Response Assessment Criteria and Their Applications in Lymphoma: Part 2

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Learning Objectives: On successful completion of this activity, participants should be able to describe (1) the diagnostic and predictive value of interim and end-of-treatment PET in HL and NHL; (2) the role of response-adapted therapy in the clinical management of lymphoma; and (3) the newly-emerging applications of interim and end-of-treatment PET in lymphoma.

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Interim and end-of-treatment PET/CT have become central to the evaluation of Hodgkin and non-Hodgkin 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 pretransplant 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.

Key Words: lymphoma; PET/CT response assessment; response-adapted therapy

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CT and PET with ^{18}F-FDG have come to play integral roles in evaluating Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Soon after the incorporation of CT into staging and response assessment criteria, the advantages of using 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 reliably identify the 80%–95% of posttreatment residual masses that are nonmalignant, thereby sparing patients unnecessary therapy and morbidity, and it was shown to alter staging in 20% of cases, most frequently upstaging patients by better detecting bone marrow involvement (*1*,*2*).

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After 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 5-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 before 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 2-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 metaanalysis performed by Terasawa et al., comprising 360 advanced-HL patients across 7 studies with varying treatment and interpretation methods. The metaanalysis 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 metaanalysis of 10 studies with 1,389 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-positive (PET+) and PET-negative (PET−) patients (Table 1). Most 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 with that of PET-2; PET-1 has been shown to be prognostically inferior (*12*), whereas PET-4 has 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 used, 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; supplemental materials are available at http://jnm.snmjournals.org). 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 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-y progression-free survival (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

TABLE 1
Studies Investigating Predictive Ability of Interim PET Imaging in HL

Study	Patient population	Cycles completed before imaging	Results	
			PET+	PET−
Gallamini, 2007 (*17*)	190 advanced-HL patients	2 (ABVD)	2-y PFS: 12.8%	2-y PFS: 95.0%
Cerci, 2010 (*18*)	115 advanced-HL patients	2 (ABVD)	3-y EFS: 53.4%	3-y EFS: 90.5%
Barnes, 2011 (*15*)	96 limited-HL patients	2–4 (ABVD)	4-y PFS: 87%*	4-y PFS: 91%*
Le Roux, 2011 (*13*)	90 patients with HL (45 limited, 45 advanced)	4 (ABVD)	2-y PFS: 16%	2-y PFS: 95%
Straus, 2011 (*49*)	99 limited-HL patients	2 (doxorubicin, vinblastine, gemcitabine)	2-y PFS: 54%	2-y PFS: 88%
Kostakoglu, 2012 (*20*)	88 limited-HL patients	2 (doxorubicin, vinblastine, gemcitabine)	2-y PFS: 54% (IHP), 46% (D5PS), 62% (CT)	2-y PFS: 88% (IHP), 87% (D5PS), 91% (CT)
Markova, 2012 (*14*)	69 advanced-HL patients	4 (escalated BEACOPP)	4-y PFS: 78%	4-y PFS: 96%
Biggi, 2013 (*6*)	260 advanced-HL patients	2 (ABVD)	3-y FFS: 28%	3-y FFS: 95%
Filippi, 2013 (*16*)	80 limited-HL patients	2 (ABVD)	3-y PFS: 100%*	3-y PFS: 97%*
Gallamini, 2014 (*7*)	207 advanced-HL patients	2 (ABVD)	3-y PFS: 28%	3-y PFS: 95%
Hutchings, 2014 (*12*)	126 HL patients (68 limited, 58 advanced)	1–2 (ABVD)	2-y PFS: 38.5% (PET-1), 23.1% (PET-2)	2-y PFS: 98.3% (PET-1), 90.2% (PET-2)
Oki, 2014 (*19*)	229 HL patients (138 limited, 91 advanced)	2–3 (ABVD)	3-y PFS: 76.9% (limited), 20.0% (limited, bulky), 44.4% (advanced)	3-y 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-y PFS: 45%	4-y PFS: 81%

*Nonsignificant.
IHP = International Harmonization Project criteria; FFS = failure-free survival.

basis of changes in residual tumor size on CT; those with a reduction in tumor size of less than 40% had a 1-y 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 nonresponders 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 adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD). Patients who are found to be PET− have gone on to complete the prescribed regimen, whereas those who are PET+ are advanced to more intensive regimens, such as escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). Although escalated BEACOPP offers a higher cure rate—85% in the case of advanced HL, as compared with 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-y PFS of PET-2+ patients advanced to BEACOPP was measured at 64%, more than double the estimate of 15%–30% for nonadapted 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 deescalated to ABVD. The authors reported comparable outcomes in the 2 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 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 radiotherapy or no further treatment, failed to demonstrate

TABLE 2
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 BEACOPP, 4 cycles BEACOPP	2-y FFS: 65%	2-y 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 BEACOPP, radiotherapy	NA	NA
Casasnovas, 2015 (*23*)	782 advanced/bulky-HL patients	PET-2 (BEACOPP); PET− deescalated to 4 cycles ABVD; PET+ completed 4 more cycles; controls completed 6 cycles BEACOPP	2-y PFS: 72.9%	2-y 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-y EFS: 50%	2-y EFS: 82%
Radford, 2015 (*25*)	602 limited-HL patients	PET-3 (ABVD); PET− underwent radiotherapy or no therapy; PET+ completed 1 more cycle or radiotherapy	PFS: 87.6%	PFS: 92.3% (radiotherapy), 88.6% (no radiotherapy)
Straus, 2015 (*52*)	164 limited-HL patients	PET-2 (ABVD); PET− completed 2 more cycles; PET+ escalated to 2 cycles BEACOPP, radiotherapy	3-y PFS: 66%	3-y PFS: 92%
Press, 2016 (*24*)	358 advanced-HL patients	PET-2 (ABVD); PET− completed 2 more cycles; PET+ escalated to 6 cycles BEACOPP	2-y PFS: 64%	2-y PFS: 82%
Zinzani, 2016 (*53*)	519 advanced-HL patients	PET-2 (ABVD); PET− completed 4 more cycles; PET+ escalated to salvage therapy, ASCT	2-y PFS: 76%	2-y PFS: 81%

FFS = failure-free survival; NA = not applicable; EFS = event-free survival.

noninferiority (*25*). Similarly, the EORTC/LYSA/FIL H10 trial, which subjected PET− early HL patients to deescalated therapy without radiotherapy, was also unsuccessful in establishing noninferiority (*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 rituximab, cyclophosphamide, vincristine, and prednisone (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 before imaging. Supplemental 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 metaanalysis 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 metaanalysis 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/T-cell lymphoma patients have been exceptionally reliable in

TABLE 3
Studies Investigating Predictive Ability of Interim PET Imaging in NHL

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

*Nonsignificant.

ACVBP = adriamycin, cyclophosphamide, vindesine, bleomycin, and prednisone; R-ACVBP = rituximab, adriamycin, cyclophosphamide, vindesine, bleomycin, and prednisone; EFS = event-free survival; IHP = International Harmonization Project criteria; SMILE = dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; OS = overall survival.

predicting outcome (*31,32*), those of follicular lymphoma 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 nonadapted 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 rituximab, ifosfamide, carboplatin, and etoposide (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 a change in management based on interim PET imaging in DLBCL. A case example of a DLBCL patient treated with response-adapted therapy is depicted in Supplemental 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 pseudoprogression 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 pseudoprogression. 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 pseudoprogression improve (*34*). Foremost among the proposed changes was the new interim response classification of "indeterminate response," which calls for biopsy and reevaluation after 12 wk to distinguish between pseudoprogression 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-y 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*).

TABLE 4
Studies Investigating Response-Adapted Therapy in NHL

Study	Patient population	Methodology	Results	
			PET+	PET−
Moskowitz, 2006 (*62*)	87 bulky/advanced-DLBCL patients	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 follicular lymphoma, 1 peripheral T-cell; 20 limited, 39 advanced)	PET-2 or PET-3; PET− completed standard therapy; PET+ escalated to salvage chemotherapy, ASCT	2-y EFS: 67%	2-y 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-y PFS: 45%	2-y 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-y PFS: 59%; 4-y OS: 73%	4-y PFS: 91%; 4-y 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-y PFS: 42%; 3-y OS: 69%	2-y PFS: 76%; 3-y OS: 93%

*Nonsignificant.

ICE = ifosfamide, carboplatin, etoposide; EFS = event-free survival; R-ICE = rituximab, ifosfamide, carboplatin, and etoposide; OS = overall survival.

TABLE 5
Studies Investigating 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-y PFS: 0%	2-y PFS: 91%
Weihrauch, 2001 (*69*)	28 HL patients (10 limited, 18 advanced/relapsed)	Nonuniform	1-y DFS: 40%	1-y DFS: 95%
Kobe, 2008 (*70*)	817 bulky/advanced-HL patients	6–8 cycles (BEACOPP)	2-y PFS: 86%	2-y PFS: 96%
Barnes, 2011 (*15*)	96 limited-HL patients	4 cycles (ABVD)	4-y PFS: 54%	4-y PFS: 94%
Kobe, 2014 (*21*)	739 advanced-HL patients	6–8 cycles (BEACOPP)	4-y PFS: 86.1%	4-y PFS: 91.5%

MOPP/ABV = mechlorethamine, vincristine, procarbazine, prednisone, adriamycin, bleomycin, and vinblastine; DFS = disease-free survival.

TABLE 6
Studies Investigating Predictive Ability of End-of-Treatment PET Imaging in NHL

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

FL = follicular lymphoma; R-FM = rituximab, fludarabine, and mitoxantrone; PMLBCL = primary mediastinal large B-cell lymphoma; ACVBP/ACE = adriamycin, cyclophosphamide, vindesine, bleomycin, prednisone/adriamycin, cyclophosphamide, etoposide; R-ACVBP = rituximab, adriamycin, cyclophosphamide, vindesine, bleomycin, and prednisone; EFS = event-free survival; R-CVP = rituximab, cyclophosphamide, vincristine, prednisone; R-HyperCVAD = rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with cytarabine, and methotrexate; OS = overall survival; SMILE = dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide; GMAL B-ALL/NHL 2002 protocol = rituximab, high-dose methotrexate, high-dose cytosine arabinoside, cyclophosphamide, etoposide, iphosphamide, corticosteroid, triple-intrathecal therapy.

END-OF-TREATMENT RESPONSE ASSESSMENT IN HL

Although it lacks the practical advantages of early response assessment, end-of-treatment imaging has generally demonstrated superior diagnostic and prognostic accuracy. A metaanalysis 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 metaanalysis 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 when interim scans are not found to be prognostic, as in early-stage disease, posttreatment PET is still predictive of outcome (*15*). Supplemental 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, whereas the latter reported ranges of 0.33–0.77 and 0.82–1.00 for sensitivity and specificity (*37,38*). When compared with 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 posttherapy 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, posttreatment 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

TABLE 7
Studies Investigating Predictive Ability of Pretransplant 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-y PFS: 27% (PET-2), 18% (PET-3)	2-y 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 mo	Median PFS: 19 mo
Filmont, 2007 (*47*)	60 patients (10 HL, 50 NHL)	After consolidative chemotherapy and before ASCT	1-y EFS: 43% (pre-ASCT), 25% (post-ASCT)	1-y EFS: 80% (pre-ASCT), 81% (post-ASCT)
Jabbour, 2007 (*81*)	211 HL patients	After high-dose chemotherapy and before ASCT	3-y PFS: 23%; 3-y OS: 58%	3-y PFS: 69%; 3-y OS: 87%
Crocchiolo, 2008 (*82*)	53 patients (14 HL, 39 NHL)	Before ASCT	3-y PFS: 55%; 5-y OS: 55%	3-y PFS: 79%; 5-y OS: 90%
Dickinson, 2010 (*83*)	39 DLBCL patients	Before ASCT	3-y PFS: 35%	3-y PFS: 81%
Moskowitz, 2010 (*84*)	153 HL patients	After ICE-based salvage chemotherapy and high-dose chemotherapy, and before/after ASCT	5-y EFS: 31%	5-y EFS: 75%
Qiao, 2010 (*48*)	31 NHL patients	Before/after ASCT	1-y PFS: 28.6% (pre-ASCT), 23.1% (post-ASCT)	1-y PFS: 88.2% (pre-ASCT), 88.9% (post-ASCT)
Mocikova, 2011 (*85*)	76 HL patients	After salvage chemotherapy and before ASCT	2-y PFS: 36.1%; 2-y OS: 61.4%	2-y PFS: 72.7%; 2-y 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-y PFS: 64%; 2-y OS: 60%	2-y PFS: 87%; 2-y OS: 100%

EFS = event-free survival; OS = overall survival.

indications for consolidative radiotherapy. The GHSG HD15 trial, which included 2,126 advanced-HL patients, reserved radiotherapy for those with residual masses larger than 2.5 cm and positive posttherapy imaging (*41*). The high predictive value (94.1%) of end-of-treatment PET justified the dramatic reduction in the rate of radiotherapy administration to 11%, as compared with 71% in the earlier HD9 trial. Similarly, a study of 163 advanced-HL patients spared PET− patients further treatment and found that their 3-y PFS (89%) remained significantly higher than that of PET+ patients who had undergone radiotherapy (55%) (*42*).

End-of-treatment PET/CT has not been as reliable a guide for radiotherapy 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 radiotherapy (63% vs. 50%) (*43*). By contrast, a larger prospective study of 262 DLBCL patients revealed that the 4-y overall survival of irradiated PET+ patients (85%) compared favorably with that of nonirradiated PET+ patients (30%) and was similar to that of nonirradiated PET− patients (83%) (*44*).

PRETRANSPLANT 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 metaanalysis by Poulou et al., which comprised 7 such studies including both HL and NHL patients, revealed hazard ratios of 3.23 and 4.53 for pooled PFS and overall survival, respectively, in patients with positive pretransplant PET scans (*45*). The familiar trade-off between the early accrual of actionable data and the prognostic accuracy of these data is present in pretransplantation 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 in which 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 radiotherapy, 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, for which 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 regard 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 support 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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