Perspective

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Interim PET-driven strategy in de novo diffuse large B-cell lymphoma: do we trust the driver?

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^{18}F-Fluorodeoxyglucose–positron emission tomography (FDG-PET) has become a central tool for both accurate initial staging and determination of prognosis after treatment of diffuse large B-cell lymphoma (DLBCL). However, the role of PET during treatment (iPET) in daily practice remains a matter of significant debate. This perspective reviews the published studies on iPET in DLBCL, including the methods used to analyze iPET, its timing, and studies of iPET-driven therapy to illuminate where daily practice may benefit from the use of iPET. When performed after 2 and/or 4 courses of immunochemotherapy, iPET has a very good negative predictive value, utilizing both visual (qualitative) and semiquantitative methods. The visual method accurately predicts outcome for patients with limited disease. The semiquantitative method, eg, the change of the difference of maximum standardized uptake value (ΔSUVmax), is for patients with advanced DLBCL, for whom iPET identifies patients with very good outcome with continuation of standard therapy. A low ΔSUVmax also helps identify patients with a risk for relapse averaging 50% and warrants review of their scheduled therapy. To date, no trial has demonstrated the superiority of an iPET-driven strategy in DLBCL. However, the very good negative and good positive predictive values of iPET support its use in daily practice as a better predictive tool than contrast-enhanced computed tomographic scan for therapeutic decision making. (*Blood*. 2017; 129(23):3059-3070)

Introduction

Even in the era of modern immunochemotherapy, 30% to 40% of patients diagnosed with diffuse large B-cell lymphoma (DLBCL) will die of their disease. To improve the situation, there is an urgent need for new drugs to overcome tumor cell resistance and new tools to tailor a curative approach for all patients. Our understanding of the biological complexity and heterogeneity of DLBCL is continuously growing, and several new targeted therapies are under investigation. The standard of care for DLBCL may change profoundly in the coming years, but, regardless of this, early prediction of outcome will always be needed to monitor therapy aimed to maximize cure with minimal toxicity.

^{18}F-Fluorodeoxyglucose (FDG)–positron emission tomography (PET)–computed tomographic scan (CT) has become a key investigational tool for many lymphoma entities, in particular, Hodgkin lymphoma (HL) and DLBCL. The 2007 guidelines recommend (but do not mandate) performing PET before treatment of initial staging, and at end of treatment (EOT), for response assessment. Monitoring therapy by means of PET was "not encouraged outside of clinical trial or as part of a prospective registry."[1,2] According to the recent 2014 International Conference Malignant Lymphoma Imaging Group consensus guidelines, the purpose and contribution of PET during treatment remain exploratory.[3] Experts acknowledge that PET is superior to CT alone when assessing early response. As PET technology has evolved in the new millennium, many reports have been published about PET performed during therapy. However, due to a lack of defined interpretation criteria in the earlier, mostly retrospective, studies, and limited standardization and quality control in prospective controlled trials during an era of changing consensus criteria to define PET status, and the difficulty interpreting results of uncontrolled prospective studies, the hematology community remains divided as to how to use PET results to change the treatment, so-called PET-driven therapy, in daily clinical practice. Indeed, although some strongly encourage it, others recommend against it. A PET-driven strategy has been investigated for >10 years and is now at a crossroad. This perspective article reviews the published data on PET during therapy and discusses how the authors perform such interim PET (iPET) in daily practice.

What is iPET?

PET performed prior to the completion of induction immunochemotherapy has been variously termed as "interim PET,", "EarlyPET," or "MidtermPET." This varied terminology describing PET scans performed after 1, 2, 3, or 4 cycles of scheduled therapy creates ambiguity. By and large, the term "interim PET" (iPET) seems generally appropriate for published reports (Tables 1, 2, 3, and 4). In this article, iPET applies to PET performed any time during treatment in order to assess response before EOT.

Many studies, in particular, early retrospective reports, remain unclear on whether iPET was planned a priori or simply performed according to investigator's choice during therapy. To our mind, the term iPET should only be used when PET scanning is specifically scheduled prior to commencing induction in order to evaluate response during chemotherapy.

When is the best time to perform iPET?

Determining when to perform iPET is a significant challenge. The timing of iPET is a key factor influencing its interpretation and direction

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Table 1. Description of studies using visual method for iPET interpretation

References	DLBCL pts (n)	Median age	Type of study	Treatment	Nb of cycles of chemotherapy before iTEP	iPET analysis method	iPET driven
Jerusalem et al[30]	16 out of 28	61	Monocentric retrospective	Various without rituximab	From 2 to 5	Local visual	No
Spaepen et al[8]	47 out of 70	50	Monocentric retrospective	Various without rituximab	3 (n = 36) or 4 (n = 34)	Local visual	No
Mikhaeel et al[40]	63 out of 121	55	Monocentric retrospective	Mostly CHOP ± rituximab	2 (n = 85) or 3 (n = 36)	Local visual 3-score scale (negative, MRU, positive)	No
Kostakoglu et al[5]	24 out of 47	63	Monocentric retrospective	CHOP × 6 or 8 ± rituximab	1	Local visual and semiquantitative	No
Querellou et al[41]	23 out of 48	55	Monocentric retrospective	Mostly R-CHOP or R-CHOP-like	2 or 3 or 4	Local visual	No
Han et al[9]	38 out of 51	59	Monocentric retrospective	R-CHOP-21 × 6 or 8	2 or 3 or 4	Local visual	No
Fruchard et al[42]	35 out of 40	56	Monocentric retrospective	CHOP or CHOP-like rituximab	2 or 3	Local visual	No
Dupuis et al[39]	103	53	Multicentric prospective	CHOP or CHOP-like ± rituximab	4	Local visual	No
Moskowitz et al[11]	98 GC = 37; nGC = 28; PMBCL = 28	47 pts < 65 y	Monocentric retrospective	R-CHOP-14 × 4 plus 3 × ICE if iPETneg and iPET+ without DLBCL in biopsy or ICE × 2/ R-ICE/ASCT if iPET+ with DLBCL biopsy	4	Local visual ΔSUV only exploratory	Yes
Cashen et al[15]	52	58	Monocentric retrospective	R-CHOP-21 × 6	2	Local (with retrospective review) visual	No
Yang et al[45]	161	61	Monocentric prospective	R-CHOP-21 × 6 or 8	3 (48.4%) or 4 (50.3%)	Local and retrospective review (Cheson 2007 plus D5S)	No
Micallef et al[46]	107	62	Multicentric prospective	R-CHOP-21 plus Epratuzumab	2	Central visual	No
Zinzani et al[47]	91; PMBCL = 13	54	Monocentric retrospective	R-CHOP or R-CHOP-like	Various	Local visual	No
Yoo et al[48]	155	56	Retrospective national database	R-CHOP	2 (5%) or 3 (52%) or 4 (43%)	Local visual	No
Safar et al[22]	112	59	Multicentric prospective	R-CHOP or R-ACVBP	2	Local visual ΔSUV exploratory	No
Carr et al[44]	327	55	Multicentric prospective	R-CHOP-21 (6 or 8 cycles)	2 (77%) or 3 (22%)	Central visual	No
Swinnen et al[49]	80	62	Multicentric prospective	R-CHOP × 4 and R-ICE if iPETpos or R-CHOP × 2 if iPETneg	3	Central visual 4 scales	Yes
Mamot et al[23]	138 GC: 34% or non-GC: 66%	58.4	Multicentric prospective and retrospective	R-CHOP-14 × 6	2 and 4	Local for visual (prospective) ΔSUV/Deauville (exploratory)	No
Hertzberg et al[31]	151	57	Multicentric prospective	Dose-dense R-CHOP-14 × 4 followed by R-CHOP-14 × 2 if iPETneg or R-ICE plus ASCT if iPETpos	4	Central visual (IHP)	Yes

ACVBP, adriamycine, cyclophosphamide, vinblastine, bleomycine, and prednisolone; D5S, Deauville 5 scales; GC, germinal center; MRU, minimal residual uptake; nb, number; neg, negative; PMBCL, primary mediastinal B-cell lymphoma; pos, positive; pts, patients; ΔSUV, Δ SUV method (see article).

of medical decisions. PET measures cellular FDG avidity, which is a reflection of glucose uptake. The higher FDG avidity of lymphoma cells exploits their inefficient aerobic glycolysis and internal trapping of glucose. Comparing PET at baseline with iPET assesses variation in tumor FDG avidity and gives a dynamic illustration of how glucose metabolism evolves during the initial chemotherapy cycles. The decrease in tumor glucose metabolism with treatment may be a surrogate marker of treatment efficiency.[4] Chemotherapy-induced reduction of lymphoma metabolism is a continuous nonlinear process. Relevant parameters are related not only to the tumor itself but also to the type of chemotherapy, the interval between chemotherapy cycles, the number of cycles, etc. Varied timing of iPET is found in the literature, but no report gives a biologic rationale for performing iPET after a given number of cycles. In designing most studies, the decision of when to perform iPET is driven by the clinical tension between the NPV of the test in identifying patients with a good prognosis and obtaining the highest PPV of scanning at an early enough time point that such patients could be salvaged with a change in therapeutic approach. In most studies, iPET is performed after 2 (iPET2) and/or 4 cycles of chemotherapy (rarely 1 or 3). Insights provided by iPET1 or iPET2 are not the same as those after >3 cycles.[4] iPET1 and iPET2 with no residual abnormal uptake can identify patients with early chemosensitive disease who will achieve a very good outcome. Limited data are published about iPET1.[5-7] iPET4 often replaces the previously commonly used midtherapy conventional contrast-enhanced CT scan, to ensure that patients have reached at least partial response before proceeding further with treatment. Clinical interest of iPET beyond the fourth cycle is limited, as it usually comes too late to modify the treatment. However, a negative iPET is truly negative (eg, high NPV) in most cases, whereas positive iPET may be truly or falsely positive, and a high percentage of patients with an iPET showing abnormal uptake before cycle 3 achieve long-term disease control without change of treatment. Depending on the criteria used, NPV for PFS after 2 or 4 cycles is between 67% and 100%, whereas the PPV ranges from 36% to 100% (Tables 2 and 4). Although published data do not include comparative studies on the clinical impact of the varied timing of iPET, there is growing evidence in the literature that the ideal times to perform iPET are after 2 and/or 4 cycles regardless of the immunochemotherapy regimen used.

Which method is best for interpreting iPET?

In early reports (Table 1), visual (qualitative) interpretation criteria were applied. Due to a lack of standardization in these interpretation criteria, studies investigating the PPV of iPET using visual assessment gave varied results. Observer experience had broadened the interpretation further (Table 1). When defining the cutoff between normal and abnormal uptake of the residual mass, some studies referred to the surrounding normal tissue and some to the mediastinum, whereas others did not describe their methodology.[8] This absence of standardization limits the comparability of these subjective results. Some authors concluded that iPET helps separate patients into high or low risk of treatment failure, while others stressed the low PPV of iPET[9,10] (Table 2). The latter highlights the high risk of iPET misinterpretation, precluding any iPET-driven strategy. In a key study challenging the validity of a positive iPET scan, Moskowitz et al[11] showed that systematic biopsy of iPET4-positive residual mass (ie, with an FDG uptake greater than the local background) after 4 cycles of dose dense rituximab plus cyclophosphamide, oncovin, prednisolone, and hydroxyadriamycine (R-CHOP) only detected active lymphoma, and a commensurate poor prognosis, in 23% of patients,[7] whereas iPET-positive patients with negative biopsy and iPET-negative patients had similar outcomes. With iPET having a false PPV in 87% of cases, they concluded that its clinical predictive value was poor and that it could not be used to drive treatment decisions. However, the study used criteria now recognized to generate a large number of false positive results. Applying a ΔSUVmax (the difference of maximum standardized uptake value [SUVmax]) of 70% could have reduced by 80% the number of patients undergoing biopsy, and hence, lowered the false positivity rate.[8] Furthermore, the low predictive value, limited feasibility, and overall yield of interim-biopsy are acknowledged in daily practice (eg, no guarantee of sampling the most informative biopsy area, poorly accessible residual mass, limited tumor material), as underlined by Juweid et al in their reply to Moskowitz's report.[12] Moskowitz et al conclude that visual interpretation of iPET is inaccurate in that iPET alone cannot drive a therapeutic strategy.

The standardization of iPET interpretation has progressed significantly since these early studies. The first attempt to provide standard criteria was derived through the consensus of experts analyzing response at EOT.[10] In the international harmonizing project (IHP), criteria remain purely visual. For residual masses ≥2 cm, the reference used is the mediastinal blood pool, and for smaller residual mass, it is the surrounding background. Strict application of IHP criteria to evaluate iPET2 and iPET4 is not robust enough to clearly identify patients with different outcomes.[13-15] The issue with the initial IHP criteria was the low PPV (~30%). The Deauville 5-point scale (5-PS), using 5-point visual analysis, brought significant progress.[16] The FDG uptake in the hottest residual mass is compared with the liver uptake, and PET is considered positive with scores of 4 (FDG uptake moderately higher than the liver) or 5 (FDG uptake markedly higher than the liver). This semiquantitative method is more accurate and reproducible when assessing residual mass with abnormal FDG uptake due to lymphoma (ie, visually higher than the liver background) vs nonspecific background uptake.[14] There is a consensus that the 5-PS should be used both for EOT and for iPET scanning with the cutoff of ≥4 applied in DLBCL.[15,17] 5-PS provides a good user reproducibility[3] and has been implemented in the Lugano ICML Imaging consensus. However, the coexistence of 2 interpretation systems, IHP and 5-PS in the literature, can easily confuse the general hematologist. It is important to acknowledge these criteria were designed to interpret PET results at EOT (where CR is established to be of paramount importance) and adopted to assessment after a few cycles of chemotherapy where the treatment purpose may not necessarily be CR but assessment of lymphoma chemosensitivity. Accurate iPET requires early distinction between patients with a low risk of relapse (albeit not necessarily in CR) and high-risk patients who might benefit from treatment escalation or introduction of a novel therapy. Indeed, PET interpretation at EOT and iPET address different challenges. The optimal interpretation methods may be timing specific and cannot be always used indiscriminately.

Comparing SUV at baseline with that at iPET offers several advantages: it is less open to personal interpretation; it corrects for the different SUVs obtained using different scanners and individual uptake times; and is easier to apply in clinical practice and is intended specifically for iPET assessment. It accounts for the reduction in metabolic activity of the lymphoma during treatment, measured by assessing change in FDG avidity.[4] Metabolic changes during treatment are measured using the ΔSUVmax method. It compares the area with the maximum SUV (SUVmax), at baseline and at iPET, after a number of cycles of chemotherapy. The lesion containing the SUVmax on iPET may not necessarily be the lesion that was hottest prior to commencing therapy. A limitation of ΔSUVmax occurs in rare DLBCL cases (<3%)

Table 2. Results of studies using visual method for iPET interpretation

References	mFU	iPETneg	PPV	NPV	PFS according to iTEP	OS according to iTEP	Conclusion(s) of the authors: iTEP
Jerusalem et al[30]	17.5 mo	82%	100%	67%	2-y PFS neg: 62% vs pos: 0%	2-y OS neg: 0% pos: 68%	"is predictive of CR, PFS and OS in NHL"
Spaepen et al[9]	36 mo	53% (all patients)	100%*	84%*	mPFS (all patients) neg: 1059 d vs pos: 45 d	3-y OS (all patients) neg: >90% pos: 30%	"may be used to tailor induction chemotherapy in patients with aggressive NHL"
Haioun et al[39]	24 mo	56.6%	44%*	90%*	2-y PFS neg: 82% vs pos: 43%	2-y OS neg: 90% pos: 61%	"should be an early guide to first-line strategies in aggressive lymphoma"
Mikhaeel et al[40]	24.4 mo	41% and 15.7% with MUR	71%*	90%*	2-y PFS (all patients) neg: 93% vs pos: 30% MRU: 59.9%	2-y OS (all patients) neg: 100% pos: 73% MRU 82.4%	"is an accurate and independent predictor of PFS and OS"
Kostakoglu et al[5]	21 mo	45%	75%	100%	2-y PFS (all patients) neg: 100% vs pos: 12.5%	—	has "a high prognostic value after 1 cycle of chemotherapy …and may offer the potential for change in treatment paradigms"
Querellou et al[41]	—	75%	83%*	83%*	mEFS neg: 233 d vs pos: 465 d	—	"can predict the outcome of patients with aggressive lymphoma and should be a useful tool to modify an ineffective therapy"
Han et al[9]	24 mo (all patients)	67.5% (all patients)	33% (all patients)	68% (all patients)	2-y PFS (all patients) neg: 83% vs pos: 77%	2-y OS (all patients) neg: 90% pos: 84%	"is not predictive of survival outcomes"
Fruchard et al[42]	22 mo (all patients)	57% (all patients)	70%§	100%§	2-y EFS neg: 85% vs pos: 30%	2-y OS neg: 84% pos: 36%	"is valuable tool to early predict outcome"
Dupuis et al[43]	53 mo	78%	—	—	5-y EFS neg: 80% pos: 36%	—	"offers a powerful tool to predict outcome"
Moskowitz et al[11]	44 mo	61%; 33 out of 38 pts with pos iPET had a negative biopsy	—	—	2-y PFS§ neg: >90% pos with neg biopsy: 80%-85% pos with pos biopsy: 60%	—	"interim or posttreatment FDG-PET evaluation did not predict outcome; we recommend biopsy confirmation of an abnormal interim FDG-PET scan before changing therapy"
Cashen et al[15]	33.9 mo	52%	42% for relapse 33% for EOT§	77% for relapse; 100% for EOT§	2-y EFS neg: 85% pos: 63%	2-y OS§ neg: 85% pos: 65%	"has a high NPV but low PPV"
Yang et al[45]	30 mo	72%	—	—	3-y PFS IWC: neg: 86% vs pos: 29.2% D5S: neg: 88.3% vs pos: 52.5%	3-y OS IWC: neg: 86.4% vs pos: 31.1% D5S: neg: 91.4% vs pos: 53.3%	"had a significant predictive value for disease progression and survival"; "might be the single most important determinant of clinical outcome in patients with the same IPI risk"

—, data not available; CR, complete remission; EFS, event-free survival; IPI, International Prognostic Index; IWC, International Workshop Criteria; mFU, median follow-up; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; OS, overall survival.

*According to Han et al.[9]

†According to Han et al[9] and Terasawa et al.[10]

‡Evaluated from publication by SLG and OC.

§According to Terasawa et al.[10]

Table 2. (continued)

References	mFU	iPETneg	PPV	NPV	PFS according to iTEP	OS according to iTEP	Conclusion(s) of the authors: iTEP
Micallef et al[46]	43 mo	78%	46%§	88.8%§	—	—	"using a positive PET2 to change therapy is not supported"
Zinzani et al[47]	50 mo	61.5%	62%§	96.5%§	4-y EFS neg: 75% vs pos: 18%	4-y OS neg: 90% vs pos: 67%	"may represent a significant step forward in helping physicians make crucial decisions on further treatment"
Yoo et al[48]	20 mo	64.5%	62%	93%	3-y PFS neg: 84% vs pos: 66%	3-y OS neg: 84% vs pos: 77%	"might be an inappropriate tool for designing risk-adaptive therapy"
Safar et al[22]	38 mo	62.5%	61%§	75.7%* for EOT according to CT/scan	3-y PFS neg: 84% vs pos: 47%	3-y OS neg: 88% vs pos: 62%	"predicts the outcome in DLBCL patients"; "still requires reproducible and universal interpretation criteria to permit reliable conclusions to be made for the routine use"
Carr et al[44]	35 mo	64%	45.8%§ for EOT	100%§ for EOT	2-y EFS neg: 90% vs pos: 58%	2-y OS neg: 93% vs pos: 72%	"does not differentiate chemoresistant residual tumor from CR, nor does it provide sound basis for early escalation of therapy"
Swinnen et al[49]	4.6 y	79%	42%§	75% for 2-y PFS	2-y PFS neg: 76% vs pos: 42%	2-y OS neg: 93% vs pos: 77%	"Treatment modification based on early PET should remain confined to clinical trials"
Mamot et al[23]	24 mo	40% at C2; 45% at C4	51.8%; 2-y EFS	71% for 2-y EFS	2-y EFS local visual: neg: 74.2% vs pos: 48.2%; Deauville central: neg: 75.9% vs pos: 41.4%	2-y OS local visual: neg: 90.6% vs pos: 87.7%; Deauville central: neg: 93.9% vs pos: 84%	"has limited prognostic value"; "is not ready for clinical use to guide treatment decisions in individual patients"
Hertzberg et al[31]	35 mo	71% at C4	—	—	2-y PFS: neg: 74% pos: 67%	2-y OS: neg: 88% pos: 78%	"this study provides support for the further investigation of early selection of poor prognosis DLBCL patients, as identified by iPET scanning"

—, data not available; CR, complete remission; EFS, event-free survival; IPI, International Prognostic Index; IWC, International Workshop Criteria; mFU, median follow-up; NHL, non-Hodgkin lymphoma; NPV, negative predictive value; OS, overall survival.

*According to Han et al.[9]

†According to Han et al[9] and Terasawa et al.[10]

‡Evaluated from publication by SLG and OC.

§According to Terasawa et al.[10]

Table 3. Description of studies using nonvisual method for iPET interpretation

References	DLBCL pts (n)	Median age	Type of study	Treatment	Nb of cycles of chemotherapy before iTEP	iTEP analysis method	iTEP-driven
Lin et al[20]	92	54	Multicentric prospective	CHOP or ACVBP ± R	2	Visual and SUV-based centrally	No
Itti et al[21]	80	53	Multicentric prospective	CHOP or ACVBP ± R	4	Visual and SUV-based centrally	No
Casasnovas et al[13,25]	113	46, all patients <60 y	Multicentric prospective	R-CHOP or R-ACVBP	2 and 4	Visual centrally reviewed in real-time IHP and ΔSUVmax	Yes, according to visual result but not to D5Smax or ΔSUV
Lanic et al[33]	57 GC: 30; non-GC: 27	65	Monocentric retrospective	R-CHOP or R-CHOP-like	3 or 4	Visual and ΔSUV (70%) local	No
Safar et al[22]	85 (subgroup analysis)	59	Multicentric prospective	R-CHOP or R-ACVBP	2	ΔSUV central	No
Pregno et al[50]	88	55	Multicentric retrospective	R-CHOP-2/14	After 2 (n = 58); after 3 (n = 9); after 4 (n = 21)	Deauville scale and ΔSUV (n = 46) central review	No
Nols et al[51]	73	60	Bicentric retrospective	R-CHOP or R-ACVBP	After 3 cycles (n = 13) or 4 (n = 60)	Deauville and ΔSUV local	No
Lee et al[7]	50 DLBCL out of 61	57	Monocentric prospective	R-CHOP	1	Semiquantitative based on SUVmax local	No
Mylan et al[6]	112	62	Multicentric prospective	R-CHOP	1	IHP and Deauville scale	No
Mamot et al[23]	138 GC: 34%; non-GC: 66%	58.4	Multicentric retrospective for Deauville and ΔSUV	R-CHOP-14	2	Central for Deauville and ΔSUV	No

with low baseline SUVmax. In this situation, a target ΔSUVmax can be lower than the cutoff defining a PET negative scan, in which case the 5-PS is preferred to evaluate iPET.[13,18] Accurate use of SUVmax reduction criteria also requires strict patient preparation, with both baseline and subsequent PET performed on the same calibrated machine using standardized procedures, including a fixed time period between 18-FDG injection and PET acquisition.[19] Assessing ΔSUVmax after 2 and/or 4 cycles of induction therapy has been shown to significantly reduce false positives and is a better predictor of outcome than visual analysis.[17,20,21] The ΔSUVmax method was applied in 2 large clinical prospective trials (PETAL and GAINED) discussed below.

Although there is no prospective comparison between these methods, several exploratory investigations compare visual and nonvisual methods.[13,17,20-24] All these studies have limitations due to their retrospective nature, limited patient numbers, or lack of a control arm. However, they all conclude in favor of quantitative methods, generally ΔSUVmax, to reduce the number of false positives and give a better PPV for both PFS and OS. In the report of Casasnovas et al of the multicenter LNH2007-3B LYSA/GELA trial with central blinded PET review, the NPV for PFS and OS is similar for the IHP, Deauville, and ΔSUVmax methods, but the PPV for ΔSUVmax is superior. Compared with the IHP criteria and the Deauville score, ΔSUVmax reduces the risk of false positives by 80% and 30%, respectively.[13,25] However, Mamot et al on behalf of the SAKK group recently challenged these findings.[23] They found no advantage for ΔSUVmax after 2 cycles of R-CHOP14, as compared with centrally reviewed Deauville, when predicting EFS and OS. The different conclusions probably reflect differences in the studied populations. The LYSA study only included high-risk (age-adjusted International Prognostic Index, aaIPI = 2-3) patients with advanced disease, whereas in the SAKK study, 71% of patients had low or intermediate risk. Indeed, the SAAK study is consistent with the finding that ΔSUVmax is less predictive for low-risk disease, in particular, for patients with localized disease,[17] and that the ΔSUVmax method is difficult to use in patients with a low baseline SUVmax, as there is limited capacity to reduce the SUVmax of such lesions. The ongoing LYSA phase 3 trial (LNH2009-1B: NCT01285765) for previously untreated DLBCL patients with no risk factor (aaIPI = 0) investigates chemotherapy reduction in PET2-negative patients using the 5-PS, and no quantitative method, to interpret iPET. Except for low-risk aaIPI = 0 patients, for whom the Deauville score is accurate, recent findings show that ΔSUVmax should be preferred when interpreting iPET scans of patients with DLBCL, because of the better PPV, NPV, and reproducibility.

What do we know about iPET-driven treatment of DLBCL?

Several groups worldwide already use iPET not just as a predictive marker, but to guide treatment strategy within the context of prospective clinical trials. Most studies are based on visual analysis of PET. Two approaches are possible, using iPET to assess either whether to deescalate consolidation treatment of iPET-negative patients or whether to intensify treatment of iPET-positive patients.

If, according to visual or semiquantitative analysis, the NPV of iPET is good, the therapeutic strategy may support deescalation of consolidation treatment. The LNH2007-3B LYSA/GELA trial demonstrated that their standard approach of treatment consolidation with high-dose therapy followed by an autologous stem cell transplantation (ASCT) can be safely avoided in ~25% of aaIPI = 2-3 patients. These patients reached a rapid complete response with a negative iPET according to IHP criteria after 2 cycles of chemotherapy and remained in first complete response after 4 cycles of R-chemo14.[26] Post hoc analysis shows that patients with ΔSUVmax > 66% and >70% (regardless of the value of residual uptake) after 2 and 4 cycles of R-chemo, respectively, might similarly safely avoid ASCT, representing 80% of the whole population. Their outcome was similar to that of aaIPI = 2-3 patients enrolled in a previous LYSA/GELA trial, where all patients in first response after 4 cycles of R-chemo14 underwent a high-dose therapy followed by ASCT.[27] This finding is important, because iPET-2- and iPET-4-negative patients represent almost 80% of young

aaIPI = 2-3 de novo DLBCL patients. In the LNH 02-03 LYSA/GOELAMS phase 3 trial for nonbulky limited stage DLBCL patients, final results presented at 2014 American Society of Hematology meeting showed that radiotherapy can be avoided when iPET4 is negative without compromising outcomes.[28]

Using iPET results to escalate therapy has also been investigated. Kasamon et al report an iPET-driven phase 2 study in 56 newly diagnosed DLBCL,[29] where iPET was performed after 2 or 3 cycles of R-CHOP and interpreted according to IHP criteria. Fifty-six percent of patients had a positive iPET and received intensified treatment, 2 cycles of platinum-based chemotherapy plus ASCT, but 27% had relapsed after 2 years. Treatment intensification did not prevent iPET-positive patients from having a higher risk of relapse than iPET-negative patients (who had a 2-year relapse rate of only 8%). This finding suggests that high-dose therapy may be insufficient to overcome the poor PPV of iPET. In another phase 2 study,[30] 50 of 150 patients had a positive iPET according to IHP after 4 cycles (PET4) of R-CHOP and received an intensified rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE) treatment, but their outcome remained less favorable (4-year PFS 59%; 4-year OS 73%) than that of patients with a negative PET4 (4-year PFS 91%; 4-year OS 96%). The R-ICE treatment did not compensate for the poor PPV of PET4, although these patients may do better than those pursuing R-CHOP treatment in historical reports. Results are a bit contradictory in a similar phase 2 study (n = 151) with high-risk DLBCL. After 4 cycles of R-CHOP, patients who remained iPET4-positive applying the IHP criteria were scheduled to undergo R-ICE chemotherapy followed by a ^{90}Y Ibritumomab tiuxetan containing ASCT. In the 42/151 (29%) iPET4-positive patients, the 2-year PFS and OS were similar to the iPET4-negative population ($P = .11$). In an exploratory analysis, the PFS and OS were markedly superior for iPET4-positive patients with a score of 4 on the 5-PS vs those with a score of 5 ($P = .0002$, and $P = .001$).[31]

The phase 3 PETAL trial (NCT00554164) (n = 853) randomized patients to either a standard R-CHOP14 treatment or an escalated therapy using a Burkitt-type regimen for patients with a ΔSUVmax $<$ 66% after 2 cycles of R-CHOP14.[32] In this study, as in the LYSA study, there was rigorous scanner quality control and standardized conditions for PET acquisition and interpretation. Thirteen percent of patients had a positive iPET2. Relapse occurred more frequently for patients with ΔSUVmax $<$ 66%. After a median follow-up of 33 months, freedom from treatment failure (time to treatment failure) at 2 years was only 47% compared with 79% in those with ΔSUVmax $>$ 66% (hazard ratio, 3.4; $P < .0001$). The PETAL trial confirms that the ΔSUVmax method has predictive value but also disappointingly that escalation to the Burkitt-type regimen failed to improve the outcome of iPET-2 high-risk patients with no significant difference in time to treatment failure and OS across both chemotherapy arms in this population.

Taken together, these trials demonstrate that an iPET-driven strategy can be used in a prospective multicenter approach and as a predictive marker. Treatment deescalation can be safely proposed in some situations (no ASCT for aaIPI = 2-3; no radiotherapy consolidation for aaIPI = 0 with good iPET2/4 results). For patients remaining iPET-positive, novel solutions beyond treatment escalation must be explored.

Is iPET suitable in daily practice for all DLBCL patients?

Elderly patients

All studies conducted on iPET are for patients $<$70 years of age. There are no data about whether iPET is of merit for elderly patients. An escalation strategy for iPET-positive patients is generally precluded in the elderly. Absence of escalation strategy, along the frequent comorbidities that preclude trial eligibility, likely explains the lack of research in this population. Nonetheless, study of an iPET-driven strategy in the elderly aiming to reduce treatment of good responders or to introduce novel agents for poor responders may prove very useful. The elderly are highly vulnerable to chemotherapy side effects and toxicities, and in the absence of data, iPET cannot be recommended in clinical practice. Prospective trials addressing this issue are encouraged.

iPET according to subtype of DLBCL

Until now, iPET studies have included all types of CD20$^+$ DLBCL, without dividing patients into subgroups. iPET efficiency according to the biological characteristics of DLBCL has not often been addressed in the literature. Lanic et al suggest using a mixed prognostic score, including IPI, cell of origin, and iPET, for tailored therapy.[33] We have no knowledge as to whether iPET could be of value for rare subgroups, eg, plasmablastic, intravascular, primary mediastinal (PMBCL), or transformed indolent lymphoma. PMBCL is a good-prognosis lymphoma that presents with a mediastinum involvement in a young patient population. Although the metabolic tumor volume at baseline has been shown to impact patient outcome,[34] it is acknowledged that residual FDG uptake at the end of induction therapy does not preclude cure. Indeed, in a report by Pinnix et al of 68 (62%) patients with PMBCL, 62% had a hypermetabolic residual mass (Deauville score $\geq$3, uptake $>$ mediastinum) at the end of induction chemotherapy,[35] all but all 9/68 (13%) patients who relapsed or progressed had a Deauville score 4 or 5. This result suggests using a liver background may be more appropriate to interpret iPET visually in this subset of DLBCL. Similarly, in the LNH2007 trial, ΔSUVmax analysis did not give different outcomes for PMBCL and DLBCL when using a 66% and 70% cutoff after 2 and 4 cycles of immunochemotherapy, respectively (R.-O.C., unpublished data). Indeed, residual abnormal FDG uptake in PMBCL can persist for some time despite successful treatment.

iPET-driven strategy in daily practice in DLBCL

The PPV of iPET is the main argument against using an iPET-driven strategy and the reason recommendations do not support implementation of iPET-driven strategy in daily clinical practice. Our interpretation of the literature is that such an argument should not preclude iPET entirely. Applying the same argument would certainly exclude use of standard contrast-enhanced CT scanning during treatment, yet this is an accepted practice to reassure both patient and clinician of the appropriateness of ongoing therapy. Despite this standard approach, few studies have investigated a CT/scan-driven strategy, and none have performed systematic biopsy, to confirm that any interim residual mass remains involved with lymphoma! iPET is simply one of the best tools among others. Provided the clinician knows the limits of its timing and interpretation and neither under- nor overestimates its capacity to predict patient outcome, we believe that iPET using the ΔSUVmax method may assist therapeutic decision making in daily practice. iPET should be reviewed by both hematologist and the nuclear medicine physician in the multidisciplinary team setting before any change in therapeutic strategy is applied.

Table 4. Results of studies using nonvisual method for iPET interpretation

References	mFU (mo)	% of neg	PPV	NPV	PFS according to iPET	OS according to iPET	Conclusion of the authors about iPET
Lin et al[20]	42	Visual: 63%; ΔSUVmax: 82.6%	For EFS visual: 50%, ΔSUVmax: 81.3%; for OS visual: 38.2%, ΔSUVmax: 73.3%	For EFS visual: 74%, ΔSUVmax: 75%; for OS visual: 86.2%, ΔSUVmax: 87%	2-y EFS visual neg: 79%, visual pos: 51%, ΔSUVneg: 79%, ΔSUVpos: 21%	—	"SUV-based assessment … improves the prognostic value of early ^{18}F-FDG PET compared with visual analysis"
Itti et al[21]	41	Visual: 77%; ΔSUVmax:78.7%	For EFS visual: 77.8%, ΔSUVmax: 70.6%; for OS visual: 55.6%, ΔSUVmax: 53%	For EFS visual: 82.3%, ΔSUVmax: 79.4%; for OS visual: 88.7%, ΔSUVmax: 87.3%	2-y EFS visual neg: 82%, visual pos: 25%, ΔSUVneg: 79%, ΔSUVpos: 32%	—	"semiquantification … performance is equivalent to visual analysis at 4 cycles"
Casasnovas et al[13,25]	19	After 2 cycles visual: 34%, ΔSUV: 78%; after 4 cycles: visual: 51% ΔSUV: 88%	—	—	2-y PFS (neg vs pos) visual after 2: 77 vs 73, visual after 4: 81% vs 73%; D5S after 2: 88% vs 79%; D5S after 4: 82% vs 69%; ΔSUV after 2: 77% vs 57%; ΔSUV after 4: 83% vs 40%	2-y OS (neg vs pos) visual after 2: 93% vs 84%, visual after 4: 94% vs 83% ΔSUV after 2: 93% vs 60% ΔSUV after 4: 50% vs 94%	"These encouraging results suggest the use of ΔSUVmax in addition to visual analysis to interpret iPET … specifically when a therapeutic decision is to be guided by iPET results"
Lanic et al[33]	—	Visual: 54.3%; ΔSUV: 63.1%	—	—	2-y PFS ΔSUVmax > 70: 77% ΔSUVmax < 70: 15% estimated	2-y OS ΔSUVmax > 70: 77% ΔSUVmax < 70: 33%	"Semiquantitative interim PET assessment was highly predictive of the outcome"; "Combination of GEP, aaIPI and interim PET more accurately predicts DLBCL prognosis and is therefore suitable for tailoring therapeutic strategies"
Safar et al[22]	38	ΔSUV: 86%	—	—	3-y PFS ΔSUV > 66%: 77% ΔSUV < 66%: 38%	3-y OS ΔSUV > 66%: 82% ΔSUV < 66%: 64%	"Both visual and quantitative evaluations can, however, be improved"; "a centralized review of imaging can also improve evaluation of the PET response and should be encouraged in clinical trials"

Table 4. (continued)

References	mFU (mo)	% of neg	PPV	NPV	PFS according to iPET	OS according to iPET	Conclusion of the authors about iPET
Pregno et al[50]	26.2	DS: 72%; ΔSUV: 84.1%	Deauville for PFS 36%	Deauville for PFS 82.5%	2-y PFS Deauville: 85% vs 72% ΔSUV > 66%: 87% ΔSUV < 66%: 68%	—	"a negative iPET predicts a good outcome"; "positive I-PET is not predictive of a worse outcome in DLBCL"
Nols et al[51]	28	Deauville: 72%; ΔSUVmax: 82%	Deauville for PFS and OS 55% and 50%; ΔSUV for PFS and OS 46% and 46%	Deauville for PFS and OS 81% and 87% ΔSUV for PFS and OS 81% and 87%; 75% and 82%	2-y PFS ΔSUV > 66%: 78% ΔSUV < 66%: 50%	2-y OS ΔSUV > 66%: 88% ΔSUV < 66%: 56%	"i-PET was highly and independently predictive of any outcome, and its negative predictive value was improved by combination with IPI"
Lee et al[7]	72	54%	53.6%	93.9%	5-y PFS 52% vs 80.7%	5-y OS 56.2% vs 81.5%	iPET "is a significant predictor of PFS and OS"
Mylan et al[6]	29	IHP: 33%; DS: 46%	IHP: 20%; DS: 25%	IHP: 76%; DS: 83%	2-y PFS: IHP: iPET1 neg: 81.9% iPET1 pos: 77.2% DS (pos if >3): iPET1 neg: 84% iPET1 pos: 77.1% DS (pos if =5): iPET1 neg: 84.8%, iPET1 pos: 50.9%	2-y OS: IHP: no difference DS (pos if >3): no difference DS (pos if =5): iPET1 neg: 87% iPET1 pos: 57.8%	"PET after one course of chemotherapy was not able to safely discriminate PET-positive and PET-negative patients"
Mamot et al[23]	24	Deauville: 54%	—	—	2-y EFS Deauville iPET-2: 41% vs 76%; iPET-4: no difference ΔSUV iPET-0-2: ΔSUV > 66%: 61% ΔSUV < 66%: 42%	2-y OS Deauville iPET-2: 84% vs 94%/ΔSUV iPET-0-3 ΔSUV > 66%: 91.3% ΔSUV < 66%: 73.7%	iPET "has limited prognostic value in patients with diffuse large B-cell lymphoma" and "is not ready for clinical use to guide treatment decisions in individual patients"

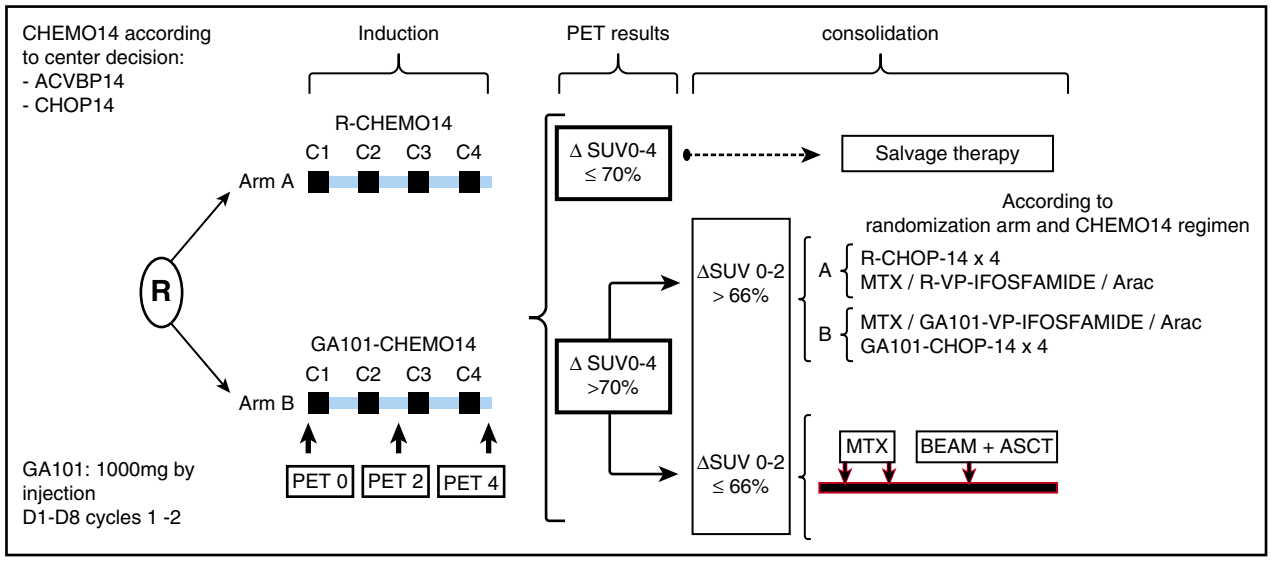

Figure 1. Example of a PET-driven strategy (GAINED trial). The GAINED trial compares Obinutuzumab (GA-101) vs Rituximab (R) plus chemotherapy (CHOP or ACVBP according to local practice) for untreated IPI 2-3 DLBCL patients younger than 60 years. PETs are performed at diagnosis, after 2 and 4 cycles of chemotherapy. iPET response is analyzed according to the ΔSUVmax method. Patients with an early good response receive the scheduled immunochemotherapy according to initial randomization (either CHOP or methotrexate [MTX]/vépéside [VP]-Ifosfamide/Aracytine [Arac]), slow responders (as defined by a ΔSUVmax: iPET2 < 66% and iPET4 > 70%) receive 2 courses of high-dose methotrexate followed by ASCT, whereas nonresponders (as defined by a ΔSUVmax: iPET2 < 66% and iPET4 < 70%) receive a salvage therapy according to local investigators. All iPET are centrally reviewed, and patient's treatments are based on central review. The study is closed for inclusion and enrolled 671 patients. BEAM, BCNU, etoposide, cytarabine, melphalan.

For an iPET-driven deescalation strategy, it is better to perform 2 iPETs (one after 2 and one after 4 cycles) to ensure that the metabolic response lasts after the induction treatment, even if PET4 could probably be omitted in most PET2-negative patients.[4] For DLBCL patients with risk factors, the LYSA and the PETAL trials demonstrate that ΔSUV > 66% iPET-2 patients (or patients without abnormal uptake using the visual method) are highly sensitive to 6 or 8 cycles of rituximab chemotherapy and achieve very good outcomes. Such patients have no need for intensive therapy and may be treated safely as initially planned.

In clinical practice, an iPET-driven strategy to intensify therapy or change to an alternative salvage or introduce a novel treatment often rests on results from a single iPET, usually after 22[6] or 4 cycles.[23] The LYSA and the PETAL trials show that iPET-2-positive patients according to the ΔSUVmax criteria are exposed to a high risk of relapse. Is this argument enough to change the treatment strategy for such individuals? Before changing any treatment according to iPET, there are additional issues: the acceptable threshold according to the clinician and patient and the efficacy of other available options. Considering the threshold, is a 50% risk of relapse enough to change ongoing therapy? Changing therapy is not an easy medical decision if the patient has reached a CT-based partial response. R-CHOP and R-CHOP-like chemotherapies have known and documented efficacy in DLBCL for years, and any change in therapy may reduce the rate of successful outcomes. To address this dilemma, alternative options must be superior to the ongoing treatment to overcome the poor predictive value of the 50% truly iPET-positive patients without jeopardizing the good outcome of the 50% falsely iPET-positive patients. The main option today, save for clinical trial participation, is more intensive treatment. In their trials, Kasamon et al and Sehn et al conclude that a change of treatment does not completely reverse the bad outcome for iPET-positive patients.[29,30] Furthermore, as mentioned above, the Burkitt-type approach failed to improve the outcome for iPET-positive patients in the PETAL trial. Judging from these trials, some may conclude that a therapeutic change for iPET-positive patients is of limited value. It does not improve patient outcome, and those who are falsely iPET-positive per IHP criteria risk being overtreated. It seems to us that assessing ΔSUVmax may change this, as it minimizes the risk for false positivity and consequently allows for safer change in therapy. However, it is clear that daily practice is probably not yet ready for a strategy of iPET-driven treatment intensification on the basis of a single positive iPET2, interpreted with visual criteria. This strategy needs to be further investigated. On the other hand, our opinion in line with the recent report of Hertzberg et al[51] is that patients with an insufficient metabolic response after 4 cycles are those who could be considered for alternative therapy or intensified treatment.

Conclusion

iPET-guided treatment of DLBCL remains debatable and cannot be considered a standard of care in daily practice. However, literature suggests that iPET can assist the clinician in predicting patient outcome, and expert consensus is that it is preferred to standard CT for interim response assessment. For aaIPI = 2-3 de novo DLBCL young patients, we recommend considering 2 different points during therapy (after 2 and 4 cycles) instead of 1 (often iPET4) to identify patients who are rapid responders (negative iPET-2/negative iPET-4) with a very good outcome from slow responders (positive iPET-2/negative iPET-4) with a higher risk for relapse (>50%). Regarding iPET-driven strategy, our opinion is that good responders according to the ΔSUVmax method for DLBCL IPI2-3 or visual method for low IPI patients can safely be treated as planned. The combination of baseline metabolic bulk with iPET may also improve the safety of this approach.[24,36] Regarding slow responders, our opinion is that these patients could be considered for alternative treatment or, at least, carefully monitored. In the GAINED

trial, we used such a design (Figure 1). The results of this approach are yet not known, but a "GAINED strategy" may soon identify whether ASCT is recommended for slow and bad responders. Alongside clinical trials, this strategy is commonly used in LYSA centers for aaIPI = 2-3 patients eligible for ASCT. It is clear that today there is no direct evidence that altering conventional chemotherapy on the basis of iPET findings significantly improves patient outcome. iPET-driven therapy could also be applied to deescalate therapy for iPET-negative low-IPI patients for whom the visual analysis of iPET suggests it is safe to omit radiotherapy.

Future findings in iPET-driven strategies will probably bring new interpretation methods, plus new parameters integrating textural features, tumor volume, and new tumor-specific tracers. These findings will need to be combined into integrative treatment algorithms, taking into account tumor characteristics, based on genetic and epigenetic abnormalities and assessment of circulating tumor DNA.[37] Currently under investigation, such a tailored approach will probably strengthen the value of iPET for therapeutic decision making.

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