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ORIGINAL REPORT

[18F]Fluorodeoxyglucose Positron Emission Tomography Predicts Survival After Chemoimmunotherapy for Primary Mediastinal Large B-Cell Lymphoma: Results of the International Extranodal Lymphoma Study Group IELSG-26 Study

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See accompanying editorial on page 1751; listen to the podcast by Dr Hamlin at www.jco.org/podcasts

A B S T R A C T

Purpose

To assess the role of [18F]fluorodeoxyglucose ([18F]FDG) positron emission tomography/computed tomography (PET/CT) after rituximab and anthracycline-containing chemoimmunotherapy in patients with primary mediastinal large B-cell lymphoma (PMLBCL).

Patients and Methods

Among 125 patients prospectively enrolled, 115 were eligible for central review of PET/CT scans at the completion of standard chemoimmunotherapy, by using a five-point scale. Consolidation radiotherapy (RT) was permitted and given to 102 patients.

Results

Fifty-four patients (47%) achieved a complete metabolic response (CMR), defined as a completely negative scan or with residual [18F]FDG activity below the mediastinal blood pool (MBP) uptake. In the remaining 61 patients (53%), the residual uptake was higher than MBP uptake but below the liver uptake in 27 (23%), slightly higher than the liver uptake in 24 (21%), and markedly higher in 10 (9%). CMR after chemoimmunotherapy predicted higher 5-year progression-free survival (PFS; 98% *v* 82%; $P = .0044$) and overall survival (OS; 100% *v* 91%; $P = .0298$). Patients with residual uptake higher than MBP uptake but below liver uptake had equally good outcomes without any recurrence. Using the liver uptake as cutoff for PET positivity (boundary of score, 3 to 4) discriminated most effectively between high or low risk of failure, with 5-year PFS of 99% versus 68% ($P < .001$) and 5-year OS of 100% versus 83% ($P < .001$).

Conclusion

More than 90% of patients are projected to be alive and progression-free at 5 years, despite a low CMR rate (47%) after chemoimmunotherapy. This study provides a basis for using PET/CT to define the role of RT in PMLBCL.

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INTRODUCTION

Primary mediastinal large B-cell lymphoma (PMLBCL) is recognized as a distinct entity with clinicopathologic[1,2] and molecular[3-5] criteria. Patients with PMLBCL tend to be younger than those with diffuse large B-cell lymphoma (DLBCL), with a median age at diagnosis in the third to fourth decade and a preponderance of females. This lymphoma is characterized by a rapidly progressive anterior mediastinal mass, often with local invasion and compressive syndromes, and by recurrence at unusual sites, such as the liver, kidneys, and CNS.[2] The response to combination chemotherapy is generally good and is usually followed by consolidation radiotherapy (RT). Since the addition of rituximab, reported progression-free survival (PFS) and overall survival (OS) rates at 3 years are approximately 75% to 80% and 85% to 90%, respectively, with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP-like regimens.[6,7] These outcomes appear better than in other DLBCL types, partly as a result of the patients' younger age and earlier stage at presentation. If the initial

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treatment fails, however, the results of salvage chemotherapy and myeloablative treatment are poor.[8] The need to maximize cure rates with initial therapy has led to controversy over its extent, in particular, whether consolidation RT to the mediastinum is always required and whether positron emission tomography with computed tomography (PET/CT) scanning of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) uptake can be used to determine this.

Many centers include irradiation after chemoimmunotherapy (rituximab combined with chemotherapy) as a routine part of initial therapy, following retrospective studies suggesting that the best outcomes are obtained when consolidation RT is given to the mediastinum.[2] However, this approach is increasingly challenged, not least by excellent results in a small series of patients treated with infusional chemoimmunotherapy alone—the dose-adjusted rituximab in combination with etoposide, prednisone, vincristine, and doxorubicin hydrochloride (R-EPOCH) regimen.[9] A residual mediastinal mass is frequently present at the end of chemoimmunotherapy, but only a minority of such masses apparently represent active disease. Functional imaging studies using PET/CT scans[10] have suggested that it may be possible to distinguish residual mediastinal masses that contain active lymphoma from those in which only sclerotic material remains. PET/CT scans are now widely used as prognostic indicators[11-13] and are incorporated in the definitions of the response criteria for DLBCL.[14] However, the studies performed to date in PMLBCL have not fully clarified whether RT might be avoided solely on the basis of a negative PET scan.

In a retrospective study of 54 patients with PMLBCL who were treated with the rituximab plus CHOP along with ifosfamide, carboplatin, and etoposide (R-CHOP + ICE) dose-dense regimen without mediastinal RT, the Memorial Sloan-Kettering Cancer Center group reported 3-year OS and PFS of 88% and 78%, respectively, in patients who were PET negative at the end of the chemotherapy regimen. However, an interim PET/CT scan was abnormal in 47% of patients and did not predict for PFS.[15]

In a British Columbia Cancer Agency (BCCA) retrospective survey,[16] 96 patients with PMLBCL were treated with R-CHOP. Before 2005, consolidation RT to the mediastinum was routinely administered following R-CHOP, although after 2005, a PET/CT scan was planned at the end of chemotherapy to guide RT; if the PET scan was negative, patients were observed, and if the PET scan was positive, consolidation RT was given if possible. Of 59 PET scans at the end of treatment, 35 (59%) were negative (two received RT) and 24 (41%) were positive (23 received RT). With a median follow-up of more than 5 years, there was no survival difference between PET-negative and PET-positive patients, suggesting that a PET-guided RT approach in patients with PMLBCL treated with R-CHOP may reduce the use of RT while maintaining good outcomes.[16]

This study (A Clinico-Pathologic Study of Primary Mediastinal B-Cell Lymphoma [IELSG-26]) was performed by the International Extranodal Lymphoma Study Group (IELSG) to gather data prospectively on some of these controversial issues in PMLBCL. Here we

Table 1. Deauville 5-Point Scale, Initially Devised to Facilitate the Interpretation of Interim PET Scans and Used in This Study to Describe End-of-Chemotherapy Results

Deauville Score	[^{18}F]FDG Uptake
1	No uptake
2	≤ Mediastinal blood pool
3	> Mediastinum and ≤ liver
4	Moderately more than liver at any site
5	Markedly more* than liver at any site and/or new sites of disease

Abbreviations: [^{18}F]FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography.
*Maximum standardized uptake value of the lesion more than two times liver uptake.

Table 2. Baseline Patient Characteristics (n = 125 unless otherwise specified)

Characteristic	No. of Patients	%
Age, years		
Median	33	
Interquartile range	27-41	
≤ 60	119	95
Female sex	77	62
ECOG performance status		
0	61	49
1	47	38
> 1	17	14
"B" symptoms at presentation	45	36
Bulky disease (maximum mediastinal lesion), cm		
> 7	106	85
> 10	65	52
Ann Arbor stage		
I	16	13
II	81	65
IIE	20	16
III	6	5
IV	2	1.5
Extramediastinal contiguous involvement	20	16
Pleural effusion	5	4
Pericardial effusion	2	1.5
Lung	3	2.5
Chest wall	10	8
Bone marrow involvement	2	1.5
Serum LDH (> upper limit of normal)	93	74
IPI		
Low risk	98	78
Low-intermediate risk	23	18
Intermediate-high risk	4	3
High risk	0	0
aaIPI (n = 119)		
Low risk	27	23
Low-intermediate risk	73	61
Intermediate-high risk	18	15
High risk	1	1
First-line chemoimmunotherapy regimen		
R-CHOP every 14 days	7	6
R-CHOP every 21 days	7	6
Intensified R-CHOP	6	5
R-VACOP-B	71	57
R-MACOP-B	34	24

NOTE. Percentages may not total 100 due to rounding.
Abbreviations: aaIPI, age-adjusted International Prognostic Index; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-MACOP-B, rituximab plus methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; R-VACOP-B, rituximab plus etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin.

present the results of the PET/CT scanning after rituximab and anthracycline-containing chemoimmunotherapy and an assessment of the predictive value of different uptake cut points.

PATIENTS AND METHODS

Study Design

This study was conducted with the cooperation of the Fondazione Italiana Linfomi (FIL) and the United Kingdom National Cancer Research Institute (NCRI). Between January 2007 and July 2010, 125 patients with histopathologically proven PMLBCL of any stage, previously untreated and eligible for intensive chemoimmunotherapy with curative intent, were enrolled at 21 institutions from five countries. All diagnoses were revised by an expert hematopathologist. The primary end point was the lymphoma remission rate (complete metabolic response [CMR]) on PET/CT scanning at the completion of chemotherapy. A sample size of 100 patients was planned to estimate the PET/CT CMR rate with an SE below 5%, assuming an expected CMR rate of approximately 50%. Patients were excluded if they were younger than age 18 years or if they had evidence of clinically significant cardiac disease within the preceding 12 months, HIV infection, or major impairment of bone marrow, renal or liver function.

This study received approval by the local research ethical committee of each participating center. All patients gave their written informed consent. All patients underwent standard staging procedures and received chemoimmunotherapy using rituximab combined with methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (MACOP-B; 71 patients), etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin (VACOP-B; 34 patients) or CHOP, either every 21 days (seven patients) or every 14 days (seven patients) or with intensified doses (six patients). These regimens (described in Appendix Table A1, online only) were prespecified in the trial protocol, and centers were required to select in advance which to use. Consolidation with mediastinal RT was allowed, with fields as indicated by local guidelines. Treatment was commenced within 8 weeks of the last dose of chemotherapy, and a dose of 30 to 42 Gy was given according to local policies. Patients were observed after the end of initial treatment at monthly intervals for 3 months and then every 2 months until 1 year post-treatment. Follow-up was every 3 months in year 2, every 4 months in year 3, every 6 months in year 4, and annually thereafter.

PET/CT Imaging

PET/CT scans were planned at baseline and 3 to 4 weeks after the end of the chemoimmunotherapy. Interim PET/CT imaging was permitted according to local protocols, but the results were not used to alter the planned therapy. Rescanning after at least 2 months from the completion of RT was scheduled for patients receiving mediastinal irradiation.

Baseline PET/CT scans were carried out within 14 days before commencing treatment. For 20 patients who required urgent treatment and for whom the PET scan could not be performed before therapy started, the baseline scan was omitted after discussion with the clinical coordinators.

PET/CT imaging was performed on full-ring integrated PET/CT systems, and the detailed PET/CT methodology is described in the Appendix. For each examination, the PET/CT data were sent together with essential information on the PET/CT acquisition to the core laboratory for central review. This was performed after the end of treatment by a single physician with expertise in

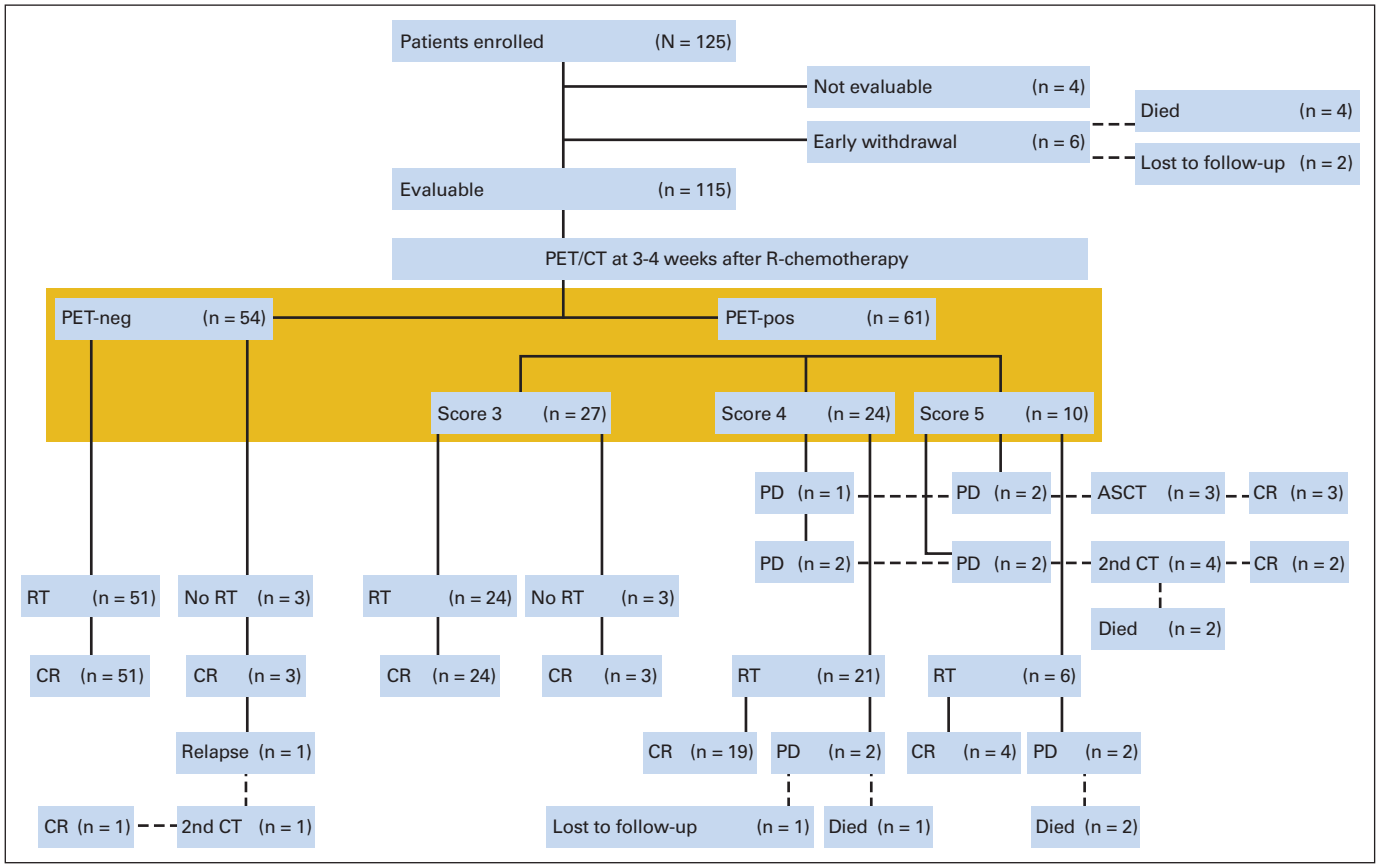

Fig 1. Patient flow and outcome according to their positron emission tomography/computed tomography (PET/CT) remission status evaluated by using the International Harmonization Project criteria (golden rectangle) after first-line chemoimmunotherapy. ASCT, autologous stem-cell transplantation; CR, complete remission; PD, progressive disease; R-chemotherapy, rituximab and chemotherapy; second CT, second-line chemotherapy, PET-neg, PET-negative; PET-pos, PET-positive; RT, radiotherapy.

nuclear medicine (L.C.). Uncertain interpretations were resolved with the agreement of a second expert (L.G.). The review was blinded to the clinical information.

The achievement of a CMR was defined according to the criteria of the International Harmonization Project (IHP) in Lymphoma, by a completely PET-negative scan or a scan having minimal residual uptake less than the mediastinal blood pool (MBP) activity.[14,17]

The postchemotherapy and post-RT scans were also visually assessed according to the Deauville criteria[18] with [^{18}F]FDG uptake of any residual lesion scored according to a 5-point scale using MBP and liver uptake as reference settings (Table 1). Diffuse uptake in the spleen or marrow on the post chemoimmunotherapy scan that was considered a result of chemotherapy was not scored as active disease. The patients achieving a CMR according to the IHP criteria equate to score 1 or 2 on the Deauville scale.

Statistical Analysis

OS and PFS were defined according to the revised National Cancer Institute criteria[14] and estimated by using the Kaplan-Meier or the life-table method, as appropriate.[19] Differences between survival curves were analyzed by using the log-rank test.[20] *P* values of .05 or less (two-sided test) were considered to indicate statistical significance. Follow-up was calculated as the median time to censoring by using a reverse Kaplan-Meier analysis.[21] The exact 95% CIs were calculated for incidence percentages. Negative predictive values (NPVs) and positive predictive values (PPVs) were calculated according to standard definition.[22] Statistical analysis was conducted by using STATA, Release 11 (STATA, College Station, TX).

RESULTS

The clinical characteristics of the 125 enrolled patients are summarized in Table 2. Treatment was administered as initially planned in 119 patients; there were six early withdrawals: four died from early progression and two were lost to follow-up. In this overall (intent-to-treat) population of 125 patients with PMLBCL at a median follow-up of 2.9 years (interquartile range, 2.5 to 3.7 years), 17 disease progressions and nine deaths were recorded, with estimated 5-year OS and PFS rates of 92% (95% CI, 86% to 96%) and 86% (95% CI, 79% to 91%), respectively.

Postchemotherapy PET imaging was not done (n = 2) or not evaluable because of technical problems (n = 2) in four patients; therefore, central review of PET/CT was possible in 115 of 119 patients. In this group of 115 patients, one patient who did not have consolidation RT relapsed after a negative PET scan, and 11 had

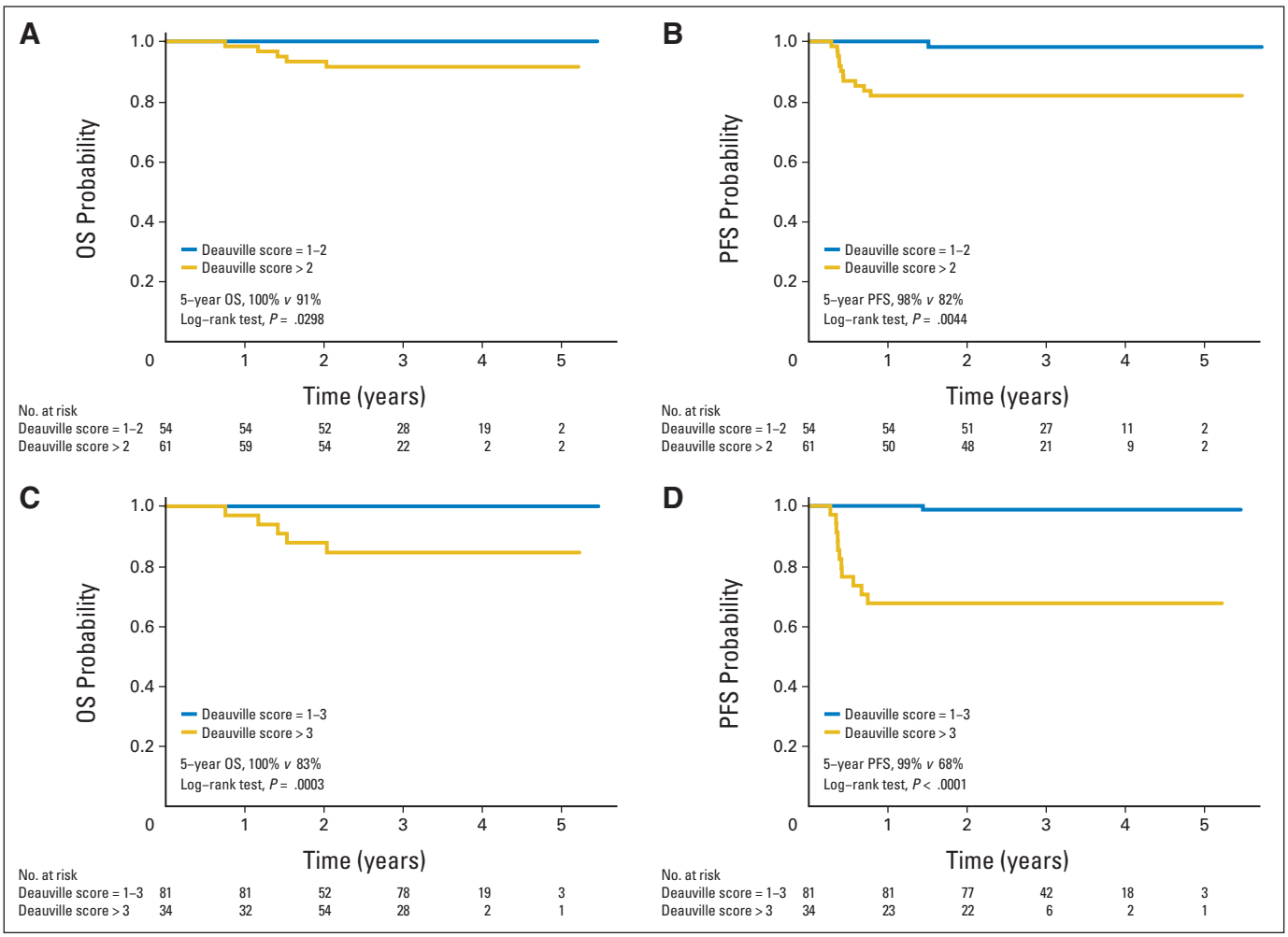

Fig 2. Kaplan-Meier estimates of overall survival (OS) and progression-free survival (PFS) in primary mediastinal large B-cell lymphoma according to positron emission tomography positivity defined at 3 to 4 weeks after chemoimmunotherapy by using (A, B) the mediastinal blood pool uptake (Deauville score 3 to 5) or (C, D) the liver uptake as a cut point (Deauville score 4 to 5). Median follow-up time was 2.9 years (95% CI, 2.7 to 3.2 years).

disease progression after positive scans and RT (Fig 1). All progressed in the initially involved mediastinal area.

According to the IHP criteria, PET/CT visual assessment at 3 to 4 weeks after chemoimmunotherapy showed CMR in 54 (47%; 95% CI, 38% to 56%) of 115 patients. In 12 patients (10%; 95% CI, 6% to 18%) the PET/CT scan was completely negative (score 1 according to the Deauville criteria), although in 42 (37%; 95% CI, 28% to 46%), there were residual masses with [^{18}F]FDG uptake less than MBP uptake (score 2).

A CMR was not attained in 61 (53%; 95% CI, 44% to 62%) of 115 patients with a PET-positive residual mediastinal mass at the end of chemoimmunotherapy. The residual uptake was higher than MBP uptake but below the liver uptake (score 3) in 27 patients (23%; 95% CI, 16% to 32%), slightly higher than the liver uptake (score 4) in 24 patients (21%; 95% CI, 14% to 29%), and markedly higher than the liver uptake (score 5) in 10 patients (9%; 95% CI, 4% to 15%). The diagram in Figure 1 summarizes the patient flow and outcome according to their PET/CT remission status evaluated by using the IHP criteria. Notably, mediastinal RT was given to 102 (92%) of the 115 evaluated patients. Fifty-one of the 54 patients with CMR received mediastinal RT and none has relapsed. Of the three who did not receive RT, one relapsed in the mediastinum at 17 months after treatment. None of 27 patients with a PET score of 3 has relapsed, of whom 24 received RT. After RT, the PET/CT converted to score 1 to 2 or remained unchanged in 18 patients (75%). Seven of 34 patients with score 4 or 5 had CT-confirmed disease progression and received immediate second-line systemic treatment, which for three patients included autologous stem-cell transplantation. All but two remain in complete remission. All the remaining 27 patients with score 4 or 5 received mediastinal RT, of whom four had relapse or progression after irradiation, with three deaths recorded. PET/CT scans were repeated after RT in 23 of 27 patients with PET scores 4 to 5, and 11 (48%) of 23 became negative (Deauville score < 3). Of the remaining 12, three had score 3, five had score 4, and four had score 5. Notably, only three patients with persistent positive PET/CT scans had clinical progression (all with score 5).

Among 115 patients with a central PET review, despite only 47% of patients attaining CMR after chemoimmunotherapy, the estimated 5-year OS and PFS rates were 95% (95% CI, 89% to 98%) and 90% (95% CI, 82% to 94%), respectively. The achievement of CMR at 3 to 4 weeks after chemoimmunotherapy predicted a higher PFS ($P = .0044$) with high sensitivity but poor specificity (NPV of 98% but PPV of only 18%), and the difference in OS was also statistically significant ($P = .0298$). Patients with score 3 also had an excellent outcome, with no recurrence or progression. Thus, moving the cut point for the definition of a CMR from the MBP uptake to liver uptake increased the specificity (Fig 2) and the PPV rose from 18% to 32% without loss of sensitivity (Fig 3). The use of liver uptake as the cutoff for PET positivity resulted in a clearer distinction between risk subgroups, both in terms of PFS ($P < .001$) and OS ($P < .001$). The International Prognostic Index (IPI), age-adjusted IPI at diagnosis, and the chemotherapy regimen used did not significantly correlate with the PET response, although initial bulky disease (> 10 cm) was significantly associated with a persistent postchemotherapy residual uptake above the liver cutoff ($P = .005$). This correlation with tumor bulk was only of borderline significance for the MBP uptake cut point ($P = .05$).

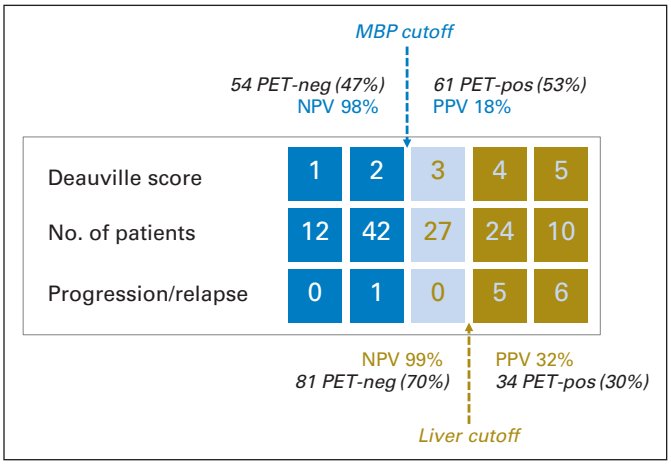

Fig 3. The chart summarizes the positron emission tomography (PET)/computed tomography interpretation after chemoimmunotherapy in a blind central review performed on 115 evaluable patients (upper panel) and the change in the positive predictive value (PPV) induced by a shift of the cut point for the definition of a complete metabolic remission from Deauville score 2 to score 3. MBP, mediastinal blood pool; NPV, negative predictive value; PET-neg, PET negative; PET-pos, PET positive.

DISCUSSION

This is the largest prospective study of the results of [^{18}F]FDG PET/CT scanning in PMLBCL. The results of treatment with rituximab and anthracycline-containing chemotherapy in this series in which the majority of patients received consolidation RT are favorable, with more than 90% projected to be alive and progression-free at 5 years despite a low proportion (47%) classified as CMR by the conventional IHP criteria.

This study is also a first attempt to validate the use of PET/CT scanning in restaging an aggressive lymphoma at the completion of chemotherapy by using the 5-point scale originally developed for interim PET evaluation during the treatment of DLBCL and Hodgkin lymphoma.[18] A cutoff for PET positivity below the uptake in the liver discriminates most effectively between groups of patients with PMLBCL at high or low risk of treatment failure.

Although the outcomes of treatment were good, after chemoimmunotherapy we saw a persistently positive PET scan in more than half the patients (53%; score 3 to 5), which contributed to a PPV significantly lower than that reported for other types of DLBCL and Hodgkin lymphoma. In those previous studies (mainly conducted in the pre-rituximab era) the PPV of restaging PET ranged between 60% and 100%.[23] A retrospective study of PMLBCL from BCCA, so far presented only as a meeting abstract, reported a PET-positive rate of 41%, a figure higher than in other patients with DLBCL, despite good clinical outcomes overall following RT.[16]

Similarly, a series of patients treated with the infusional dose-adjusted R-EPOCH (DA-R-EPOCH) regimen showed 50% PET positivity, defined by [^{18}F]FDG uptake greater than the MBP uptake at the completion of chemotherapy, with only three of 18 treatment failures, all among patients with residual disease at the completion of chemotherapy without the use of consolidation RT.[9] All the patients who had recurrences had a standardized uptake value of at least 5, and the authors therefore suggested that RT might reasonably be omitted for nearly all patients treated with this regimen.[9] Our own findings probably reflect a similarly high false-positive rate, although PMLBCL

is clearly radiosensitive, so it is also possible that the almost universal use of consolidation RT to the mediastinum in this study (and for PET-positive residual masses in the BCCA study[16]) was capable of eradicating residual lymphoma in some instances. This might also be the case in the group with score 4 to 5, although about half the patients did not show a Deauville score improvement after RT. There were still four recurrences among the 27 patients treated with RT in this setting, and some investigators would advocate more intensive salvage chemotherapy for these patients. This was the approach for seven PET-positive patients who were found to have CT-confirmed disease progression with a good success rate, although only three patients went on to have myeloablative treatment, and another two were apparently cured by second-line chemotherapy and RT. In our study, the three patients with score 3 who were not irradiated also remained disease-free, but clearly these numbers are too small to draw firm conclusions.

It has been suggested that an inflammatory response produced by the addition of rituximab to chemotherapy may cause increased [^{18}F]FDG uptake and thus reduce PPV and specificity,[24] something made more likely by the conduct of post-treatment scans less than a month after the completion of chemoimmunotherapy. This range was chosen as the best compromise to enable all participating centers to avoid overlap between PET restaging and procedures for planning RT. A longer interval might result in a lower rate of false-positive scans, but at the potential risk of missing the opportunity for curative RT in some patients with persistent disease. Another potential cause of false-positive PET results is thymic rebound, which is particularly relevant in this group, given the location of the disease and their generally young age.

Our findings suggest that using the conventional cutoff for PET positivity according to the IHP criteria may not be the most appropriate and may overestimate the proportion of patients with residual disease. They suggest that the liver uptake (the upper limit for score 3), which is consistently higher than the MBP activity, may be a better cutoff to identify CMR and those patients with a significant risk of relapse or progression. However, it should be noted that the majority of patients with PET/CT score 3 (89%) received RT, so this finding may not necessarily apply to patients treated with chemoimmunotherapy alone.

The excellent outcome for patients reaching conventional CMR suggest that it may be possible to safely reduce the number of patients to whom RT is given, although the numbers not irradiated were too small for drawing reliable conclusions in this study and will require prospective trials for confirmation. The study from the National Cancer Institute and Stanford University that used DA-R-EPOCH has further strengthened this argument, with 95% event-free survival among 67 patients, only two of whom received RT.[9] This represents a selected series of patients accrued over more than a decade, but it confirms the impression that even a positive [^{18}F]FDG-PET scan is by no means a certain indicator of active PMLBCL. It is possible that DA-R-EPOCH is qualitatively different from R-CHOP or the dose-dense regimens mainly used in this series that resulted in more durable remissions, although the rates of metabolic response are strikingly similar: 50% after DA-R-EPOCH, 47% in this series, and 41% in the series from BCCA. The recurrence rate among PET-negative patients after R-CHOP managed without RT in BCCA was six of 34 (and one of three in this series), compared with none of the 51 treated with RT in this series, suggesting that at least a small proportion of PET-negative patients may benefit from consolidation RT, although a prospective randomized trial is certainly required to confirm or refute this. The ongoing IELSG-37 randomized trial (NCT01599559) will assess whether RT can be safely omitted in patients with PMLBCL in CMR after conventional chemoimmunotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
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Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

Recruiting Centers (Investigators) Contributing With at Least One Patient Onto the IELSG 26 Study Were As Follows:

Chile (PANDA): Santiago—Medicine Faculty, Del Salvador Hospital (*Maria Elena Cabrera*); **Italy (FIL):** Alessandria—Haematology, SS Antonio e Biagio Hospital (*Flavia Salvi*); Bari—Haematology, Clinical and Experimental Oncology, IRCCS Istituto Tumori Giovanni Paolo II (*Attilio Guarini*); Bologna—Onco-Haematology "Seragnoli," Sant'Orsola Policlinico (*Pier Luigi Zizani*); Cagliari—Haematology, Businco Hospital (*Maria Giuseppina Cabras*); Firenze—Haematology, Careggi Policlinico (*Luigi Rigacci*); Messina—Haematology, Papardo Hospital (*Maura Brugiatelli*); Milano—Haematology, Nigurada Ca'granda Hospital (*Livio Gargantini, Enrica Morra*); Medical Oncology, San Raffaele Hospital ((*Andrès J.M. Ferreri*); Modena—Oncology and Haematology, Modena and Reggio Emilia University (*Stefano Luminari, Massimo Federico*); Pavia—Haematology, S. Matteo Policlinico (*Luca Arcaini, Manuel Gotti, Ercole Brusamolino*); Reggio Calabria—Haematology, Bianchi-Melacrino-Morelli Hospitals (*Caterina Stelitano*); Reggio Emilia—Santa Maria Nuova Hospital (*Francesco Merli*); Roma—Haematology, Sapienza University (*Erica Finolezzi, Eleonora Russo, Maurizio Martelli*); Rozzano—Oncology and Haematology, Humanitas Clinical Institute (*Monica Balzarotti, Armando Santoro*); Torino—Haematology, S. Giovanni Battista Hospital (*Umberto Vitolo*); Varese—Medical Oncology, Fondazione Macchi Hospital (*Graziella Pinotti*); **Spain:** Barcelona—Hematology, Hospital Clinic (*Armando Lopez Guillermo*); **Switzerland:** Bellinzona—Oncology Institute of Southern Switzerland (*Emanuele Zucca, Anastasios Stathis, Michele Ghielmini, Franco Cavalli*); **United Kingdom:** London—Haematology, The Royal Marsden Hospital (*David Cunningham*); Medical Oncology, St Bartholomew's Hospital (*Silvia Montoto*)

Positron Emission Tomography/Computed Tomography Imaging Methodology for the International Extranodal Lymphoma Study Group IESLG-26 Study

Positron emission tomography/computed tomography (PET/CT) scans were planned at baseline and 3 to 4 weeks after the end of the chemoimmunotherapy. Patients receiving mediastinal irradiation were also rescanned after at least 2 months from the completion of radiotherapy. PET/CT imaging was permitted at other time points (eg, midchemotherapy) according to local protocols, but the results were not used to alter the planned therapy.

Baseline PET/CT scans were carried out within 14 days before commencing treatment. Prior treatment with corticosteroids alone for up to 1 week for the relief of local compressive symptoms was allowed. For 20 patients who required urgent treatment and for whom the PET scan could not be performed before therapy started, the baseline scan was omitted after discussion with the clinical coordinators.

PET/CT imaging was performed on full-ring integrated PET/CT systems. PET and CT images were acquired in the same session. The CT scan with a low-dose protocol was used for attenuation correction of the PET images and consecutive qualitative analysis.

Intravenous CT contrast media were not administered before the PET study. If a diagnostic CT scan using contrast was routinely performed as part of the PET/CT examination, it was performed after the PET scan.

Baseline and response PET/CT examinations for a patient were performed in the same center by using the same PET/CT system. Each center was required to follow active quality control and quality assessment programs.

All patients fasted for at least 6 hours before the injection of 250 to 370 MBq (4.5 MBq/kg) of [^{18}F]fluorodeoxyglucose ([^{18}F]FDG). Serum glucose level measured before injection of the radiotracer was less than 160 mg/dL in all patients. After a standardized uptake time of 60 minutes ($\pm$ 5 minutes), PET data were acquired from the midthigh toward the base of the skull in two-dimensional or three-dimensional mode. The PET acquisition time was at least 3 minutes per cradle position.

For each examination, the center sent the data on CD-ROM together with essential information on the PET/CT acquisition to the core laboratory for central review.

The achievement of a metabolic complete response was defined, according to the criteria of the International Harmonization Project (IHP) in Lymphoma,[17] by a completely PET-negative scan or one having minimal residual uptake less than the mediastinal blood pool activity.

The postchemotherapy and postradiotherapy scans were also assessed according to the Deauville criteria (initially developed to help interpret the interim PET scans during the treatment of diffuse large B-cell lymphoma and Hodgkin lymphoma), which adopted a 5-point scale[18] for reporting the visual analysis. The [^{18}F]FDG uptake of any residual lesion was scored by using mediastinal blood pool activity (ie, large mediastinal vessels excluding the uptake in the aortic wall) and liver as reference settings according to the 5-point scale. Diffuse uptake in the spleen or marrow on the post-chemoimmunotherapy scan considered a result of chemotherapy was not scored as active disease. The patients achieving a metabolic complete response according to the IHP criteria equate to score 1 or 2 on the Deauville scale.

Table A1. Rituximab-Chemotherapy Regimens

Chemotherapy	Cycle	Dose (mg/m^2 unless otherwise specified)	Route of Administration	Days
R-MACOP-B				
Rituximab		375	IV	1, 22, 43, 64, 85, 106
Cyclophosphamide		350	IV	1, 15, 29, 43, 57, 71
Doxorubicin		50	IV	1, 15, 29, 43, 57, 71
Methotrexate		400	IV	8, 36, 64
Vincristine		1.4	IV	8, 22, 36, 50, 64, 78
Bleomycin		10	IV	22, 50, 78
Prednisone		40	PO	1 to 84, then tail off
R-VACOP-B				
Rituximab		375	IV	1, 22, 43, 64, 85, 106
Cyclophosphamide		350	IV	1, 29, 57
Doxorubicin		50	IV	1, 15, 29, 43, 57, 71
Etoposide		75	IV	15, 16, 43, 44, 71, 72
Vincristine		1.4	IV	8, 22, 36, 50, 64, 78
Bleomycin		10	IV	8, 22, 36, 50, 64, 78
Prednisone		40	PO	1 to 84, then tail off
R-CHOP 21	21-day			
Rituximab		375	IV	1
Cyclophosphamide		750	IV	1
Doxorubicin		50	IV	1
Vincristine		1.4	IV	1
Prednisone		100 mg	PO	1 to 5
R-CHOP 14	14-day			
Rituximab		375	IV	1
Cyclophosphamide		750	IV	1
Doxorubicin		50	IV	1
Vincristine		1.4	IV	1
Prednisone		100 mg	PO	1 to 5
G-CSF		300 mg	SC	5 to 12
Intensified R-CHOP 14	14-day			
Rituximab		375	IV	1
Cyclophosphamide		1,750	IV	1
Doxorubicin		75	IV	1
Vincristine		1.4	IV	1
Prednisone		100 mg	PO	1 to 5
G-CSF		300 mg	SC	6 to 12

Abbreviations: G-CSF, granulocyte colony-stimulating factor; IV, intravenously; PO, orally; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-MACOP-B, rituximab plus methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; R-VACOP-B, rituximab plus etoposide, doxorubicin, cyclophosphamide, vincristine, prednisone, and bleomycin; SC, subcutaneously.