (CT) with cross-sectional images providing more accurate staging, and the more recent introduction of functional imaging, notably positron emission tomography (PET) and PET/CT, which is now the cornerstone of lymphoma imaging.
3. Last and not least; improved treatment regimens, including the introduction of monoclonal anti-CD20 antibodies and high-dose chemotherapy with autologous stem cell support.

The introduction of CT in the 1980s resulted in improved staging accuracy, and CT replaced cumbersome staging procedures such as lymphangiography and staging laparotomy. The introduction of CT was not based on much evidence, as opposed to the more than 1,000 studies investigating PET and PET/CT in lymphoma. During the last 15 years, a large number of studies have shown superior accuracy and sensitivity of PET/CT over CT. Along with patient symptoms and clinical examination, CT and PET/CT are now the cornerstone of all lymphoma

imaging. The recent international guidelines for imaging in the staging and response assessment of lymphoma recommend PET/CT for staging and response assessment of all most NHL subtypes [2, 3]. The only PET tracer in widespread clinical use for lymphoma is still 2-[<sup>18</sup>F]fluor-2-deoxyglucose (FDG). In the following and if not otherwise specified, PET refers to FDG-PET and PET/CT refers to FDG-PET/CT.

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## 2 Staging

### 2.1 PET/CT for Staging in Non-Hodgkin Lymphomas

Accurate disease staging in NHL is crucial for pretherapy risk assessment and selection of optimal therapy [4, 5]. The main purpose of the staging process, however, depends on the type of the non-Hodgkin lymphoma. Indolent NHL are often considered incurable unless localized at the time of diagnosis. Accordingly, the main question in the staging of indolent NHL is: localized or non-localized disease? Most aggressive NHL, including both B- and T-cell subtypes, are potentially curable when patients are fit for first-line treatment. However, the actual prognosis depends on the specific lymphoma subtype and the presence of high-risk features. The most widely used prognostic scores for NHL are derived from simple clinicopathological features and include disease stage or measures related to disease burden [6–10]. Thus, staging of aggressive non-Hodgkin lymphoma contributes to prognostication and eventually selection of therapy intensity.

The modified Ann Arbor classification originally developed for Hodgkin lymphoma still provides the backbone of disease staging in NHL [3, 11]. The staging workup generally includes clinical examination, blood tests, a routine bone marrow biopsy, and imaging. Contrast-enhanced CT (ceCT) of the neck, chest, and abdomen is required as a minimum, but PET/CT imaging is recommended for all FDG-avid NHL. FDG-PET is routinely used for lymphomas and measures tissue glucose metabolism by use of a short-lived radioactive glucose analog tracer. An advantage of PET-based imaging over stand-alone CT is higher sensitivity and a better discrimination between lymphoma and non-malignant lesions. When PET and CT are combined in a single procedure (PET/CT), the abnormal glucose metabolism is correlated with detailed anatomy, and the increased sensitivity comes not at the expense of decreased specificity; hence, the overall accuracy is increased [12].

### 2.2 PET/CT Staging in Indolent Non-Hodgkin Lymphomas

**Follicular lymphoma (FL):** FL is the most common subtype of indolent lymphoma, and the vast majority of FL cases are FDG-avid [13]. The main purpose of FL staging is to identify patients with true localized disease, potentially curable with radiotherapy, but also to risk stratify patients according to the follicular lymphoma international prognostic index (FLIPI) [8]. Compared to conventional

stand-alone CT staging, PET/CT detects abnormal activity in normal sized lymph nodes as well as additional involvement of extranodal sites, all resulting in upstaging of 18–32 % of patients and leading to a treatment change in 11–28 % of patients [14–16]. In particular, a large number of patients considered to have limited-stage disease by conventional staging are upstaged by PET/CT to advanced-stage disease (31–62 % according to recent studies) [17, 18]. Upstaging in these cases will change therapy and therefore be clinically relevant. Use of PET/CT also assigns 18 % of the patients to poorer FLIPI risk group, whereas only 6 % are reallocated to lower-risk groups by PET/CT [17]. A replacement of the original FLIPI by a new PET/CT-based risk score has been proposed, as PET/CT-specific findings such as osteomedullary uptake and extranodal disease may be associated with a worse outcome [14].

**Mantle cell lymphoma:** Mantle cell lymphomas are FDG-avid, and staging with PET/CT results in change of the CT-assessed stage in almost half of the patients, most of whom are upstaged [13, 19]. Therefore, it is possible that patients with truly localized mantle cell lymphoma are more accurately identified with PET/CT. Patients with high FDG-avidity at baseline have a worse outcome than patients with low-grade uptake, which suggests that metabolic activity correlates with tumor aggressiveness [19].

**Other indolent lymphomas:** The value of PET/CT-based staging in MALT lymphoma and small lymphocytic lymphoma is controversial, and the reported FDG-avidity in these lymphomas is inconsistent [13, 20]. In FDG-avid cases, the uptake is usually discrete, and as for CLL, PET/CT is useful for selecting biopsy site in suspected Richter's transformation [21, 22]. Nodal marginal zone lymphomas are usually FDG-avid, while this is rarely the case for extranodal marginal zone [13].

**Summary:** PET/CT for staging of indolent NHL is not well investigated, and the present evidence is derived from few retrospective series. FL, mantle cell lymphoma, and nodal marginal zone lymphoma are FDG-avid, and PET/CT is likely to discriminate between localized and non-localized diseases more accurately than CT. For other indolent lymphomas, PET/CT can guide selection of biopsy site in case of suspected Richter's transformation. For all indolent lymphomas, the impact on patient outcome of the changes in risk stratification and treatment approach caused by PET/CT is yet largely unclear. Nevertheless, PET/CT is recommended for staging of all FDG-avid indolent lymphomas, while CT remains the recommended imaging tool for non-FDG-avid lymphomas [2].

### 2.3 PET/CT Staging in Staging of Aggressive Non-Hodgkin Lymphomas

**Diffuse large B-cell lymphoma (DLBCL):** Even though DLBCL is the most common of all lymphomas, the value of PET/CT for staging of DLBCL has mainly been studied in groups of mixed lymphoma histologies. When compared to CT, PET/CT provides more sensitive and accurate staging and results in upstaging of

10–20 % of patients, some of whom will be allocated to a more advanced treatment [23–25]. The reason for more upstaging is the high sensitivity of PET/CT for extranodal DLBCL. PET/CT accurately identifies bone marrow involvement by DLBCL, and the reported sensitivity and specificity for bone marrow involvement was 94 and 100 % in a recent study [26]. Although most cases of bone marrow involvement by DLBCL are correctly identified by focal bone marrow lesions on PET/CT, a low-grade discordant bone marrow infiltration can be missed [26, 27]. PET/CT staging impacts on pretherapy risk assessment since the number of extranodal sites and that of disease stage are both factors in the widely used IPI risk score [6], and since >1 extranodal site is a risk factor for CNS relapse which often leads to additional CNS prophylactic therapy [28]. The validity of IPI in PET/CT-staged patients is currently investigated. A number of groups have looked at different quantitative applications of PET for staging in DLBCL. While the role of the standardized uptake value (SUV) is unclear, the metabolic tumor volume (MTV) seems to be prognostic of long-term outcome [29, 30]. Furthermore, recent studies demonstrate a good prognostic value of total lesion glycolysis (TLG) which is a combined assessment of volume and metabolism [31, 32].

**Burkitt:** Burkitt lymphoma is the most aggressive type of non-Hodgkin lymphoma. All cases of Burkitt lymphoma are FDG-avid, and PET/CT staging detects more extranodal disease than conventional staging. Of interest, occult bone marrow involvement is found and occasional clinically important upstagings occur [33].

**Peripheral T-cell lymphomas (PTCLs):** PTCLs are a heterogeneous group of diseases, and FDG uptake is variable. While the cutaneous T-cell lymphomas have low or no FDG uptake, most nodal PTCLs are FDG-avid albeit with lower FDG uptake than the corresponding B-cell lymphomas [13, 34, 35]. PET/CT identifies additional disease sites in non-cutaneous PTCLs in almost 50 % of the patients, but only changes disease stage in 5 % [35]. Since most nodal PTCLs are disseminated at the time of diagnosis, the additional diagnostic information by PET/CT is less likely to impact overall stage. PET has low sensitivity for detection of bone marrow involvement in PTCLs (20 %) and cannot replace the iliac crest bone marrow biopsy [34]. Nasal-type NK/T-cell lymphoma is most often a disease localized to the head-and-neck region, but PET/CT staging will change stage in one fifth of these patients, and in few patients, disseminated disease is found by PET/CT. Change of treatment by PET/CT in nasal-type NK/T-cell lymphomas is even more common as PET/CT [often accompanied by magnetic resonance imaging (MRI)] modifies radiotherapy planning in many cases [36].

**Summary:** PET/CT is recommended and widely used for staging of aggressive NHL. Disease stage and pretherapy risk assessment is modified in a large proportion of patients, and for some patients, the additional diagnostic information by PET/CT will change treatment intensity. The impact of PET/CT staging on patient outcome, however, is unknown.

### **3 PET and PET/CT for Early Treatment Monitoring and Response-Adapted Therapy**

A number of well-established pretreatment prognostic factors have been shown to predict survival in large cohort studies of lymphoma patients [6–9]. These prognostic factors are used along with the clinical stage to determine the initial treatment strategy. However, in both indolent and aggressive lymphomas, the tumor response to induction treatment is an important surrogate for other measures of clinical benefit from the treatment, including progression-free survival and overall survival. A reliable and early prediction of response to therapy can possibly separate good-risk patients who will be cured with conventional therapy or even less intensive and less toxic regimens from poor-risk patients for whom an early switch to alternative, more aggressive treatment strategies could improve the likelihood of remission and cure. This concept called risk-adapted therapy is widely recognized as a potential way to achieve higher cure rates with lower or equal risk of treatment-related morbidity and mortality.

Conventional methods for treatment response monitoring are based on morphological criteria, and a reduction in tumor size on CT is the most important determinant [37–39]. However, size reduction is not necessarily an accurate predictor of outcome. But even more importantly, tumor shrinkage takes time and depends on a number of factors in the host. So the rate of structural regression cannot form the basis for therapy response assessment until rather late during treatment, at which point a treatment modification might be less useful.

As opposed to the morphological changes of the lymphoma occurring later during therapy, functional imaging with FDG-PET enables early evaluation of the metabolic changes that take place very early during the treatment induction. Several studies of FDG-PET after 1–4 cycles of chemotherapy in aggressive NHL [40–48] and FL have shown that these early metabolic changes are highly predictive of final treatment response and progression-free survival (PFS). However, treatment-induced inflammation and concomitant infections may lead to false-positive interim scans, and this risk is particularly pertinent in patients treated with intensive regimens [49]. Most evidence is available for performing early interim FDG-PET after 2–4 cycles of chemotherapy. However, reports from Kostakoglu et al. [44, 48] strongly suggest that the predictive value may be as high after only one cycle of chemotherapy. This is of importance for early PET response-adapted treatment regimens, since the treatment adaptation is best performed as early as possible in order to increase the chance of satisfactory remission and to avoid unnecessary ineffective chemotherapy.

Interim treatment monitoring is more a tradition than an evidence-based practice. Even though it is well established that continued treatment in patients with progression or no response during first-line therapy will invariably lead to treatment failure, the widespread use of CT for treatment monitoring has never been proven to improve the outcome of lymphoma patients. This is true for PET/CT imaging as well, and until we have data from the studies of PET response-adapted therapy,

**Table 1** The Deauville five-point scale for PET response in lymphoma

1	No uptake
2	Uptake $\leq$ mediastinum
3	Uptake $>$ mediastinum but $\leq$ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

interim imaging should only be performed if clinically justified. The recently revised lymphoma imaging recommendations state that if PET-CT is superior to CT alone to assess early response, if such an assessment is needed, but changing therapy solely on the basis of interim PET-CT is not recommended, unless there is clear evidence of progression. It is recommended that both interim and post-treatment PET scans are interpreted and reported according to the Deauville five-point scale (Table 1) [2]. Figure 1 shows examples of PET images with response scored using the five-point scale.

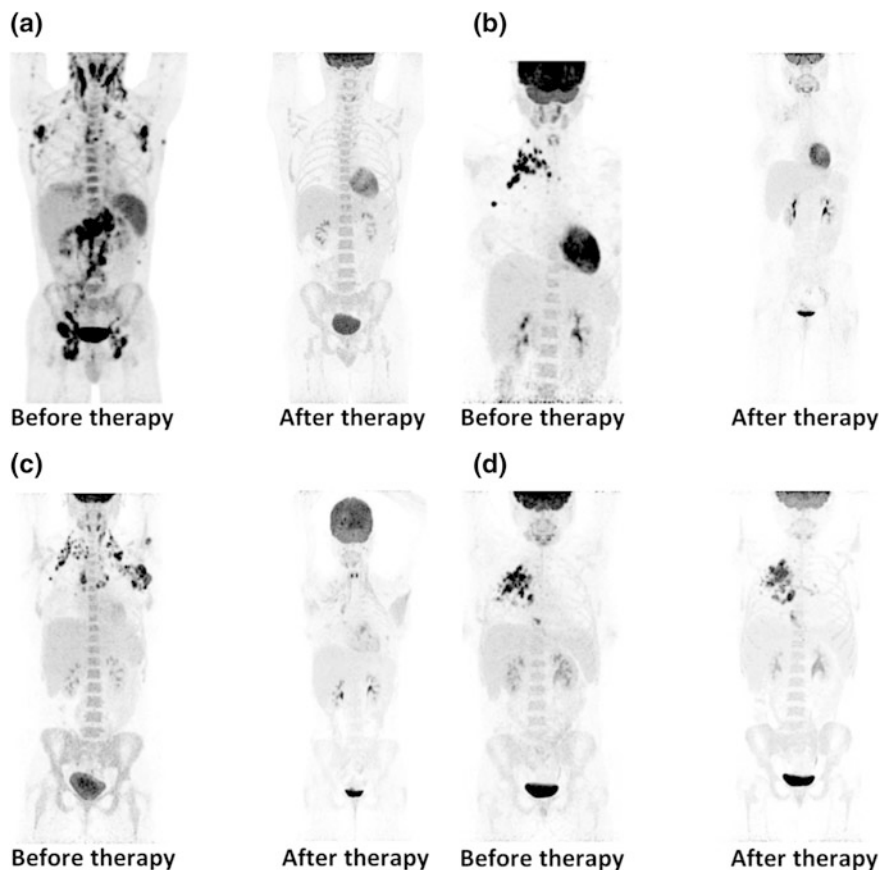
### 3.1 Interim PET in Indolent NHL

There is a relative paucity of data on the value of interim FDG-PET in indolent lymphomas. Bishu et al. reported a retrospective series of 31 patients with advanced-stage FL, of whom 11 had FDG-PET scans midway through four cycles of induction chemotherapy. The number of patients was too small for any firm conclusions. Still, the results showed interesting differences: Four patients with some persistent FDG uptake had a mean PFS of 17 months and seven interim PET-negative patients had a mean PFS of 30 months [50]. There are only casuistic reports on the value of interim FDG-PET in localized FL or the more uncommon subtypes of indolent NHL, such as marginal zone lymphoma and small lymphocytic lymphoma.

Even if a clear correlation between interim FDG-PET and treatment outcome is shown in the future, the clinical implications are uncertain, since advanced-stage indolent lymphoma is very different from aggressive NHL. First of all, current first-line therapies for advanced-stage FL are not curative, and it is unclear whether early treatment intensification with autologous stem cell transplant (ASCT) or allogeneic bone marrow transplantation is of any benefit to poor-risk patients. Secondly, the long natural history of FL and the relative success of subsequent treatment lines in inducing lasting remissions mean that a longer time to first progression does not necessarily translate into longer survival.

### 3.2 Interim PET in Aggressive NHL

In aggressive NHL, PFS ranges from 10 to 50 % at 1 year for early PET-positive patients and from 79 to 100 % at 1 year for early PET-negative patients. The high



**Fig. 1** Legend Examples of baseline and interim PET images with response assessed according to the Deauville five-point scale. **a** Deauville score 1. **b** Deauville score 1. **c** Deauville score 1. **d** Deauville score 1

risk of relapse seen among PET-positive patients is consistently shown in both early and advanced stages. Mikhaeel et al. studied a large cohort of 121 high-grade NHL patients, retrospectively and with a median follow-up of 28.5 months. They confirmed that response on FDG-PET after two or three cycles strongly predicts PFS and OS. Estimated 5-year PFS was 89 % for the PET-negative group, 59 % for patients with minimal residual uptake (MRU) on FDG-PET, and 16 % for the PET-positive group. Survival analyses showed strong associations between early FDG-PET results and PFS and OS [46]. Haioun et al. prospectively studied 90 patients with aggressive NHL, performing FDG-PET after two cycles of chemotherapy. They similarly found 2-year PFS rates of 82 and 43 % in early PET-negative and early PET-positive patients, respectively, and 2-year OS rates of 90 and 60 % [47]. Spaepen et al. compared interim FDG-PET after two cycles of chemotherapy with



the International Prognostic Index (IPI). In multivariate analysis, FDG-PET at mid-treatment was a stronger prognostic factor for PFS and OS than was the IPI ( $P < 0.58$  and  $P < 0.03$ , respectively) [42]. A number of other more recent studies have investigated the value of interim PET specifically in DLBCL cohorts and found negative predictive values similar to those found in the above-mentioned studies of mixed aggressive NHL populations. But the positive predictive value is variable and generally poor [51, 52]. A possible explanation for the low positive predictive value in aggressive NHL cohorts is the higher risk of inflammation and infections among patients who are treated with the more dose-dense and dose-intensive NHL regimens, as mentioned above. In order to overcome the low positive predictive value of interim PET, some investigators have proposed a semiquantitative approach (relative or absolute change in SUV from baseline to interim scan) as superior to visual PET assessment in patients with DLBCL [53, 54].

Aggressive NHL covers a number of lymphoma subtypes where first-line treatment of both localized and advanced disease stages is given with a curative intent. Aggressive NHL patients who respond poorly to first-line treatment or relapse soon afterward generally have a very poor prognosis even with high-dose salvage regimens. Such poor-risk patients could benefit from having their treatment failure recognized early during first-line therapy in order to switch a more intensive regimen as soon as possible. Much inspired by a similar and more widespread trend in Hodgkin lymphoma, a number of trials are currently investigating early PET response-adapted treatment strategies (Table 2). Most studies test whether early or mid-treatment PET-positive patients with aggressive NHL (mainly DLBCL) will benefit from early escalation to more intensive regimens or even high-dose therapy with autologous stem cell support (ASCT) [55–60]. One de-escalation study compares standard treatment with six cycles R-CHOP to good-risk DLBCL patients to abbreviated therapy with four cycles R-CHOP in patients with a negative PET after two cycles of therapy [61].

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#### **4 PET/CT for Post-therapy Response Evaluation of Lymphomas**

Response to treatment serves as an important surrogate for other measures of clinical benefit such as progression-free survival and overall survival. Response is also an important guide in decisions regarding continuation or change of therapy. Until recently, response evaluation in NHL was done according to the International Workshop Criteria [62], based mainly on morphological evaluation with a reduction in tumor size on CT being the most important factor. But after completion of therapy, CT scans will often reveal residual masses, and the presence of such masses is not highly predictive of outcome. By conventional methods, it is very difficult to assess whether this represents viable lymphoma or fibrotic scar tissue. An extensive number of studies have shown that FDG-PET performed post-treatment is highly predictive of PFS and OS with and without residual masses on CT.

**Table 2** PET response-adapted trials in aggressive NHL

Study title/description	Study group	Ref	Patients	Main PET-driven intervention	Study type
Risk-adapted dose-dense immunochemotherapy determined by interim FDG-PET in advanced DLBCL	MSKCC	52	DLBCL	Salvage with HD + ASCT if PET positive after 4 × R-CHOP	Phase II
FDG-PET in predicting relapse in NHL patients undergoing chemotherapy with or without ASCT	Johns Hopkins	55	Aggressive NHL	Salvage with HD + ASCT if PET positive after 2-3 × (R-)CHOP	Phase II
Positron emission tomography-guided therapy of aggressive non-Hodgkin's lymphomas (PETAL)	University Hospital, Essen	57	Aggressive NHL	(R-)CHOP versus Burkitt regimen if PET positive after 2 × (R-)CHOP	Phase III
Tailoring treatment for B-cell non-Hodgkin's lymphoma based on PET scan results mid-treatment	British Columbia Cancer Agency	58	Advanced DLBCL	4 cycles R-ICE if PET positive after 4 × R-CHOP	Phase II
FDG-PET-stratified R-DICEP and R-Beam/ASCT for diffuse large B-cell lymphoma (PET CHOP)	Alberta Cancer Board	59	DLBCL	Salvage with HD + ASCT if PET positive after 2 × R-CHOP	Phase II
A study of associations between rituximab and chemotherapy, with PET-driven strategy in lymphoma (LNH2007-3B)	LYSA	60	DLBCL	Salvage with HD + ASCT if PET positive after 2 × R-CHOP	Phase III <sup>a</sup>
Therapy for aaIPI intermediate or high-risk DLBCL	MSKCC	56	DLBCL	High dose if PET positive and biopsy positive after 3 cycles of immunochemotherapy	Phase II
Treatment adapted to the early PET compared to a standard treatment in low risk (aaIPI = 0) DLBCL	LYSA	61	DLBCL	4 × R-CHOP versus 6 × R-CHOP for early PET-negative patients	Phase III

<sup>a</sup>No randomization regarding PET response-adapted therapy

DLBCL diffuse large B-cell lymphoma; HD + ASCT high-dose chemotherapy with autologous stem cell transplantation; R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; NHL non-Hodgkin lymphoma; R-ICE rituximab, ifosfamide, carboplatin, etoposide; LYSA the Lymphoma Study Association; MSKCC Memorial Sloan-Kettering Cancer Center

The vast number of studies in aggressive NHL has been summarized in a systematic review [63], while the data on indolent NHL are based on fewer studies [64–66].

Based on these findings, the International Harmonization Project developed new recommendations for response criteria for aggressive malignant lymphomas, incorporating FDG-PET into the definitions of end-of-treatment response in FDG-avid lymphomas [67, 68]. Subsequent retrospective analyses confirmed the superiority of the new PET/CT-based response criteria [69]. The recent revision of the international lymphoma staging and response criteria still uses PET response (according to the Deauville five-point scale) as the main determinant for post-treatment assessment, while measurements of the sum of the product of perpendicular diameters of measurable lesions are mainly important for the definition of progressive disease [3]. The negative predictive value of post-treatment PET/CT is high in most NHL subtypes, but due to a relatively low positive predictive value, treatment failure suspected due to a positive PET should be confirmed by biopsy before additional therapy is initiated. Alternatively, it is often preferable to wait and repeat the PET/CT after 1–2 months, provided the patient is not in clinical progression.

Unlike in Hodgkin lymphoma, the role of post-treatment PET/CT for selection of NHL patients for consolidation radiotherapy is unclear. Based on promising data showing a very high negative predictive value of PET/CT in primary mediastinal B-cell lymphoma [70], the International Extranodal Lymphoma Study Group conducts an experimental approach where consolidation radiotherapy is given only to patients with a PET-positive residual mass [71]. Also, the British Columbia Cancer Agency has since 2005 routinely used post-chemotherapy PET for all patients with residual masses larger than 2 cm. Only PET-positive patients receive consolidation radiotherapy. With 262 patients included in the series and a median follow-up of 45 months, only one of 179 PET-negative patients has received radiotherapy. The 4-year PFS and OS are 74 and 83 %, respectively. Since the data have still only been presented in abstract form, it is unfortunately unclear whether the relapses were predominantly located within or outside the sites of residual disease. If most relapses occur outside the sites of residual disease, there seems to be little value of consolidation radiotherapy in PET-negative patients, but this is not quite so clear whether a substantial number of relapses are seen within the sites of residual disease after first-line treatment [72].

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## **5 Disease Surveillance After First Remission**

### **5.1 Aggressive Non-Hodgkin Lymphomas**

The value of routine surveillance imaging in aggressive NHL in first remission is controversial. Despite the lack of evidence, surveillance imaging is often performed with regular intervals during the first years in remission. The rationale behind this may be a presumed better outcome in patients with early and asymptomatic relapse as compared to those patients presenting with overt lymphoma symptoms.

Early detection of relapse could in theory be advantageous for the following reasons: (1) lower tumor burden at relapse (and maybe reduced tumor heterogeneity and prevention of treatment resistant clones) and (2) less disease-related impairment of function and organs with better tolerability of treatment. Low disease stage and ECOG performance status 0–1 at relapse are associated with a better outcome in DLBCL [73]. With less than a quarter of the relapses being imaging detected, routine imaging did not contribute significantly to relapse detection in studies based on imaging modalities less sensitive than PET/CT [74–78]. Furthermore, the number of scans per relapse exceeded 100 per preclinical relapse for both DLBCL and PTCLs in first complete remission, and out of all patients in complete remission entering intensive follow-up protocols, only a very small minority (2–3 %) will experience imaging-detected relapse [78]. Few studies have investigated the value of PET/CT in the surveillance of aggressive NHL, mainly reporting on DLBCL. Generally, the rate of imaging-detected relapse seems to be higher when using regular PET/CT surveillance in first remission, and depending on the surveillance protocol, 31–100 % of relapses were detected by imaging [79–81]. However, with the number of PET/CT scans per relapse ranging between 35 and 120 [81, 82] and an estimated cost of up to US\$85,550 per preclinical PET/CT-detected relapse, an indiscriminate use of PET/CT surveillance is not likely to be cost-effective. Restricting the use of PET/CT to high-risk patients (IPI > 2) decreases the number of PET/CT scans per relapse to 22 and may tip the balance toward better cost-effectiveness [81]. In patients with transformed indolent lymphomas undergoing routine imaging with PET/CT at least one time during follow-up, the PET/CT-detected relapses were all indolent histologies and less important from a clinical perspective. On the contrary, cases of relapsed DLBCL were symptomatic [83]. Since FDG uptake is unspecific and not restricted to lymphoma recurrence, the positive predictive value (PPV) of PET/CT surveillance in aggressive NHL has been reported low to moderate with values between 21 and 60 % [79, 81, 84]. The increasing use of PET/CT for lymphoma has probably led to safer recognition of uptake patterns characteristic for lymphoma and hence less false-positive reporting. Still, a confirmatory biopsy of lymphoma suspicious findings on PET/CT is mandatory whenever possible. As opposed to the problematic PPV of PET/CT, the negative predictive value has been reported uniformly high and often 100 % [79, 81, 84]. This means that a negative PET/CT study virtually rules out recurrent disease and the need for further investigations in patients with symptoms suggesting lymphoma relapse. Finally, the use of routine surveillance imaging in aggressive NHL can only be justified if early relapse detection is associated with improved survival. Some studies have suggested that imaging-detected relapse of aggressive non-Hodgkin lymphoma could be associated with improved outcome, whereas others found no difference in outcome [76, 78, 81]. However, the retrospective design of these studies does not allow firm conclusions about the causal role of imaging due the presence of important bias (lead time, length time, and guarantee time). Interestingly, a recent randomized trial of surveillance

strategies in Hodgkin lymphoma showed that the use of chest X-ray and ultrasound was just as effective as PET/CT in early relapse detection, but at a much lower cost and with higher PPV [85].

## 5.2 Indolent Non-Hodgkin Lymphomas

While use of routine imaging in the follow-up of aggressive NHL is still widespread, the use of routine imaging in the follow-up of indolent NHL is not recommended. An observational approach without initial treatment is often chosen for patients with an asymptomatic relapse of an indolent lymphoma. An exception could be specific cases where an asymptomatic relapse could lead to unrecognized compression of vital organs such as vascular structures. In any case, PET/CT has no role in this setting.

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## 6 Response Prediction with FDG-PET Before High-Dose Salvage Therapy

Duration of remission prior to relapse and the response to induction therapy are important prognostic factors that predict a good outcome after high-dose chemotherapy with autologous stem cell support (HD + ASCT) [86, 87]. A number of studies have shown that PET performed after induction therapy and before HD + ASCT is predictive of long-term remission. These studies all report short PFS in patients with persistent disease on pretransplant PET [88–93]. In relapsed Hodgkin lymphoma, Moskowitz and his group demonstrated that patients could benefit from changing to another non-cross-resistant regimen before HD + ASCT rather than proceeding straight to high-dose therapy if the PET was still positive after the initial induction therapy [94]. Even though no such data are yet available in NHL, it seems clear that achieving a negative PET before HD + ASCT should be a goal for all patients.

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## 7 Other Imaging Methods than FDG-PET and CT

### 7.1 Newer PET Tracers

Like other cancers, lymphoma is characterized by deregulated cell cycle progression and most anticancer drugs are designed to inhibit cell proliferation. So a tracer enabling imaging of cell proliferation could be useful for both initial characterization and treatment monitoring of the disease. FDG uptake is somewhat correlated with cell proliferation, but this correlation is weakened by a number of factors, including FDG uptake in non-malignant lesions [95, 96]. The nucleoside [ $^{11}\text{C}$ ]thymidine was the first PET tracer to specifically address cell proliferation. Early studies showed

that [ $^{11}\text{C}$ ]thymidine could determine both disease extent and early response to chemotherapy in aggressive NHL patients [97, 98]. However, the short 20-min half-life of  $^{11}\text{C}$  along with rapid in vivo metabolism has limited the clinical application of [ $^{11}\text{C}$ ]thymidine. The thymidine analogue 3'-deoxy-3'-[ $^{18}\text{F}$ ]fluorothymidine (FLT) offers a more suitable half-life of 110 min and is stable in vivo [99]. More recent studies have shown that FLT-PET can sensitively identify lymphoma sites [100]. FLT uptake is highly correlated with proliferation rate and may thus be able to distinguish between high- and low-grade lymphomas [101, 102]. And furthermore, recent studies have showed a potential of FLT for imaging early response to treatment in NHL [103–106]. Amino acid metabolism of cancer cells is influenced by catabolic processes favoring tumor growth [107]. It has been shown that increased uptake of amino acids reflects the increased transport and protein synthesis of malignant tissue [108, 109]. This is the background for PET imaging of amino acid metabolism with the labeled amino acids L-[methyl- $^{11}\text{C}$ ]methionine (MET) and O-2-[ $^{18}\text{F}$ ]fluoroethyl-L-tyrosine (FET) [110]. Nuutinen et al. [111] studied 32 lymphoma patients and found MET-PET highly sensitive for the detection of disease sites although there was no correlation between MET uptake and patient outcome. Also, MET-PET has an advantage over FDG-PET in imaging of CNS lymphoma [112]. While these results are encouraging, it should be noted that no studies have shown the usefulness or cost-effectiveness of amino acid or nucleoside tracers in large patient cohorts. Furthermore, high physiological tracer uptake in the abdomen limits the usefulness of these tracers for imaging of abdominal and pelvic lymphomas.

With CD20 expressed as a cell surface antigen in most cases of B-NHL, and with CD20 as an important therapeutic target, it is logical to also target CD20 for the purpose of lymphoma imaging. However, most of the available so-called *immunoPET* tracers are based on full-size, intact antibodies, and as a result of this, it takes a long time for the background activity levels to drop sufficiently to provide acceptable target-to-background ratios. Therefore, Olafsen and colleagues generated a recombinant anti-CD20 fragment which, labeled with a PET tracer, produced high-contrast images in a small-animal model [113]. This and similar targeted PET methods may in the future provide very lymphoma-specific images and prove useful in the staging and treatment monitoring of NHL.

## 7.2 Magnetic Resonance Imaging

MRI has long been the main structural imaging methods in pediatric lymphomas, due to the reduction in radiation exposure. MRI is used in adult patients to evaluate central nervous system disease and for disease sites in the head-and-neck region (e.g., NK/T-cell lymphomas of nasal type). Recent studies show that diffusion-weighted MRI early during treatment may identify responders before a reduction in tumor size occurs [114].

## 8 Conclusions and Recommendations

Supported by a large number of studies and in line with the recent consensus recommendations for lymphoma imaging as well as the revised criteria for lymphoma staging and response evaluation, PET/CT is recommended for staging and post-treatment response assessment of all FDG-avid NHLs [2, 3]. There are sufficient data to support the use of interim PET for treatment monitoring in aggressive B-NHL when interim imaging is appropriate. CT is still the preferred imaging method for non-FDG-avid lymphomas, as well as for selected cases where routine surveillance imaging is considered necessary. For interim and post-treatment imaging, the Deauville five-point scale is recommended for interpretation and reporting of PET results. The use of interim PET imaging to guide therapeutic decisions is still investigational and should preferably be done in the setting of clinical trials. Semiquantitative and quantitative PET assessments (SUV, MTV, TLG) are promising, but their role is still to be defined. Currently, much effort is put into the standardization of PET/CT methodology and interpretation, making the results of trials more comparable and ensuring a better translation into clinical practice. Upcoming results of interim PET response-adapted therapy trials are likely to impact on the management of de novo and relapsed NHL patients in the near future. The dissemination of novel and more disease-specific PET tracers may improve the basis for risk- and response-adapted therapy, hopefully in combination with better pretreatment predictive molecular pathology markers.

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