

## Original article

# Interim fluorine-18 fluorodeoxyglucose PET-computed tomography and cell of origin by immunohistochemistry predicts progression-free and overall survival in diffuse large B-cell lymphoma patients in the rituximab era

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**Objective** The aim of this study was to analyze the prognostic value of the interim PET (iPET)-computed tomography (CT) (iPET-CT) after two cycles of immunochemotherapy with the R-CHOP protocol in patients with diffuse large B-cell non-Hodgkin lymphoma (DLBCL) treated with a curative intent in combination with the neoplastic cell origin defined by Hans's immunohistochemistry algorithm followed in a reference center for cancer treatment in Brazil.

**Materials and methods** We prospectively evaluated 147 DLBCL patients treated with R-CHOP-21 to assess the value of the International Prognostic Index, iPET-CT, and cell of origin by immunohistochemistry as prognostic markers in the rituximab era. Fluorine-18 fluorodeoxyglucose PET-CT was performed after two cycles (iPET-CT) and at the end of treatment in 111 patients. Lymphoma cases were categorized into germinal center (GC) and nongerminal center subtypes by immunohistochemistry according to Hans's algorithm.

**Results** The median age of GC-DLBCL patients (52.7 years) was lower than that of nongerminal center-DLBCL patients (59.4 years) ( $P=0.021$ ); in addition, it was lower in patients with negative iPET-CT findings (52.7 years) versus positive findings (59.4 years) ( $P=0.031$ ). The overall

survival at 48 months was 100% for iPET-CT-negative GC-DLBCL patients and 61.2% for iPET-CT-positive GC-DLBCL patients ( $P=0.002$ ). Progression-free survival at 30 months was 100% for iPET-CT-negative GC-DLBCL patients and 60.3% for iPET-CT-positive GC-DLBCL patients ( $P=0.001$ ).

**Conclusion** We conclude that iPET-CT associated with cell of origin identified a very good prognostic group in DLBCL patients treated with R-CHOP. *Nucl Med Commun* 37:1095–1101 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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**Keywords:** diffuse large B-cell lymphoma, immunohistochemistry, interim <sup>18</sup>F-FDG PET-CT, polychemotherapy, prognostic, rituximab

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## Introduction

Diffuse large B-cell lymphoma (DLBCL) represents the most common subtype of non-Hodgkin's lymphoma (NHL) [1] and corresponds to 49.5% of all NHL in our institution [2]. The WHO classification recognizes various subtypes of DLBCL on the basis of morphology, immunohistochemistry (IHC), and molecular analysis [1]. Although DLBCL is considered a heterogeneous

disease, patients have been treated uniformly with anti-CD20 monoclonal antibody (rituximab) and doxorubicin-based chemotherapy regimens [3,4]. Unfortunately, almost half of DLBCL patients remain incurable; thus, it is critical to recognize these patients and improve their prognosis. Before the rituximab era, one of the best ways to identify NHL high-risk groups was the International Prognostic Index (IPI), which is based on clinical features such as age, performance status, stage, number of extranodal sites, and lactate dehydrogenase (LDH) [5]. Although clinical prognostic factors are commonly used, they cannot identify a risk group with a less than 50% chance of cure in the rituximab era [5,6]. By gene expression profile (GEP), Alizadeh *et al.* [7] showed that DLBCL could be stratified into different risk groups

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independent of IPI. In this study, patients with malignant cells with a gene signature similar to germinal center (GC) cells presented with a better prognosis than patients with signatures similar to activated B cells [7]. Because microarray analysis is unavailable in daily lymphoma practice, IHC algorithms have been proposed by analyzing different proteins such as BCL-6, MUM-1, CD10, and FOXP1 and DLBCL cases can be classified into GC-like or nongermlinal center (NGC)-like subtypes [8–11]. However, the use of these prognostic indicators has been questioned in the rituximab era [6,11,12]. Currently, PET-computed tomography (CT) with fluorine-18 fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) is recommended at diagnosis and at the end of treatment of DLBCL to improve the accuracy of staging and response evaluation, respectively [13]. Recently, however, this technology has been tested as a prognostic marker for DLBCL and some trials showed better survival for PET-CT-negative patients after two out of three cycles than for PET-CT-positive patients [14]. However, the impact of interim PET-CT (iPET-CT) as a prognostic tool for DLBCL remains controversial [15]. Furthermore, iPET-CT should not be used to guide therapy and is not recommended outside clinical trials [13].

In clinical practice, the best way to accurately discriminate different prognostic risk groups in DLBCL is not clear. The primary aim of this prospective cohort study was to investigate the association between the clinical prognostic index by IPI, the image-based response assessed by iPET-CT and DLBCL cell of origin (COO), using the Hans algorithm as prognosis predictors in patients treated with R-CHOP-21. Our initial hypothesis was that these three variables could be useful to identify different risk groups in DLBCL.

## Patients and methods

### Study design and end points

This was a unicentric and prospective study with the primary end point of overall survival (OS). OS was defined as the time from the date of diagnosis until the date of death as a result of any cause or last patient follow-up. The secondary end point was progression-free survival (PFS) and was defined as the time from the date of diagnosis to the date of disease progression, relapse, or death as a result of any cause or last patient follow-up.

### Patients

After receiving approval from the Ethics Committees of HC-FMUSP, we prospectively evaluated 147 consecutive de-novo adult DLBCL patients, all treated at the Clinical Hospital/Sao Paulo Cancer Institute of the Medical School of Sao Paulo University (FMUSP), from June 2008 to November 2011. Written informed consent was obtained from all patients. The tumor histology was reviewed by two experts in hematopathology from the Pathology Department at FMUSP. Baseline clinical and

disease features, including age, sex, Ann Arbor stage, number of extranodal sites involved in lymphoma, LDH dosage, performance status, B symptoms, and bulky disease (tumor size  $\geq 10$  cm or cardiothoracic index over 1/3), were obtained from medical records by a specific researcher. Also, hepatitis B virus, hepatitis C virus, HIV serology and kidney, liver, and biochemical exams; ECG; bone marrow biopsy; neck, chest, abdomen, and pelvis CT scan; and whole-body tomography with  $^{18}\text{F}$ -FDG-PET-CT were performed at diagnosis. The IPI was calculated for all patients as originally described [5]. Patients were treated with 6–8 cycles of R-CHOP-21 (rituximab: 375 mg/sqm intravenously day 1, cyclophosphamide: 750 mg/sqm intravenously day 1, vincristine: 1.4 mg/sqm maximum of 2 mg intravenously day 1, doxorubicin 50 mg/sqm intravenously day 1, and prednisone 100 mg/day orally from day 1 to 5). Patients with stage I/II nonbulky disease were treated with four cycles of R-CHOP-21 plus radiotherapy. Patients with bulky disease and involvement of the sinuses, bones, testes, breast, and Waldeyer involvement underwent 3600 cGy radiation at the end of the treatment. Patients with involvement of the testes, ovaries, breast, sinuses, paravertebral region, and high IPI received four intrathecal injections of methotrexate (12 mg) and dexamethasone (2 mg) as prophylaxis against relapse in the central nervous system. Patients were re-evaluated after two cycles of chemotherapy with a PET-CT (iPET-CT), after four cycles with a CT scan, and at the end of treatment with PET-CT and bone marrow biopsy in cases with bone marrow involvement at diagnosis. The response at the end of treatment was categorized as complete remission, partial remission, or progressive disease according to the Cheson criteria [13]. Patients in complete remission were followed every 2 months in the first year, 3 months in the second year, 6 months in the 3rd to 4th year, and once a year for life after 5 years. The refractory and relapsed patients received an IVAC-modified regimen [16] as salvage therapy, followed by autologous stem cell transplantation. Patients with HIV and severe congestive heart failure were not included in the study.

### Immunohistochemistry

Patients underwent an incisional or excisional biopsy, and the tumor was classified using hematoxylin–eosin and IHC staining as originally described [1]. Immunohistochemical staining by immunoperoxidase was performed on 4 mm sections from formalin-fixed paraffin-embedded tissue using standard procedures [17]. For CD10 staining, we used clone P1F6 (Novocastra, Newcastle, UK) at a 1:1000 dilution. We used clone MUM-1p (Dako, Glostrup, Denmark) diluted 1:2000 for BCL6 and clone 56C6 (Novocastra) for MUM1 diluted 1:2000. The GC and non-GC phenotypes were defined using the decision tree established by Hans *et al.* [8] with indicated cutoffs. All cases were centrally reviewed by two experts in

hematopathology from the Pathology Department at FMUSP.

### **<sup>18</sup>F-FDG PET-CT scan protocol**

Of the 147 patients, 139/147 (94.5%) underwent staging with a dedicated PET-scan or on an integrated PET-CT scan (baseline PET) before starting any therapy for lymphoma, including corticosteroids. iPET-CT was performed at day 20 after the 2nd cycle of chemotherapy in 111/147 (75.5%) patients. Thirty-six patients did not undergo iPET-CT because 12 of them died before the procedure and 24 of them because of logistical issues. End therapy PET was performed 4–8 weeks after chemotherapy (minimum 12 weeks in cases of radiotherapy) in 122/147 (82.9%) patients.

Patients fasted for at least 6 h before the <sup>18</sup>F-FDG injection, and their serum glucose level was measured before administration to ensure optimal blood glucose levels lower than 180 mg/ml. Each patient was injected intravenously with a standard dose of 5 MBq/kg of <sup>18</sup>F-FDG after resting for 60 min. A whole-body acquisition was performed 60 min after injection. The <sup>18</sup>F-FDG-PET-CT scans were performed in two sites: (a) on an integrated PET/CT system associated with a 16-channel CT (Discovery PET/CT 690; GE Healthcare, Waukesha, Wisconsin, USA) or (b) in a dedicated PET-scan equipment (PET Advance Nxi; GE Healthcare), interpreted with concurrently CT scans of the neck, chest, abdomen, and pelvis at the same institution. PET/CT scans were acquired from the base of the skull to the mid-thigh and dedicated PET scans from the top of the skull to the mid-thigh. Analysis of staging PET-CT was carried out visually by at least one certified nuclear medicine physician and a radiologist with experience in PET/CT interpretation. End of treatment and iPET-CT analysis were reported according to the 5-point scale (5-PS) using the Deauville criteria. Scores 1, 2, and 3 were considered to indicate a complete metabolic response (CMR or PET negative) and scores 4 and 5 were considered to indicate a partial metabolic response (residual metabolic disease or PET positive) [18]. The results of all PET scans were then centrally reviewed by one board-certified nuclear medicine physician (A.M.C.), who was blinded to clinical details and patient outcomes.

### **Statistical analysis**

Statistical analyses were carried out using IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, New York, USA). OS was calculated from the date of diagnosis to death or last patient follow-up. PFS was calculated from the date of diagnosis until disease progression, relapse, or death (from any cause) or last patient follow-up as described previously [13]. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was carried out using a Cox proportional-hazards regression model and a hazard ratio (HR) was calculated.

Differences between the results were considered statistically significant if *P* value less than 0.05.

## **Results**

The clinical characteristics of 111 available for iPET-CT patients are shown in Table 1. The median age of the patients was 58.9 years (16–86) and 85 patients (57.8%) were women. The median follow-up duration of patients was 41.5 months (range 0.6–71.1 months). The OS rate at 48 months was 73.8% and PFS was 84.3%.

### **Immunohistochemistry**

IHC was performed for 114 patients and 56/114 (49.1%) were classified as GC-DLBCL and 58/114 (50.9%) as non-GC-DLBCL (Table 1). The median age of GC patients (52.7 years) was statistically significantly lower than that of non-GC patients (59.4 years) (*P*=0.021). At follow-up (median: 42.8 months, range: 6–71.2 months), OS was 74.1% for GC-DLBCL and 78.2% for non-GC-DLBCL (*P*=0.86) patients. At follow-up (median: 48 months, range: 6–52.4 months), the PFS was 85% for GC and 82% for non-GC-DLBCL (*P*=0.76).

### **<sup>18</sup>F-FDG-PET-CT scan**

PET-CT was performed in 139/147 (94.5%) patients and was positive in 135/139 (97.2%) at diagnosis. PET-CT changed the Ann Arbor staging in 40/139 (28.7%) patients, with 23/139 (16.5%) patients upstaged and 17/139 (12.2%) downstaged. The iPET-CT was available for 111/147 (75.5%) patients; it was negative in 60/111 patients (54.1%) and positive in 51/111 (45.9%) patients. The median age of iPET-CT-negative patients was 58 years and that of iPET-CT-positive patients was 64 years (*P*=0.051). In the iPET-negative group, 25/111 (22.5%) patients received radiotherapy versus 23/111 (20.7%) in the positive group. The OS rates at 48 months were 89.3% for iPET-CT-negative patients and 77.5% for iPET-CT-positive patients (*P*=0.04), and the PFS were 87.7 and 81.2%, respectively (*P*=0.44).

### **DLBCL classification and iPET-CT prognostic value**

The iPET-CT and IHC analysis were carried out in 78 patients and showed that OS at 48 months in GC-DLBCL patients was 100% for iPET-CT-negative patients and 61.2% for iPET-CT-positive patients (*P*=0.002) (Fig. 1). PFS was 100% for iPET-CT-negative patients and 60.3% for iPET-CT-positive patients (*P*=0.001) (Fig. 2). There were no statistically significant differences for OS or PFS in the non-GC-DLBCL subgroup according to interim <sup>18</sup>F-FDG-PET.

### **Univariate and multivariate analyses**

To validate the prognostic value impact of iPET, univariate and multivariate analyses were carried out using factors that could have influenced patient prognosis and previously known prognostic factors such as sex (male vs. female), age ( $\leq 60$  vs.  $> 60$  years), Ann Arbor stage (I/II

Table 1 Patient characteristics according to interim PET/<sup>18</sup>F-FDG and GC/non-GC classification

Characteristics	All (n = 147) [n (%)]	Interim PET (n = 111) [n (%)]			Cell of origin (n = 114) [n (%)]		
		Negative	Positive	P value	GC	Non-GC	P value
Age (year)							
Median	58.9	56.5	58.3	0.512	55.4	62	0.021
≤ 60	72 (49)	35 (58.3)	23 (44.4)		33 (29.1)	24 (21)	
≥ 60	75 (51)	25 (41.7)	28 (54.9)		23 (20.1)	34 (29.8)	
Sex							
Female	85 (57.8)	35 (58.3)	26 (51)	0.451	29 (51.8)	35 (60.3)	0.450
Male	62 (42.2)	25 (41.7)	25 (49)		27 (48.2)	23 (39.7)	
ECOG <sup>a</sup>							
0	34 (30.6)	20 (33.3)	14 (27.5)	0.474	20 (36.4)	13 (22.4)	0.335
1	57 (51.4)	29 (48.3)	28 (54.9)		23 (41.8)	34 (58.6)	
2	8 (7.2)	3 (5)	5 (9.8)		3 (5.5)	4 (6.9)	
3	9 (8.1)	5 (8.3)	4 (7.8)		6 (10.9)	6 (10.3)	
4	3 (2.7)	3 (5)	0 (0)		3 (5.5)	1 (1.7)	
Extranodal sites <sup>b</sup>							
Yes	90 (61.6)	41 (69.5)	28 (54.9)	0.166	32 (58.2)	36 (62.1)	0.704
No	56 (38.4)	18 (30.5)	23 (45.1)		23 (41.8)	22 (37.9)	
B symptoms <sup>c</sup>							
No	43 (35)	21 (35)	13 (25.5)	0.553	21 (45.7)	14 (29.2)	0.135
Yes	80 (65)	31 (51.7)	31 (60.8)		25 (54.3)	34 (70.8)	
Ann Arbor stage <sup>d</sup>							
I	13 (8.9)	7 (11.7)	2 (3.9)	0.197	6 (10.9)	3 (5.2)	0.489
II	37 (25.3)	19 (31.7)	12 (23.5)		11 (20)	17 (29.3)	
III	22 (15.1)	5 (8.3)	9 (17.6)		10 (18.2)	8 (13.8)	
IV	74 (50.7)	29 (48.3)	28 (54.9)		28 (50.9)	30 (51.7)	
Bulky <sup>e</sup>							
No	99 (68.3)	40 (66.7)	36 (70.6)	0.687	31 (57.4)	47 (81)	0.008
Yes	46 (31.7)	20 (33.3)	15 (29.4)		23 (42.6)	11 (19)	
LDH							
≤ 1	73 (49.7)	30 (50)	28 (54.9)	0.148	31 (55.4)	28 (48.3)	0.254
> 1–2	50 (34)	25 (41.7)	14 (27.5)		19 (33.9)	22 (37.9)	
> 2–4	15 (10.2)	2 (3.3)	7 (13.7)		3 (5.4)	5 (8.6)	
> 4–6	5 (3.4)	2 (3.3)	2 (3.9)		0 (0)	3 (5.2)	
> 6–8	2 (1.4)	1 (1.7)	0 (0)		1 (1.8)	0 (0)	
> 8	2 (1.4)	0 (0)	0 (0)		2 (3.6)	0 (0)	
IPI <sup>f</sup>							
Low	41 (28.1)	22 (36.7)	13 (25.5)	0.405	17 (30.9)	15 (25.9)	0.961
L-I	43 (29.5)	16 (26.7)	17 (33.3)		16 (29.1)	18 (31)	
H-I	37 (25.3)	12 (20)	15 (29.4)		14 (25.5)	16 (27.6)	
High	25 (17.1)	10 (16.7)	6 (11.8)		8 (14.5)	9 (15.5)	

CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; <sup>18</sup>F-FDG, fluorine-18 fluorodeoxyglucose; GC, germinal center; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

<sup>a,b,d,f</sup>Ignored in one patient.

<sup>c</sup>Ignored in 24 patients.

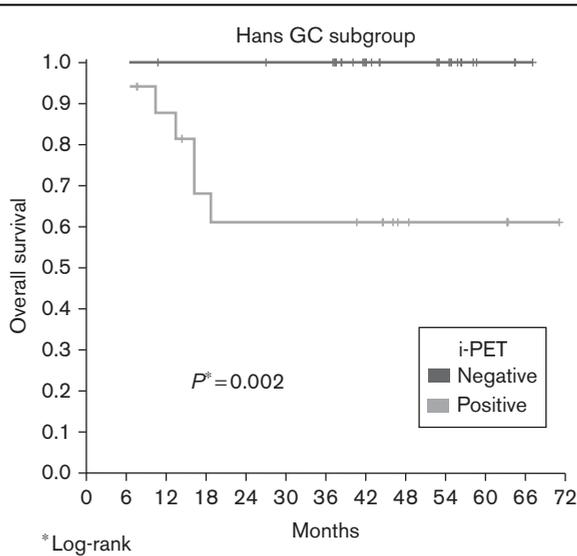
<sup>e</sup>Ignored in two patients.

vs. III/IV), B symptoms (yes vs. no), bulky disease (yes vs. no), extranodal involvement (0–1 vs. ≥ 2), iPET (positive vs. negative), LDH (normal vs. > normal), IPI (0–2 vs. ≥ 3), Eastern Cooperative Oncology Group (ECOG) (0–1 vs. ≥ 2), and IHC subgroup (GC vs. NGC). For OS, age more than 60 years ( $P=0.001$ ), III/IV stage ( $P=0.005$ ), IPI more than or equal to 3 ( $P<0.001$ ), iPET-CT-positive ( $P=0.047$ ), and ECOG at least 2 ( $P<0.001$ ) were associated with worse prognosis, but in multivariate analysis, only bulky disease ( $P=0.049$ ) and iPET-CT ( $P=0.045$ ) remained as prognostic factors. The HR associated with a positive iPET result was 5.02 [95% confidence interval (CI), 1.04–24.2] and that for bulky disease was 3.49 (1.00–13.50). For PFS, univariate analysis showed that male sex ( $P=0.024$ ), LDH > normal ( $P<0.001$ ), III/IV stage ( $P=0.022$ ), IPI at least 3 ( $P<0.034$ ), and ECOG more than or equal to 2 ( $P<0.022$ ) presented were associated with a poor

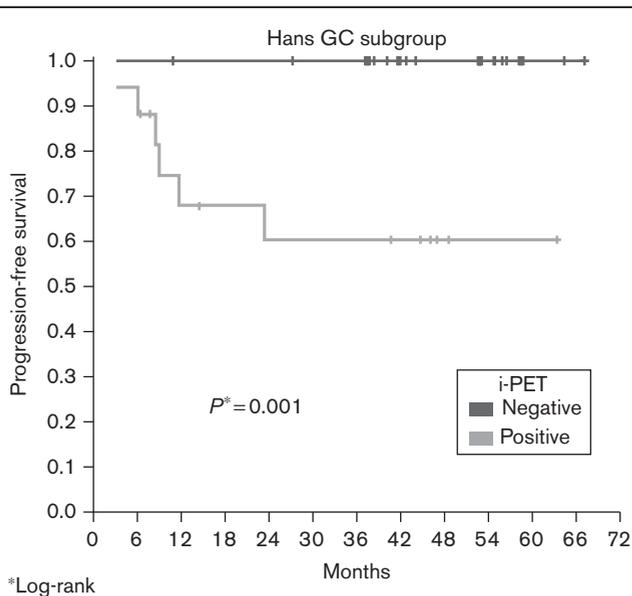
prognosis. However, in multivariate analysis, only male sex ( $P=0.035$ ) and LDH > 2 × normal ( $P=0.038$ ) had prognostic impact. The HR associated with male sex was 4.16 (95% CI, 1.10–15.69) and LDH > 2 × normal was 4.27 (94% CI, 1.08–16.87).

## Discussion

The aim of this study was to analyze the value of IPI, the COO determined by IHC, and iPET-CT as prognostic tools in DLBCL patients treated homogeneously with R-CHOP in a single center in Brazil. We showed that the GC subgroup, determined by IHC using Hans' algorithm, and a negative interim <sup>18</sup>F-FDG/PET after two cycles of treatment identified a group with a very good outcome. Among the GC-DLBCL patients, the OS at 48 months was 100% when the iPET-CT was negative and 61.2% when it was positive ( $P=0.002$ ). Furthermore, there was a better PFS for the GC subgroup when the

**Fig. 1**

Overall survival (OS) according to Hans subgroups and interim PET-CT. CT, computed tomography; GC, germinal center; iPET, interim PET.

**Fig. 2**

Progression-free survival (PFS) according to Hans subgroups and interim PET-CT. CT, computed tomography; GC, germinal center; iPET, interim PET.

iPET-CT was negative versus when it was positive (100 vs. 60.3%,  $P = 0.001$ ).

Lanic and colleagues reported similar results in GC-DLBCL patients who were iPET-CT-negative (OS and PFS of 100% in 2 years), and conversely, a poor prognosis group defined by iPET-CT-positive patients (33% OS

and 0% PFS in 2 years). In addition, the subgroup of patients who had signatures similar to activated B cells and were iPET-CT-negative showed an unfavorable outcome with a 2-year OS of 57% when iPET-CT was performed after three of four cycles of R-CHOP-like therapy [19]. It is noteworthy that the authors obtained similar outcomes using GEP or IHC to determine DLBCL origin. In our study, the subgroups of DLBCL were determined only by IHC analysis and Hans' algorithm [8]. This algorithm utilizes CD10, Bcl-6, and MUM-1/IRF4 markers in a hierarchical model with a 30% cut-off for positivity [8]. Although this is the most common criterion used to discriminate GC from non-GC subgroups of DLBCL, its prognostic value has been questioned in the rituximab era [20]. Even though a GEP is the standard used to determine the COO in DLBCL, it is not yet widely available, is time consuming, and expensive [21]. Recently, the feasibility of quantifying GEP using formalin-fixed paraffin-embedded tissue was published by Scott *et al.* [22] who described a robust method with more than 95% concordance of COO assignment between two independent laboratories. Although the results using Hans's algorithm correlate highly with those from GEP (86%), our findings need to be validated with new methodologies as reported above [21,22].

Before the rituximab era, IPI was the most important predictor of survival and the strongest index to recognize low-risk and high-risk NHL groups. However, this potential has been lost in the rituximab era [6]. Since functional imaging by  $^{18}\text{F}$ -FDG-PET has changed the paradigm of staging and response monitoring in DLBCL [13], iPET-CT after a few cycles of chemotherapy has been studied exhaustively as a prognostic marker to identify patients who could benefit from earlier change in treatment. However, the role of iPET-CT as a real prognostic tool remains unclear. Some studies have reported that a negative iPET-CT is associated with better OS and event-free survival [23]. Yet, other studies have not confirmed these outcomes, in part because they have used different analysis methods for  $^{18}\text{F}$ -FDG-PET imaging and determining response [15,24,25]. Lanic *et al.* [19], using GEPs in 57 cases of DLBCL, applied a semiquantitative method to interpret the iPET-CT using  $\text{SUV}_{\text{max}}$  reduction with a value less than 70% for slow metabolic responders and higher than 70% for fast responders [19,26,27]. In our trial, a qualitative method was utilized that considered the 5-PS (Deauville criteria) as recommended by the Consensus of the International Conference on Malignant Lymphomas Imaging Working Group [18,28]. The 5-PS is feasible, simple, and has high interobserver agreement, with an improvement in the positive predictive value. Furthermore, it has been validated for use at interim and end of treatment in several trials [28].

Using the 5-PS, we found that 60/111 (54.1%) patients were iPET-CT negative. Nols *et al.* [29] carried out an iPET-CT qualitative and quantitative analysis and reported that iPET was highly and independently predictive for PFS and OS in DLBCL and its negative predictive value (NPV) was improved by combination with IPI. Silvia and colleagues also observed similar outcomes in terms of OS and PFS using iPET-CT analyzed by qualitative or semiquantitative methods [24]. However, other data showed that a favorable iPET was not associated with improved PFS in DLBCL patients [30].

In our study, we showed that iPET and bulky disease were independently predictive for OS. However, in the subgroup of GC-DLBCL, iPET presented a high rate of NPV. IPI was predictive for OS and PFS only in univariate analysis. Similarly, using a qualitative method, Lanic *et al.* [19] detected 14/45 (31%) iPET-CT-negative cases, although 36/45 patients (80%) were characterized as slow responders on the basis of semiquantitative criteria. In this study, using qualitative and quantitative methods, the authors identified a favorable group of DLBCL patients, with GC origin and iPET-CT-negative [19].

Our results are in agreement with previous studies that showed that iPET-CT is associated with a high NPV, but low positive predictive value [15,31]. Thus, we believe that a negative iPET-CT result may be used as a prognostic predictor for survival, but not iPET-CT-positive. In the future, these 'favorable' patients could be selected to receive less chemotherapy, especially the most vulnerable and very elderly.

## Conclusion

The iPET-CT results and discrimination of DLBCL subgroups, on the basis of Hans' algorithm of IHC, identified the iPET-CT-negative GC subgroup to have a very good prognosis. Further studies are needed to confirm our results.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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