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Standardized Response Assessment Criteria and their Applications in Lymphoma: Part 2

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ABSTRACT

Interim and end-of-treatment PET/CT have become central to the evaluation of Hodgkin's and non-Hodgkin's lymphoma. This review article seeks to aid clinical decision-making by providing an overview of available data on the diagnostic and prognostic value of PET/CT imaging for response assessment and pre-transplant evaluation in lymphoma. The relative strengths and limitations of these techniques in various disease subtypes and clinical scenarios are explored, along with their current standards for reporting and latest developments. Particular attention is given to response-adapted therapy, which is emerging as a cornerstone of clinical management.

KEYWORDS

Lymphoma, PET/CT, response assessment, response-adapted therapy

INTRODUCTION

Computed tomography (CT) and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) have come to play integral roles in evaluating Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Soon after the incorporation of CT into staging and response assessment criteria, the advantages of utilizing PET's metabolic data in conjunction with CT's structural information for these applications began to become apparent. This combination was especially helpful in the staging and restaging of lymphoma; it was shown to (a) reliably identify the 80-95% of post-treatment residual masses that are nonmalignant, thereby sparing patients unnecessary therapy and morbidity; and (b) alter staging in 20% of cases, most frequently upstaging patients by better detecting bone marrow involvement (*1*,*2*).

Following the integration of PET into the International Working Group criteria in 2007, PET/CT was widely adopted as a first-line imaging tool for evaluating end-of-treatment response in lymphoma (*3*). Subsequent studies laid the groundwork for the Deauville five-point scale (D5PS) criteria, designed for the visual interpretation of PET scans (*4*). This was expanded by the Lugano guidelines, which established PET/CT as the modality of choice for staging and response assessment in ^{18}F-FDG-avid subtypes of lymphoma, but maintained CT as the preferred tool for the small histologic subset with low or variable avidity (*5*). These guidelines are particularly important for interim response assessment, a novel approach offering actionable data to inform prognosis and management prior to the completion of treatment. The D5PS criteria have now been validated as the preferred interpretation method for both interim and end-of-treatment PET in HL and NHL (*6*-*9*).

Response assessment in lymphoma, in the interim and end-of-treatment settings, is the focus of this two-part review. Part 1 provided a historical overview of response assessment and described the numerous criteria that have been developed for this application in lymphoma. This installment builds on that foundation by reviewing published data on the diagnostic and prognostic accuracy of interim and end-of-treatment response assessment in HL and NHL. The methodologies and findings of prior studies that have compared survival data between patients according to their imaging results are presented below. The most recent developments in response assessment, along with their implications for the future, are also explored. Overall, the aim of this review is to guide clinical strategies for the diagnosis and treatment of lymphoma.

INTERIM RESPONSE ASSESSMENT IN HL

PET-based interim response assessment in HL has been a focus of intense research since the mid-2000s. Many of the earliest studies were presented in a meta-analysis performed by Terasawa et al, comprising 360 advanced HL patients across 7 studies with varying treatment and interpretation methods. The meta-analysis lent credence to interim PET by demonstrating pooled sensitivity and specificity values of 0.81 and 0.97, indicating accuracy comparable to that of end-of-treatment imaging (*10*). A more recent meta-analysis of 10 studies with 1389 patients reported slightly lower pooled sensitivity and specificity values of 0.71 and 0.90, respectively (*11*).

The predictive value of interim scans has also been validated by a host of studies comparing outcomes in PET+ and PET- patients (Table 1). The majority of these studies performed PET scans after 2 cycles of chemotherapy (PET-2) and at the completion of therapy and follow-up. The value of interim imaging at other points during treatment has been compared to that of PET-2; PET-1 has been shown to be prognostically inferior (*12*), while PET-4 been comparable (*13,14*). PET-2 has therefore come to be the most common and well-validated interim response measurement in HL. Similarly, several methods of image interpretation have been employed, but most studies have come to favor D5PS. Within the context of this 5-point visual scale, scores of 1-3 and 4-5 have generally been taken to represent PET- and PET+ results, respectively (Supplemental Table 1). A case example of HL evaluated by interim PET and accompanied by a sample imaging report drafted according to the Lugano guidelines is included in Supplemental Figure 1.

Studies evaluating response assessment in HL have controlled for disease severity and found that the utility of interim PET varies considerably between limited and advanced disease. In the case of the limited HL, the prognosis is typically excellent regardless of PET status, and so interim imaging frequently fails to distinguish between patients in terms of outcome (*15,16*). By contrast, studies that have exclusively enrolled subjects with advanced HL have found not only poorer outcomes overall, but also sizeable differences in survival based on interim PET status (*6,17,18*). This is borne out by analyses that have stratified outcomes by disease severity and noted similar findings (*19*).

Studies that have accounted for CT findings alongside PET-based response assessment have demonstrated improved stratification of patients and prediction of clinical outcomes. One such study in early HL reported striking differences across these strata, with PET-/CT-, PET-/CT+, PET+/CT-, and PET+/CT+ patients demonstrating 2-year PFS values of 95%, 78%, 71%, and

36%, respectively (*20*). A similar study of end-of-treatment PET in advanced HL illustrated the ability to distinguish between PET+ patients on the basis of changes in residual tumor size on CT; those with a reduction in tumor size of less than 40% had a 1-year relapse rate of 23.1%, whereas those with a reduction exceeding 40% had a rate of only 5.3% (*21*).

RESPONSE-ADAPTED THERAPY IN HL

The ability to reliably differentiate between responders and non-responders using interim imaging gave rise to response-adapted therapy, wherein treatment regimens are adjusted in accordance to findings on interim scans. Studies of response-adapted therapy have varied in their patient populations and methodologies, but many adhere to a common framework. Typically, studies have called for PET-2 imaging during standard treatment with ABVD. Patients who are determined to be PET- have gone on to complete the prescribed regimen, while those who are PET+ are advanced to more intensive regimens, such as escalated BEACOPP (eBEACOPP). Although eBEACOPP offers a higher cure rate—85% in the case of advanced HL, as compared to 70% for ABVD (*22*)—it also carries a significantly higher risk of adverse events such as anemia, leukopenia, febrile neutropenia, and sepsis (*23*). Thus, response-adapted therapy promises to improve outcomes while minimizing toxicities by identifying patients who are most likely to benefit from more potent treatment regimens.

Patient outcomes in studies of response-adapted therapy in HL have tended to be better than those of earlier trials without risk stratification (Table 2). The potential survival benefit was exemplified by a study involving patients with advanced HL, where the 2-year PFS of PET-2+ patients advanced to BEACOPP was measured at 64%, more than double the estimate of 15-30% for non-adapted treatment with ABVD (*24*). On the other hand, the possible improvement in morbidity was illustrated by a study comparing a control arm receiving 6 cycles of BEACOPP with a response-adapted experimental arm where interim PET- patients were de-escalated to ABVD. The authors reported comparable outcomes in the two groups, but a significant decrease in the rate of serious adverse events from 24% to 15% in the response-adapted group (*23*). Collectively, these results support the use of interim scans in HL to abbreviate therapy in PET- patients and to escalate treatment in PET+ patients.

Studies that have omitted radiotherapy (RT) based on interim PET findings have not been as encouraging. The RAPID trial, which randomized early HL patients who were PET-3- to receive

either RT or no further treatment, failed to demonstrate non-inferiority (*25*). Similarly, the EORTC/LYSA/FIL H10 trial, which subjected PET- early HL patients to de-escalated therapy without RT, was also unsuccessful in establishing non-inferiority (*26*).

INTERIM RESPONSE ASSESSMENT IN NHL

Studies of interim imaging in NHL have displayed more heterogeneity in their methodologies and revealed less diagnostic and prognostic accuracy in their results than their counterparts investigating HL. The standard treatment regimen administered in these cases has been R-CHOP, but several experimental regimens have also been tested, especially in subtypes of NHL other than diffuse large B-cell lymphoma (DLBCL). Moreover, there has been less of a consensus on when to acquire interim scans, with most studies calling for 2-4 cycles of treatment prior to imaging. Figure 2 illustrates a case example of a DLBCL patient evaluated by interim PET.

The diagnostic accuracy of interim imaging in NHL was addressed in the aforementioned meta-analysis by Terasawa et al, which included 311 patients with DLBCL (*10*). The authors reported pooled sensitivity and specificity values of 0.78 and 0.87, respectively, both slightly lower than the pooled metrics for HL. There is evidence to suggest that the diagnostic accuracy of PET-based response assessment is particularly limited in patients receiving immunochemotherapy. A meta-analysis by Sun et al, which compiled 6 studies and 605 DLBCL patients receiving R-CHOP, reported low pooled sensitivity and specificity values of 0.52 and 0.68, respectively (*27*).

The prognostic value of interim PET across several subtypes of NHL has been the focus of numerous studies (Table 3). Those involving DLBCL have typically found—with a few notable exceptions (*28-30*)—that a significant distinction can be drawn in the prognoses of interim PET+ and PET- patients. The results for non-DLBCL subtypes have been more mixed. Whereas interim scans of natural killer (NK)/T-cell lymphoma patients have been exceptionally reliable in predicting outcome (*31,32*), those of follicular lymphoma (FL) patients have shown only marginal prognostic ability (*33*).

RESPONSE-ADAPTED THERAPY IN NHL

Several studies have validated response-adapted therapy in NHL, almost exclusively in DLBCL (Table 4). They are methodologically analogous to their non-adapted counterparts, with

interim imaging performed after 2-4 cycles of R-CHOP. Patients identified as high-risk by virtue of being interim PET+ are advanced to stronger treatments, including R-ICE and autologous stem cell transplantation (ASCT). The survival of high-risk patients in these studies is higher than in those without response-adapted therapy, supporting its efficacy in NHL. However, there is presently insufficient evidence to support changing management based on interim PET imaging in DLBCL. A case example of a DLBCL patient treated with response-adapted therapy is depicted in Figure 3.

FUTURE TRENDS IN INTERIM RESPONSE ASSESSMENT

Immune checkpoint inhibitors have shown promise in an array of cancers, including lymphoma, but have also demonstrated a tendency to produce pseudo-progression through delayed response and tumor flare, a potential byproduct of drug-mediated immune activation. Inspired by the immune-related response criteria that modified RECIST, a workshop was convened to adapt the Lugano classifications to prevent the curtailing of effective immunomodulatory treatment in patients demonstrating pseudo-progression. The result was the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC), a set of provisional guidelines that are expected to evolve as the understanding of immunomodulatory therapy and the ability to identify pseudo-progression improve (*34*). Foremost among the proposed changes was the new interim response classification of "indeterminate response," which calls for biopsy and re-evaluation after 12 weeks to distinguish between pseudo-progression and true progression.

Another area of growing interest is the pairing of interim PET with biomarkers that enhance predictive value. In a study of 310 HL patients, the expression of neoplastic cell-associated and microenvironment-associated biomarkers such as CD68, PD-1, and STAT-1 allowed for the reclassification of PET- patients as either low-risk or high-risk, with corresponding 3-year PFS values of 95% and 63%, respectively (*35*). Similarly, bcl-2 expression has served as a complement to interim PET in NHL patients, helping to stratify risk. In a study of 48 DLBCL patients, those who were PET-2- had a relapse rate of 38% if they had high blc-2 expression and 0% if they had low expression (*36*).

END-OF-TREATMENT RESPONSE ASSESSMENT IN HL

While it lacks the practical advantages of early response assessment, end-of-treatment imaging has generally demonstrated superior diagnostic and prognostic accuracy. A meta-analysis by Zijlstra et al collected 408 HL patients across 15 studies, reporting a sensitivity of 0.84 and a specificity of 0.90 for end-of-treatment scans (*37*). Terasawa et al's meta-analysis of 19 studies with 474 HL patients reported a wide range of sensitivities (0.50-1.00) and specificities (0.67-1.00), but skewed toward the upper range of these values (*38*). Studies investigating the prognostic ability of end-of-treatment PET have sharply differentiated patients with respect to survival (Table 5). In fact, studies have shown that even in cases where interim scans are not found to be prognostic, as in early-stage disease, post-treatment PET is still predictive of outcome (*15*). Figure 4 shows a case example of an end-of-treatment PET scan of an HL patient.

END-OF-TREATMENT RESPONSE ASSSESSMENT IN NHL

The accuracy of end-of-treatment imaging in NHL has been established by meta-analyses by Zijlstra et al and Terasawa et al, which included 350 and 254 NHL patients. The former published sensitivity and specificity values of 0.72 and 1.00, while the latter reported ranges of 0.33-0.77 and 0.82-1.00 for sensitivity and specificity (*37,38*). When compared to their respective HL cohorts, the NHL patients in these studies showed lower sensitivity and higher specificity.

In terms of predicting outcomes, studies have validated the prognostic utility of post-therapy PET in numerous NHL subtypes (Table 6). These studies are highly varied in methodology, but they consistently corroborate the reliability of end-of-treatment imaging. Similar to HL, studies of NHL have shown that even when interim imaging fails to significantly distinguish between patients, post-treatment PET is reliably prognostic (*39,40*).

FUTURE TRENDS IN END-OF-TREATMENT RESPONSE ASSESSMENT

The reliable prognostic information of end-of-treatment PET, specifically in identifying patients at higher risk for treatment failure, has prompted investigations into its use in determining indications for consolidative RT. The GHSG HD15 trial, which included 2126 advanced HL patients, reserved RT for those with residual masses larger than 2.5 cm and a positive post-therapy imaging (*41*). The high predictive value (94.1%) of end-of-treatment PET justified the dramatic reduction in the rate of RT administration to 11%, as compared to 71% in the earlier HD9 trial. Similarly, a study of 163 advanced HL patients spared PET- patients further treatment and found

that their 3-year PFS (89%) remained significantly higher than that of PET+ patients who had undergone RT (55%) (*42*).

End-of-treatment PET/CT has not been as reliable a guide for RT in NHL patients. A study of 77 DLBCL patients failed to demonstrate a significant difference in the relapse rates of PET+ patients who did and did not receive RT (63% vs. 50%) (*43*). By contrast, a larger prospective study of 262 DLBCL patients revealed that the 4-year OS of irradiated PET+ patients (85%) compared favorably to that of non-irradiated PET+ patients (30%) and was similar to that of non-irradiated PET- patients (83%) (*44*).

PRE-TRANSPLANT ASSESSMENT

Another established application of functional imaging in lymphoma has been to predict outcomes in patients with relapsed or refractory disease who undergo ASCT. Studies investigating this have generally acquired PET scans after patients receive salvage and high-dose chemotherapy but before they undergo transplantation. These studies have shown that in HL and NHL alike, the failure rate of ASCT is significantly higher in patients who remain PET+ after chemotherapy (Table 7). A meta-analysis by Poulou et al, which comprised seven such studies including both HL and NHL patients, revealed hazard ratios of 3.23 and 4.53 for pooled PFS and OS, respectively, in patients with positive pre-transplant PET scans (*45*). The familiar trade-off between the early accrual of actionable data and the prognostic accuracy of these data is present in pre-transplantation imaging, as reports have shown that imaging acquired later in treatment, especially after ASCT, is better able to predict survival (*46-48*).

CONCLUSION

The vast array of data presented in this review illustrates several points of strength of interim and end-of-treatment PET as diagnostic and prognostic tools in lymphoma, but also outlines their current limitations. At the heart of every comparison between the two methods is the trade-off between how early in the course of treatment a PET/CT scan is acquired and how accurate its predictions will be. This phenomenon is exemplified by studies where end-of-treatment imaging was successful in significantly predicting outcomes but interim imaging was not (*15,39,40*). However, the difference in accuracy between interim and end-of-therapy results has been marginal in many cases (*38*), and is often outweighed by the tremendous advantages of gleaning information

as early as possible to determine whether to stay the course of treatment or change the management strategy. The prevailing trend in recent years has therefore favored interim response assessment.

An especially promising development has been the emergence of response-adapted therapy, which has been widely validated by an assortment of studies in both HL and NHL. There is mounting evidence to suggest that this management strategy significantly improves survival in high-risk patients by promoting escalation to more intense regimens and reduces toxicity in low-risk patients by sparing them unnecessary treatment (*23,24*). Therefore, response-adapted therapy will likely become established as a cornerstone of clinical decision-making. Other innovations, such as the complementation of interim imaging with biomarkers and the use of end-of-treatment imaging as a guide to adjuvant RT, require further investigation before being adopted as the standard of care.

Despite these advances, there remain caveats and limitations to response assessment in lymphoma. Both interim and end-of-treatment imaging have generally been slightly less reliable in patients with NHL (*38*), especially those who are treated with immunochemotherapy (*27*). And unlike in HL, where studies have established PET-2 as optimal for interim imaging, there is no consensus on the timing of interim response assessment in NHL. In a broader sense, a lack of standardization with regards to response assessment criteria affects all subtypes. Although the D5PS criteria and Lugano guidelines have been widely adopted in academic institutions, the choice of criteria in the clinical setting has yet to be standardized. Nevertheless, it can be said that the available data largely supports the indispensable role that PET/CT imaging has come to play across the many stages of treatment and subtypes of disease encompassed by lymphoma.

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TABLES

Table 1: Overview of studies investigating the predictive ability of interim PET imaging in HL

Study	Patient Population	Cycles Completed Prior to Imaging	Results	
			PET+	PET-
Gallamini, 2007 (*17*)	190 advanced HL patients	2 (ABVD)	2-year PFS: 12.8%	2-year PFS: 95.0%
Cerci, 2010 (*18*)	115 advanced HL patients	2 (ABVD)	3-year EFS: 53.4%	3-year EFS: 90.5%
Barnes, 2011 (*15*)	96 limited HL patients	2-4 (ABVD)	4-year PFS: 87%*	4-year PFS: 91%*
Le Roux, 2011 (*13*)	90 patients with HL (45 limited, 45 advanced)	4 (ABVD)	2-year PFS: 16%	2-year PFS: 95%
Straus, 2011 (*49*)	99 patients with limited HL	2 (doxorubicin, vinblastine, gemcitabine)	2-year PFS: 54%	2-year PFS: 88%
Kostakoglu, 2012 (*20*)	88 limited HL patients	2 (doxorubicin, vinblastine, gemcitabine)	2-year PFS: 54% (IHP), 46% (D5PS), 62% (CT)	2-year PFS: 88% (IHP), 87% (D5PS), 91% (CT)
Markova, 2012 (*14*)	69 advanced HL patients	4 (eBEACOPP)	4-year PFS: 78%	4-year PFS: 96%
Biggi, 2013 (*6*)	260 advanced HL patients	2 (ABVD)	3-year FFS: 28%	3-year FFS: 95%
Filippi, 2013 (*16*)	80 limited HL patients	2 (ABVD)	3-year PFS: 100%*	3-year PFS: 97%*
Gallamini, 2014 (*7*)	207 advanced HL patients	2 (ABVD)	3-year PFS: 28%	3-year PFS: 95%
Hutchings, 2014 (*12*)	126 HL patients (68 limited, 58 advanced)	1-2 (ABVD)	2-year PFS: 38.5% (PET-1), 23.1% (PET-2)	2-year PFS: 98.3% (PET-1), 90.2% (PET-2)
Oki, 2014 (*19*)	229 HL patients (138 limited, 91 advanced)	2-3 (ABVD)	3-year PFS: 76.9% (limited), 20.0% (limited, bulky), 44.4% (advanced)	3-year PFS: 95.9% (limited), 83.3% (limited, bulky), 71.0% (advanced)
Rossi, 2014 (*50*)	59 HL patients (22 limited, 37 advanced)	2 (anthracycline-based chemotherapy)	4-year PFS: 45%	4-year PFS: 81%

* - Non-significant

Table 2: Overview of studies investigating response-adapted therapy in HL

Study	**Patient Population**	**Methodology**	**Results**	
			PET+	**PET-**
Gallamini, 2011 (*51*)	165 HL patients (78 limited, 87 advanced)	PET-2 (ABVD); PET- completed 6 more cycles; PET+ escalated to 4 cycles of eBEACOPP, 4 cycles BEACOPP	2-year FFS: 65%	2-year FFS: 92%
Raemaekers, 2014 (*26*)	1,137 early HL patients (444 favorable, 693 unfavorable)	PET-2 (ABVD); PET- completed 2 more cycles if favorable, 4 more cycles if unfavorable; PET+ escalated to 2 cycles eBEACOPP, RT	N/A	N/A
Casasnovas, 2015 (*23*)	782 advanced/ bulky HL patients	PET-2 (BEACOPP); PET- de-escalated to 4 cycles ABVD; PET+ completed 4 more cycles; Controls completed 6 cycles BEACOPP	2-year PFS: 72.9%	2-year PFS: 92.8%
Ganesan, 2015 (*22*)	50 advanced/ bulky HL patients	PET-2 (ABVD); PET- completed 4 more cycles; PET+ escalated to 4 cycles BEACOPP	2-year EFS: 50%	2-year EFS: 82%
Radford, 2015 (*25*)	602 limited HL patients	PET-3 (ABVD); PET- underwent RT or no therapy; PET+ completed 1 more cycle or RT	PFS: 87.6%	PFS: 92.3% (RT), 88.6% (no RT)
Straus, 2015 (*52*)	164 limited HL patients	PET-2 (ABVD); PET- completed 2 more cycles; PET+ escalated to 2 cycles BEACOPP, RT	3-year PFS: 66%	3-year PFS: 92%
Press, 2016 (*24*)	358 advanced HL patients	PET-2 (ABVD); PET- completed 2 more cycles; PET+ escalated to 6 cycles BEACOPP	2-year PFS: 64%	2-year PFS: 82%
Zinzani, 2016 (*53*)	519 advanced HL patients	PET-2 (ABVD); PET- completed 4 more cycles; PET+ escalated to salvage therapy, ASCT	2-year PFS: 76%	2-year PFS: 81%

Table 3: Overview of studies investigating the predictive ability of interim PET imaging in NHL

Study	**Patient Population**	**Cycles Completed Prior to Imaging**	**Results**	
			PET+	**PET-**
Lin, 2007 (*54*)	92 DLBCL patients (11 limited, 81 advanced)	2 (CHOP, R-CHOP, ACVBP, R-ACVBP)	2-year EFS: 51%	2-year EFS: 79%
Casasnovas, 2011 (*55*)	102 NHL patients	2-4 (R-ACVBP, R-CHOP)	2-year PFS: 73% (IHP), 79% (D5PS)	2-year PFS: 77% (IHP), 88% (D5PS)
Cashen, 2011 (*56*)	50 advanced DLBCL patients	2 (R-CHOP)	2-year EFS: 63%	2-year EFS: 85%
Yang, 2011 (*57*)	161 DLBCL patients (94 limited, 67 advanced)	3-4 (R-CHOP)	3-year PFS: 52.5%	3-year PFS: 88.3%
Yoo, 2011 (*28*)	155 DLBCL patients (68 limited, 87 advanced)	2-4 (R-CHOP)	3-year PFS: 66%*	3-year PFS: 84%*
Dupuis, 2012 (*33*)	121 FL patients	4 (R-CHOP)	2-year PFS: 61%	2-year PFS: 86%
Pregno, 2012 (*29*)	88 DLBCL patients (29 limited, 59 advanced)	2-4 (R-CHOP)	2-year PFS: 72%*	2-year PFS: 85%*
Safar, 2012 (*58*)	112 DLBCL patients (21 limited, 91 advanced)	2 (R-CHOP, R-ACVBP)	3-year PFS: 47%	3-year PFS: 84%
Itti, 2013 (*59*)	114 DLBCL patients	2 (rituximab)	3-year PFS: 59%	3-year PFS: 81%
Carr, 2014 (*60*)	61 DLBCL patients (24 limited, 37 advanced)	2-3 (R-CHOP)	2-year EFS: 58%; 2-year OS: 72%	2-year EFS: 90%; 2-year OS: 93%
Khong, 2014 (*31*)	24 patients NK/T-cell lymphoma patients	2 -3 (SMILE)	2-year PFS: 17%; 2-year OS: 17%	2-year PFS: 62%; 2-year OS: 81%
Nols, 2014 (*61*)	73 DLBCL patients (23 limited, 50 advanced)	3-4 (R-CHOP, ACVBP)	PFS: 47% (D5PS)	PFS: 84% (D5PS)
Huang, 2015 (*30*)	32 DLBCL patients (9 limited, 23 advanced)	2 (R-CHOP)	2-year PFS: 82%*	2-year PFS: 88%*
Fukumoto, 2015 (*32*)	79 NK/T-cell lymphoma patients	2-4	5-year PFS: 9.2%	5-year PFS: 66%
Mamot, 2015 (*8*)	138 DLBCL patients (64 limited, 74 advanced)	2 (R-CHOP)	2-year EFS: 48%; 2-year OS: 88%*	2-year EFS: 74%; 2-year OS: 91%*

* - Non-significant

Table 4: Overview of studies investigating response-adapted therapy in NHL

Study	**Patient Population**	**Methodology**	**Results**	
			PET+	**PET-**
Moskowitz, 2006 (*62*)	87 bulky/advanced DLBCL	PET-4 (R-CHOP); PET- and PET+/biopsy- completed 3 cycles ICE; PET+/biopsy+ completed 3 cycles ICE, high-dose chemotherapy, ASCT	EFS: 87%*	EFS: 91%*
Kasamon, 2009 (*63*)	59 patients (56 DLBCL, 10 primary mediastinal large B-cell lymphoma, 2 FL, 1 peripheral T-cell; 20 limited, 39 advanced)	PET-2 or PET-3; PET- completed standard therapy; PET+ escalated to salvage chemotherapy, ASCT	2-year EFS: 67%	2-year EFS: 89%
Moskowitz, 2010 (*64*)	98 DLBCL patients (15 limited/bulky, 83 advanced)	PET-4 (R-CHOP); PET- and PET+/biopsy- completed 3 cycles ICE; PET+/biopsy+ completed 3 cycles ICE, high-dose chemotherapy, ASCT	PFS: 60% (biopsy+), 79% (biopsy-)	PFS: 86%
Swinnen, 2012 (*65*)	78 bulky/advanced DLBCL patients	PET-3 or PET-4 (R-CHOP); PET- completed 2 more cycles; PET+ escalated to 4 cycles R-ICE	2-year PFS: 45%	2-year PFS: 77%
Sehn, 2014 (*66*)	155 DLBCL patients (50 limited, 105 advanced)	PET-4 (R-CHOP); PET- completed 2 more cycles; PET+ escalated to 4 cycles R-ICE	4-year PFS: 59%; 4-year OS: 73%	4-year PFS: 91%; 4-year OS: 96%
Swinnen, 2015 (*67*)	80 DLBCL patients (8 limited, 72 advanced)	PET-3 or PET-4 (R-CHOP); PET- completed 2 more cycles; PET+ escalated to 4 cycles R-ICE	2-year PFS: 42%; 3-year OS: 69%	2-year PFS: 76%; 3-year OS: 93%

* - Non-significant

Table 5: Overview of studies investigating the predictive ability of end-of-treatment PET imaging in HL

Study	**Patient Population**	**Treatment Regimen**	**Results**	
			PET+	**PET-**
Spaepen, 2001 (*68*)	60 HL patients (25 limited, 35 advanced)	Stanford V, MOPP/ABV	2-year PFS: 0%	2-year PFS: 91%
Weihrauch, 2001 (*69*)	28 HL patients (10 limited, 18 advanced/relapsed)	Non-uniform	1-year DFS: 40%	1-year DFS: 95%
Kobe, 2008 (*70*)	817 bulky/advanced HL patients	6-8 cycles (BEACOPP)	2-year PFS: 86%	2-year PFS: 96%
Barnes, 2011 (*15*)	96 limited HL patients	4 cycles (ABVD)	4-year PFS: 54%	4-year PFS: 94%
Kobe, 2014 (*21*)	739 advanced HL patients	6-8 cycles (BEACOPP)	4-year PFS: 86.1%	4-year PFS: 91.5%

Table 6: Overview of studies investigating the predictive ability of end-of-treatment PET imaging in NHL

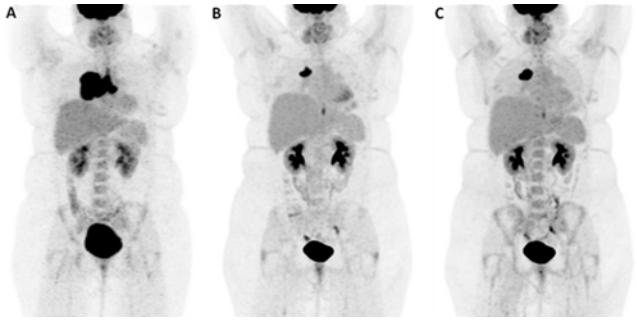
Study	**Patient Population**	**Treatment Regimen**	**Results**	
			PET+	**PET-**
Bishu, 2007 (*71*)	31 FL patients	Non-uniform	Median PFS: 5.8 months	Median PFS: 29.5 months
Zinzani, 2007 (*72*)	45 FL patients	6 cycles (R-FM, R-CHOP)	2-year PFS: 20%	2-year PFS: 90%
Itti, 2009 (*73*)	80 DLBCL patients (10 limited, 70 advanced)	4 cycles (CHOP, R-CHOP, ABVBP/ACE, R-ACVBP)	2-year EFS: 25%	2-year EFS: 82%
Le Dortz, 2010 (*74*)	45 FL patients	6 cycles (R-CHOP)	Median PFS: 17.2 months	Median PFS: 48.0 months
Trotman, 2011 (*9*)	122 FL patients (14 limited, 108 advanced)	6 cycles (R-CHOP), 8 cycles (R-CVP)	42-month PFS: 32.9%	42-months PFS: 70.7%
Dupuis, 2012 (*33*)	121 FL patients	6 cycles (R-CHOP)	2-year PFS: 51%	2-year PFS: 87%
Pregno, 2012 (*29*)	88 DLBCL patients (29 limited, 59 advanced)	2-4 cycles (R-CHOP)	2-year PFS: 64%	2-year PFS: 83%
Mato, 2012 (*75*)	148 mantle cell lymphoma patients	R-HyperCVAD, R-araC/methotrexate	Median PFS: 11.1 months; Median OS: 56.9 months	Median PFS: Not reached; Median OS: Not reached
Zinzani, 2013 (*76*)	142 intermediate-high risk FL patients	6 cycles (R-FM)	5-year PFS: 42%	5-year PFS: 76%
Khong, 2014 (*31*)	24 NK/T-cell lymphoma patients	6 cycles (SMILE)	2-year PFS: 0%; 2-year OS: 0%	2-year PFS: 68%; 2-year OS: 91%
Lu, 2014 (*39*)	47 indolent FL patients	6 cycles (R-CHOP)	Median OS: 45.0 months	Median OS: 95.2 months
Luminari, 2014 (*77*)	202 FL patients	8 cycles (R-CVP), 6 cycles (R-CHOP, R-FM)	3-year PFS: 35%	3-year PFS: 66%
Martelli, 2014 (*78*)	115 PMLBCL patients	Rituximab, anthracycline	5-year PFS: 68%; 5-year OS: 83%	5-year PFS: 99%; 5-year OS: 100%
Tychyj-Pinel, 2014 (*79*)	119 FL patients	6 cycles (R-CHOP), 8 cycles (R-CVP)	42-month PFS: 25.0%	42-month PFS: 61.4%
Priel, 2015 (*40*)	33 Burkitt's lymphoma patients	6 cycles (GMALL B-ALL/NHL 2002 protocol)	3-year OS: 30%	3-year OS: 90%

Table 7: Overview of studies investigating the predictive ability of pre-transplant PET imaging

Study	**Patient Population**	**PET Acquisition**	**Results**	
			PET+	**PET-**
Schot, 2006 (*46*)	39 patients (11 HL, 28 NHL)	Before second-line chemotherapy, 2 cycles into treatment, and before ASCT	2-year PFS: 27% (PET-2), 18% (PET-3)	2-year PFS: 71% (PET-2), 60% (PET-3)
Svoboda, 2006 (*80*)	50 patients (19 HL, 31 NHL)	After 2 cycles of salvage chemotherapy and before ASCT	Median PFS: 5 months	Median PFS: 19 months
Filmont, 2007 (*47*)	60 patients (10 HL, 50 NHL)	After consolidative chemotherapy and before ASCT	1-year EFS: 43% (pre-ASCT), 25% (post-ASCT)	1-year EFS: 80% (pre-ASCT), 81% (post-ASCT)
Jabbour, 2007 (*81*)	211 HL patients	After high-dose chemotherapy and before ASCT	3-year PFS: 23%; 3-year OS: 58%	3-year PFS: 69%; 3-year OS: 87%
Crocchiolo, 2008 (*82*)	53 patients (14 HL, 39 NHL)	Before ASCT	3-year PFS: 55%; 5-year OS: 55%	3-year PFS: 79%; 5-year OS: 90%
Dickinson, 2010 (*83*)	39 DLBCL patients	Before ASCT	3-year PFS: 35%	3-year PFS: 81%
Moskowitz, 2010 (*84*)	153 HL patients	After ICE-based salvage chemotherapy and high-dose chemotherapy, and before/after ASCT	5-year EFS: 31%	5-year EFS: 75%
Qiao, 2010 (*48*)	31 NHL patients	Before and after ASCT	1-year PFS: 28.6% (pre-ASCT), 23.1% (post-ASCT)	1-year PFS: 88.2% (pre-ASCT), 88.9% (post-ASCT)
Mocikova, 2011 (*85*)	76 HL patients	After salvage chemotherapy and before ASCT	2-year PFS: 36.1%; 2-year OS: 61.4%	2-year PFS: 72.7%; 2-year OS: 90.3%
Moskowitz, 2012 (*86*)	97 HL patients	After salvage chemotherapy	EFS: 28.6%	EFS: >80%
Cohen, 2013 (*87*)	29 mantle cell lymphoma patients	Before ASCT	2-year PFS: 64%; 2-year OS: 60%	2-year PFS: 87%; 2-year OS: 100%

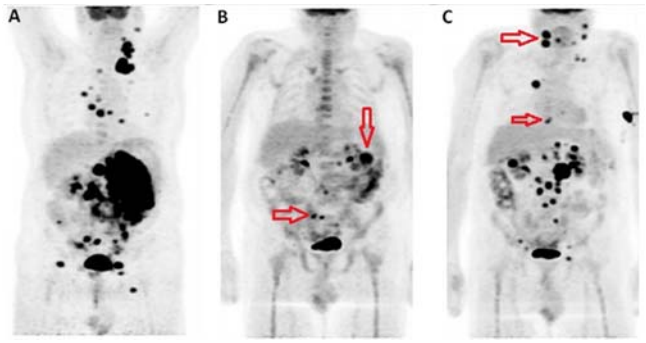
SUPPLEMENTALS

CASE EXAMPLES



Supplemental Figure 1: 30-year-old woman with classical HL. A, MIP image from initial FDG PET/CT study shows hypermetabolic mediastinal lymphadenopathy. B, Interim FDG PET/CT study acquired after 4 cycles of ABVD chemotherapy shows interval improvement, but with persistent intense hypermetabolism within the dominant nodal lesion in the right anterior mediastinum. D5PS score of 5 was assigned, suggesting persistent active disease. Decision was made to continue with ABVD given suggestion of responding disease. C. FDG PET/CT study acquired at completion of ABVD chemotherapy shows interval increase in size and metabolic activity of the dominant right anterior mediastinal nodal lesion. D5PS score of 5 was again assigned. Subsequent biopsy of this mass confirmed persistent active lymphoma, resulting in conversion to second-line therapy.

Sample Standardized Report for Case in Figure 2:



CLINICAL HISTORY: 30-year-old woman with classical HL, after 4 cycles of ABVD chemotherapy, referred for evaluation of response to therapy.

COMPARISON: FDG PET/CT on [].

TECHNIQUE: [] MBq ([] mCi) of FDG was administered intravenously following a 6-hour fast. Prior to injection, the blood glucose level was [] mmol/L. After an uptake time of [] minutes, low mA non-contrast CT and co-registered emission PET images were acquired from the base of the brain to the proximal thighs.

FINDINGS:
HEAD AND NECK: []

CHEST: Decreased size and FDG uptake of previously noted large anterior mediastinal mass.

ABDOMEN/PELVIS: []

MUSCULOSKELETAL: []

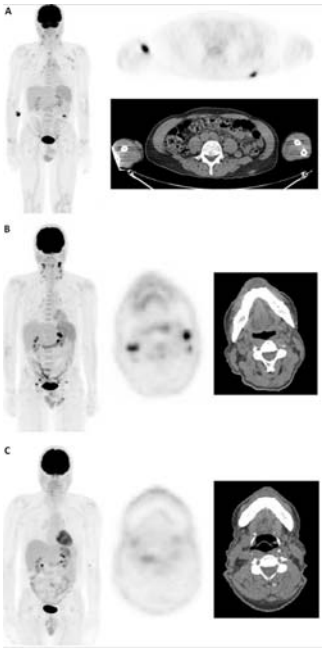
INDEX LESIONS:

1. Dominant mediastinal mass, CT image [], 2.8 x 3.7 cm, SUVmax 10.9 (previously CT image [],4.7 x 6.8 cm, SUVmax 12.8).

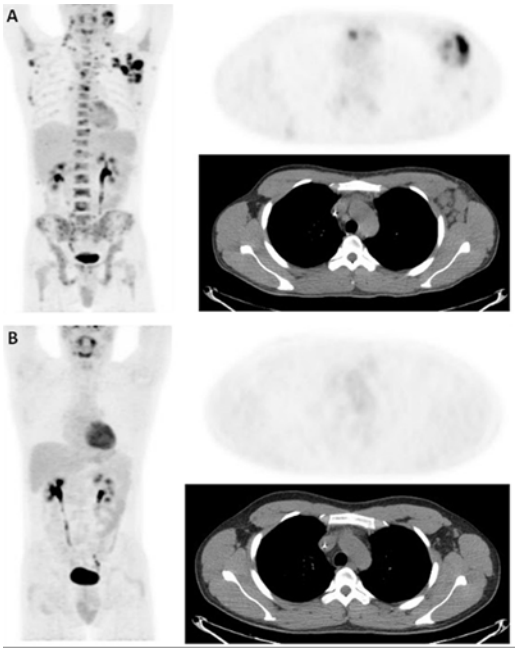
Deauville 5 Point Scale: 5.

IMPRESSION:
1. Decrease in metabolic activity and size of a mediastinal mass is consistent with a partial metabolic response.

Supplemental Figure 2: 66-year-old man with DLBCL. A, Initial FDG PET/CT study showed extensive hypermetabolic lymphadenopathy in addition to a bulky hypermetabolic extra-nodal mass surrounding the left kidney. B, Interim FDG PET/CT study acquired after 2 cycles of R-CHOP chemotherapy showed all lesions to have decreased in size and metabolic activity, but with several persistent intensely FDG-avid lesions (e.g., left pararenal mass and lower retroperitoneal nodes as highlighted by arrows). These residual lesions showed FDG uptake which was moderately to markedly greater than liver activity (D5PS score of 4-5), but less intense than baseline activity level. Per Lugano response criteria, at the time of interim scan this suggests responding disease (D5PS score 4 or 5 with reduced uptake compared to baseline and no new or progressive lesions). R-CHOP chemotherapy was continued. C. Subsequent FDG PET/CT study acquired at completion of R-CHOP chemotherapy showed mixed changes: some of the previous FDG-avid lesions showed interval improvement or resolution, but there were multiple new and/or progressive FDG-avid nodal lesions elsewhere when compared with the interim scan. Of note, some of the FDG-avid nodal lesions on this study (highlighted by arrows) were new when compared the baseline study. Based on Lugano response criteria, category of progressive disease was assigned given D5PS score of 5 including new FDG-avid lesions when compared with the baseline study.



Supplemental Figure 3: 66-year-old man with DLBCL. A, Initial FDG PET/CT study showed hypermetabolic subcutaneous soft tissue masses at several sites (selected axial images highlight lesions along right forearm and left flank) and multifocal hypermetabolic lymphadenopathy. B, Interim FDG PET/CT study acquired after 3 cycles of R-CHOP showed mixed changes: all subcutaneous lesions showed metabolic resolution, while lymphadenopathy showed generalized progression at most sites (selected axial images highlight cervical nodal lesions). Based on metabolic progression of nodal lesions, D5PS score of 5 was assigned. This triggered biopsy of a cervical node, which confirmed active lymphoma, resulting in conversion to second-line chemotherapy. C. Subsequent FDG PET/CT study acquired at completion of second-line (R-ICE) chemotherapy showed complete metabolic treatment response. All nodal lesions showed marked interval decrease in size and metabolic activity, with small residual nodal lesions showing only minimal FDG uptake less intense than the mediastinal blood pool (D5PS score of 2). Based on Lugano response criteria, category of complete response was assigned.



Supplemental Figure 4: 25-year-old man with classical HL. A, Initial FDG PET/CT study showed multifocal lymphadenopathy above and below the diaphragm and multifocal bone marrow involvement (MIP and selected axial images highlighting axillary lymphadenopathy and marrow-based lesion in manubrium). B, Interim FDG PET/CT study acquired after 2 cycles of ABVD chemotherapy showed complete metabolic resolution of all previous nodal and bone marrow lesions. D5PS score of 1 was assigned, indicating complete metabolic response.

Supplemental Table 1: Tumor response classifications of the Deauville 5-point scale (D5PS) criteria

Classification	Criteria
1	No uptake above background activity
2	Uptake equal to or lower than mediastinal blood pool activity
3	Uptake between mediastinal blood pool and liver activity
4	Uptake moderately higher than liver activity
5	Uptake markedly higher than liver activity

TREATMENT REGIMENT ABBREVIATIONS

ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine

BEACOPP: Bleomycin, etoposide, Adriamycin, cyclophosphamide, oncovin, procarbazine, prednisone

GMAL B-ALL/NHL 2002 protocol: rituximab, high-dose methotrexate, high-dose cytosine arabinoside, cyclophosphamide, etoposide, ifosphamide, corticosteroids, triple intrathecal therapy

MOPP/ABV: Mechlorethamine, oncovin, procarbazine, prednisone, adriamycin, bleomycin, vinblastine

R-ACVBP: Rituximab, Adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone

R-CHOP: Rituximab, cyclophosphamide, oncovin, prednisone

R-CVP: Rituximab, cyclophosphamide, vincristine, prednisone

R-HyperCVAD: rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with cytarabine, methotrexate

R-ICE: Rituximab, ifosfamide, carboplatin, etoposide

SMILE: Dexamethasone, methotrexate, ifosfamide, L-asparaginase, etoposide

R-FM: rituximab, fludarabine, mitoxantrone