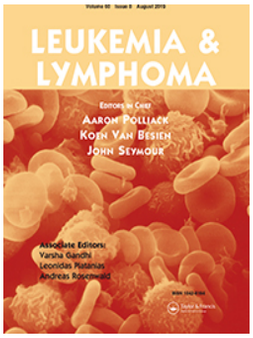

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ORIGINAL ARTICLE

The prognostic role of end of treatment FDG-PET-CT in patients with diffuse large B cell lymphoma can be improved by considering it with absolute monocyte count at diagnosis

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ABSTRACT

It is well established that some patients with diffuse large B-cell lymphoma (DLBCL) and the negative end of treatment PET-CT (EOT-PET-CT) will relapse, while a proportion with positive uptake can still obtain long-term EFS. We reviewed data of 200 consecutive, previously untreated patients with DLBCL recorded in Italy and Israel between 2007 and 2015. We found that patients with negative EOT-PET-CT with AMC $>$ 630/mmc have a 3-years EFS of 72%, compared to those with AMC $\leq$ 630/mmc that have an EFS of 84%. Furthermore, considering patients with positive EOT-PET-CT, those with AMC $>$ 630/mmc have a 3-years EFS of 8%, while those with AMC $\leq$ 630/mmc have an EFS of 38%. Thus, it appears that combining the gold standard for response evaluation EOT-PET-CT with a simple and inexpensive parameter like AMC at diagnosis, further improves prognostication in DLBCL. Applying this simple method can be useful for all doctors working in lymphoma clinical practice.

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AMC; EOT-PET-CT; DLBCL; prognosis

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), and 27,650 new cases were diagnosed in the United States in 2016 with an annual incidence of 3–4 persons per 100,000 in Europe [1,2]. In the immunochemotherapy era, more than 50% of patients with advanced-stage *de novo* DLBCL are cured with rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). A small proportion of the remaining patients are candidates for stem cell transplants, but only a fraction is cured [3,4]. 2-deoxy-2-[fluorine-18] fluoro-D-glucose-positron emission tomography-computed tomography (PET-CT), using the 5-points Deauville scale for evaluation [5] is currently considered the most valid method to define complete remission in patients with DLBCL [6]. The role of interim PET (I-PET-CT) in predicting the outcome is still ill-defined. Although the negative predictive value of I-PET-CT is high, inflammation and tumor necrosis may cause false-positive interpretation of results. Further, it is also common knowledge that a small proportion of patients with negative EOT-PET-CT will still relapse. For these reasons, it is important to improve the prognostic value of the EOT-PET-CT.

Here we planned a retrospective study with the aim of assessing whether combining the most utilized prognostic criteria at the time of diagnosis, such as International Prognostic Index (IPI) with EOT-PET-CT, would strengthen the already strong predictive value of EOT-PET-CT. Furthermore, since in our previous studies, we had already demonstrated the prognostic

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value of the absolute monocyte count (AMC), absolute lymphocyte count (ALC) and lymphocyte monocyte ratio (LMR) in patients with DLBCL [7], we also examined whether combining the result of EOT-PET-CT with AMC, ALC, and LMR at diagnosis can better stratify patients with DLBCL and improve the prognostic role of isolated PET-CT.

Patients and methods

This retrospective study included previously untreated patients diagnosed with DLBCL according to the World Health Organization criteria. We reviewed the clinical and laboratory data of consecutive 'therapy-'aïve' patients, recorded at Modena Cancer Center, S. Andrea Hospital, Rome and Bnai Zion Medical Center in Haifa, Israel from 2007 to 2015, who were uniformly treated with R-CHOP or R-CHOP-like regimens. The study was performed in accordance with the Declaration of Helsinki after approval by local institutional review boards. The inclusion criteria were: histopathological diagnosis of DLBCL (excluding double hit lymphoma), no previous therapy, age $\geq$18 years, HIV negativity, availability of all required clinical characteristics, peripheral blood differential count, baseline and end of treatment CT (BAS-CT and EOT-CT), EOT-PET-CT, data from long-term follow-up and survival outcomes. Response evaluation was based on 2007 Cheson criteria by CT scan with a visual interpretation of PET-CT [8]. PET results were revised using Deauville criteria; a score of 1–3 was considered PET negative while a score of 4 and 5 was regarded as PET positive. We choose not to evaluate whether baseline total metabolic tumor value and total lesion glycolysis interact with AMC since, to date, these parameters are not used in clinical routine due to the lack of agreement on the method to segment FDG-positive lesions. Based on our previous results we also included the value of AMC $>$ 630/mmc, of ALC $\leq$ 1000/mmc and of LMR $\leq$ 2.1, respectively, has already been considered to predict poor prognosis [7].

Statistical methods

Patients baseline characteristics are expressed as median and with 2.5–97.5 percentile for continuous variables and they are compared with Mann–Whitney or Kruskal–Wallis test. Categorical variables are reported as absolute and percent frequency. Comparison between categorical variables was performed using the Fisher's exact test or Chi^2 test. Event-free survival (EFS) is defined as the time from diagnosis to the time of last follow-up, or to one of the following events: any response other than complete remission (CR) at the end of therapy (chemotherapy ± radiotherapy), stable disease (SD), progression, relapse, or death from any cause. Overall survival (OS) is defined as the time from diagnosis to the last observation or death for any cause. EFS and OS are assessed by Kaplan–Meier estimates and groups of risk are compared using the log-rank test. The effect of covariate on hazard function is performed by means of Cox proportional hazard (PH) regression and expressed as hazard ratio (HR) with 95% confidence interval (95% CI).

Harrell's C is a rank parameter and it is computed as measures of the predictive power of Cox proportional hazard (PH) with a scale from 0–1 and is expected to be at least 0.5 for a positive predictor of lifetime, such as an inverse hazard ratio [9]. Statistical analyses were performed using Stata/IC 14.2 US package.

Results

Of the 236 registered patients, 16 were excluded as they received some form of therapy before starting R-CHOP or R-CHOP like regimens and 20 lacked EOT-PET-CT or documentation of AMC at time of diagnosis. The remaining 200 patients had a median age of 62 years (range 24–81 years) and a median AMC of 500/mmc (range 131–1368/mmc); 52% were male, 65% had clinical stage III–IV, 30% presented with B-symptoms, 39% had IPI scores 3–5, 31% had AMC $>$ 630/mm3, 47% had LDH upper normal limit, and 26% had more than 1 extranodal site of disease . We did not calculate National Comprehensive Cancer Network – International Prognostic Index score as one of the three centers recorded the value of LDH in dichotomous form as normal or high. Further, we were not able to combine the result of EOT-PET with COO by IHC and Nanostring with Lympho2Cx, since the cutoffs used for CD10, BCL2, BCL6, and MUM1 were similar but not the same in the 3 centers, and we are still centralizing samples for the nanostring analysis. The response was evaluated either with 2007 Cheson criteria by CT scan with a visual interpretation of PET-CT and with EOT-PET-CT after revision using Deauville criteria.

By Cheson criteria, 159 patients (80%) obtained CR and 41 (20%) had partial response, stable disease or progression on treatment. At EOT-PET-CT using the Deauville five-point scale, 21 patients (11%) and 15 (7%) had a score of 4 and 5, respectively (Table 1). Patients with EOT-PET CT score 4 and 5 were more frequently in clinical stage III–IV, with B-symptoms and IPI 3–5 at diagnosis, compared to patients with EOT PET-CT score 1–3; the differences were statistically

Table 1. Correlation between response evaluated by 2007 Cheson criteria using CT scan with visual interpretation of PET-CT and response evaluated on EOT-CT-PET according to Deauville score.

PET DV	CR	PR	SD	PD	NA	Total
1	113 (71%)	3 (12%)	–	2 (25%)	2 (100%)	120 (60%)
2	19 (12%)	3 (12%)	1 (20%)	1 (12%)		24 (12%)
3	13 (8%)	7 (27%)	–	–		20 (10%)
4	13 (8%)	8 (31%)	–	–		21 (11%)
5	1 (1%)	5 (19%)	4 (80%)	5 (62%)		15 (7%)
Total	159 (100%)	26 (100%)	5 (100%)	8 (100%)	2 (100%)	200 (100%)

DV: Deauville; CR: complete remission; PR: partial remission; SD: stable disease; PD: progression disease; NA: not assessed.

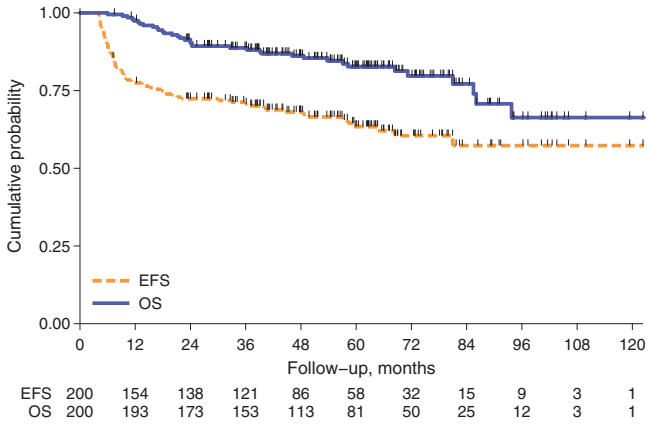

Figure 1. Event-free survival (EFS) and overall survival (OS) of the 200 patients enrolled in the study.

significant. After a median follow-up of 60 months (range 6–122 months) OS and EFS were 89% (CI% 95: 83–92%), and 71% (CI 95%: 64–77%), respectively (Figure 1). By univariate and multivariate analysis, we found statistically significant differences in EFS and OS between patients with EOT-PET-CT score 1–3 versus 4–5, IPI 0–2 versus IPI 3–5, AMC $>$ 630/mmc versus AMC $\leq$ 630/mmc, ALC $\leq$ 1000/mmc versus ALC $>$ 1000/mmc and LMR $\leq$ 2.1 versus LMR $>$ 2.1 Given the strong prognostic value of EOT-PET-CT and IPI, AMC, ALC, and LMR, we performed Cox proportional hazard regression analysis of EOT-PET-CT interacted with IPI and AMC, ALC, and LMR (Table 2, Supplementary Appendix Tables 1 and 2). We then evaluated the discrimination power by C-Harrel and we found a better prognostic value for AMC in comparison with IPI, ALC, and LMR resulting in EFS (0.706 vs 0.683, 0.700 and 0.690, respectively) and OS (0.696 vs 0.649, 0.632 and 0.637, respectively). Thus, we stratified patients on the basis of EOT-PET-CT scan results and AMC. We identified 4 risk groups: the 3-years EFS in the low risk patients (EOT-PET-CT negative and AMC $\leq$ 630/mmc) was 84% (CI 95% 76–-89%), in the intermediate 1 risk level (EOT-CT-PET negative and AMC $>$ 630/mmc) was 72% (CI 95% 57–83%), the intermediate 2 risk level

Table 2. Multivariate Cox proportional hazard regression in EFS and OS with EOT-CT-PET by AMC and IPI.

Factor	EFS - HR (95%CI)	*p*
PET - / AMC $\leq$ 630	1.00	
PET - / AMC $>$ 630	1.99 (1.08–3.66)	.027
PET + / AMC $\leq$ 630	6.43 (3.41–12.1)	$<$.001
PET + / AMC $>$ 630	9.47 (4.42–20.3)	$<$.001
Test for trend: $p < .001$		
Factor	EFS - HR (95%CI)	*p*
PET - / IPI 0–2	1.00	
PET - / IPI 3–5	1.29 (0.54–3.10)	.563
PET + / IPI 0–2	2.79 (0.90–8.70)	.076
PET + / IPI 3–5	5.97 (2.57–13.9)	$<$.001
Test for trend: $p < .001$		
Factor	OS - HR (95%CI)	*p*
PET - / AMC $\leq$ 630	1.00	
PET - / AMC $>$ 630	3.02 (1.29–7.10)	.011
PET + / AMC $\leq$ 630	5.98 (2.33–5.30)	$<$.001
PET + / AMC $>$ 630	6.39 (2.08–19.7)	$<$.001
Test for trend: $p < .001$		
Factor	OS - HR (95%CI)	*p*
PET - / IPI 0–2	1.00	
PET - / IPI 3–5	1.29 (0.54–3.10)	.563
PET + / IPI 0–2	2.79 (0.90–8.70)	.076
PET + / IPI 3–5	5.97 (2.57–13.9)	$<$.001
Test for trend: $p < .001$		

EFS: event free survival ($N = 200$, # failures = 70); OS: overall survival ($N = 200$, # failures = 36); AMC: absolute monocyte count; IPI: international prognostic index. HR: hazard ratio; 95%CI: 95% confidence interval.

(EOT-PET-TC positive and AMC $\leq$ 630/mmc) was 38% (CI 95% 19–56%) and high risk (EOT-PET-TC positive and AMC $>$ 630/mmc) was 8% (CI 95% 1–31%). Figure 2(a,b) and Figure 3(a,b) illustrate EFS and OS stratified by EOT-PET-CT and both AMC or IPI scores (Supplementary Appendix Figures 1 and 2 show EFS and OS stratified by EOT-CT-PET and ALC and by EOT-CT-PET, and LMR, respectively). As was predictable on the basis of the evaluation of discriminatory power by C-Harrel, by combining EOT-PET-CT and AMC we could define 4 risk groups that are more clearly distinguished than those determined by combining EOT-PET-CT and IPI scores alone. Even if, ALC are able to better discriminate the OS in EOT-PET-CT positive patients, we would like to underline that we consider more useful to recognize the patients with poor prognosis in the group with EOT-PET-CT negative patients.

Discussion

During the last 30 years, we have witnessed impressive advances in the field of imaging for lymphomas [5,10]. Juweid et al. [11] were the first to incorporate FDG- PET into standard response criteria. They noted that the long-term outcome of patients with DLBCL was similar regardless of whether they obtained a complete or partial response based on CT, while PET-CT had the ability to better predict patient outcome. In 2007, the International Harmonization Project on

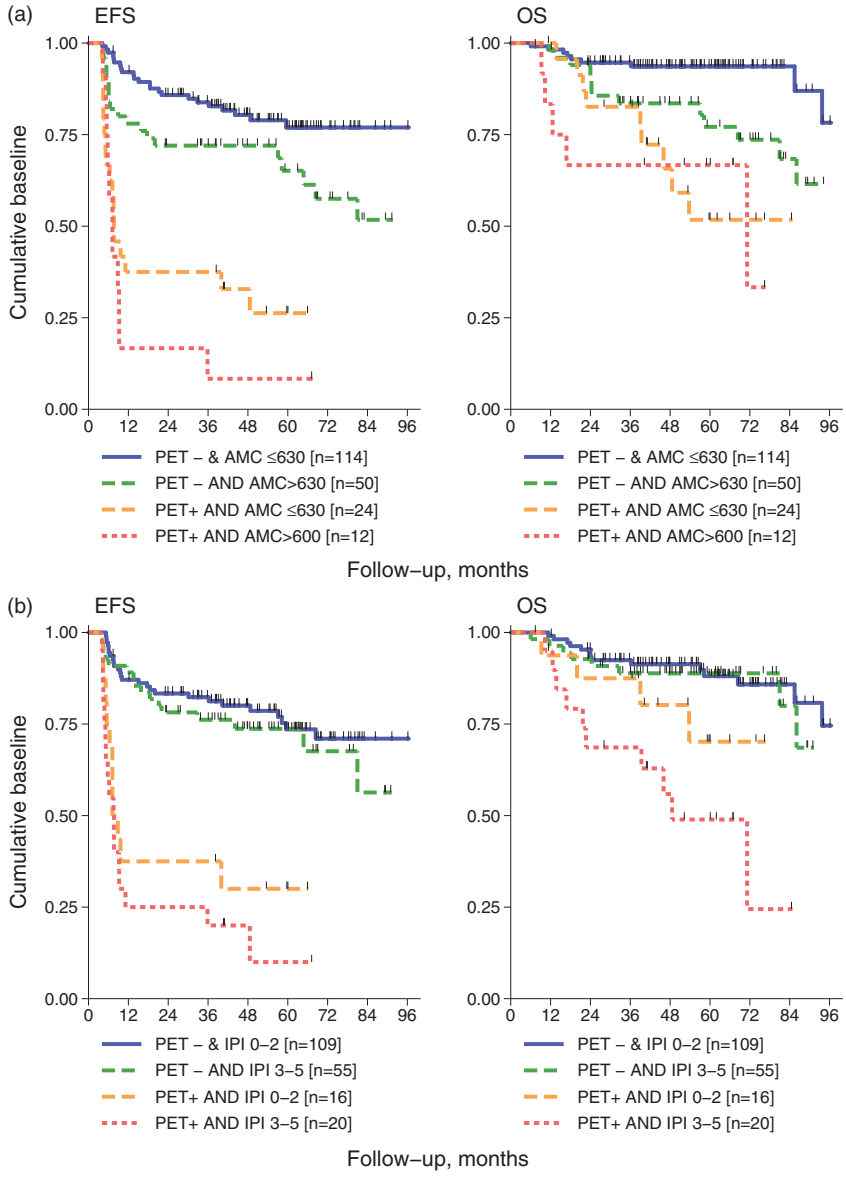

Figure 2. (a and b) Event-free survival (EFS) and overall survival (OS) stratified by EOT-PET-TC and absolute monocyte count (AMC).

Lymphoma described how best to perform visual interpretation of the PET-CT scan where the mediastinal blood pool was used as a comparator [8]. However, with this method variability among observers was a major limitation [12]. Later on, the use of the 5-points scale Deauville score for the interpretation of FDG-avid histologic subtypes improved the quality and homogeneity of the PET interpretation [5]. Thus, the Deauville score is currently considered the gold standard for response evaluation. However, it is a common experience that about 20% of patients with DLBCL in complete metabolic response at the end of treatment will relapse, while a small proportion of patients with EOT-PET-CT positive can still achieve long-term EFS. It is, therefore, extremely important to continue to develop strategies to improve the quality of the evaluation of the complete response at the end of induction treatment and perhaps also to improve the predictive value of the interim PET. In fact, it would be preferable and most important to predict the non-response to treatment/early relapse sooner rather than to just wait for eventual failure of treatment or for relapse.

Several studies evaluating the predictive value of pretreatment tumor metabolic volume (TMV) and of total lesion glycolysis (TLG) have shown conflicting results, probably related to the different baseline clinical characteristics and to the different software utilized [13]. A new interesting approach is to combine the total metabolic tumor volume (TMTV) measured

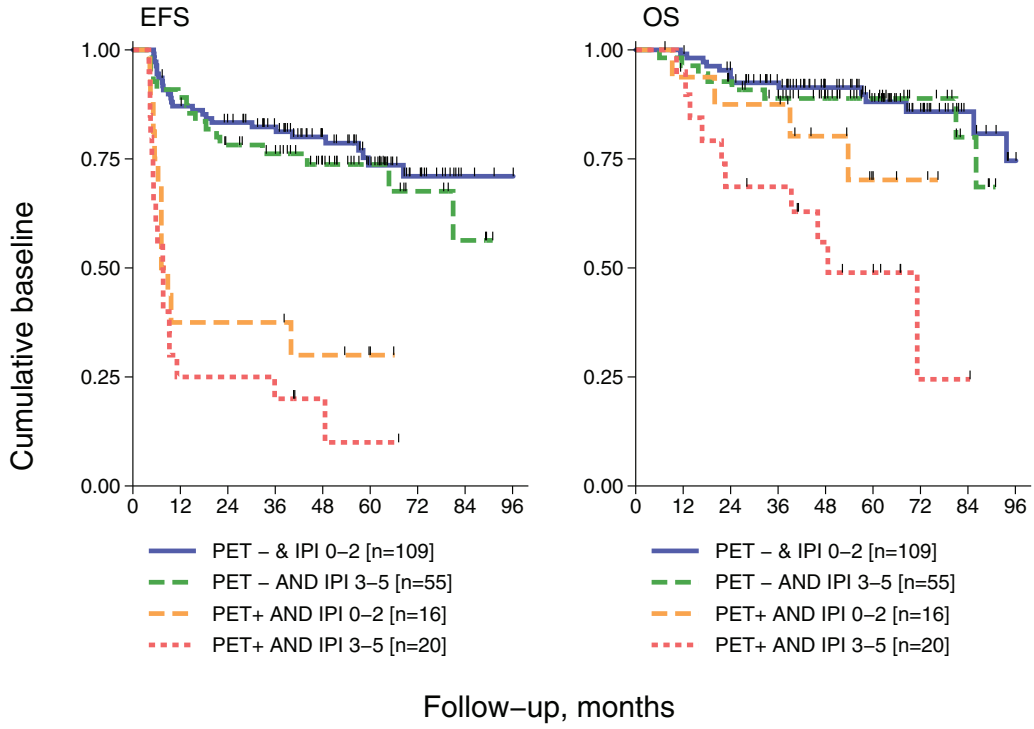

Figure 3. (a and b) Event-free survival (EFS) and overall survival (OS) stratified by EOT-PET-CT and IPI score.

on baseline PET-CT and cell of origin (COO) as determined by gene expression profiling (GEP). Toledano et al. [14] in a retrospective analysis including 114 patients with DLBCL treated with R-CHOP or R-CHOP-like chemotherapies showed that this method allows for better stratification of patients into different risk groups. However, the classification of COO by GEP analysis is not easy to perform in every institute, is not always reliably reproducible, and above all, this is only performed in a few specialized laboratories.

In the past few years, several studies have shown that ALC, AMC, and LMR are prognostic in DLBCL patients. Although cutoff values in the various studies were slightly different, similar conclusions were drawn by each research group separately, indicating that an elevated monocyte count or lymphopenia at diagnosis has an adverse impact on survival in non-Hodgkin lymphoma [7,15–24]. Cox et al. demonstrated that an ALC < 840 mmc at diagnosis has a marked adverse prognostic impact independently of the R-IPI score [15]. A validation study by Bari et al. confirmed these results but noted that the strong prognostic value of ALC was not evident in patients treated with chemotherapy without rituximab [22]. In our previous study [7], we analyzed a large cohort of 1017 therapy-naïve DLBCL patients with a median follow up of 48 months and 5-year overall survival rate of 68%. Using multivariate analysis, we showed that an ALC < 1000/mmc correlate with a high IPI score ($p < .001$) but was not statistically significant for overall survival in multivariate analysis [22]. Further, we showed that an elevated monocyte count retained a negative prognostic value even when adjusted for IPI. Although the precise mechanisms underlying the association between high AMC and low ALC poor prognosis in DLBCL are unclear, it could be hypothesized that the low ALC correlate with a reduction of the host immunological response to the tumor resulting in immune escape. Also, the prognostic significance of the AMC and the underlying biologic mechanism responsible for the relationship between peripheral blood monocytes and the clinical behavior of DLBCL are not fully understood. Gene expression profiling has identified the tumor microenvironment (TME) and host inflammatory response signatures as defining features of DLBCL. Lenz et al., [25] showed that stromal-2 signature genes encoded for markers of monocytic lineages that were predictive of unfavorable survival in DLBCL patients. Monocytic myeloid-derived suppressor cells and tumor-associated macrophages (TAMs) are probably the central cellular types in the stromal-2 signature, as these cells also exhibited prognostic significance for DLBCL [26,27]. Further, a number of studies have shown that a high AMC at diagnosis is useful for prognostic stratification of patients with DLBCL [7,16–18,20,21,23]. These studies clearly demonstrated that in the pathophysiology of DLBCL monocytes play an important role, that can be by their role as

progenitors of TAMs, particularly those with the M2 phenotype. Thus, low ALC and elevated AMC might reflect the host immune status, including the response to the tumor. In our series of 200 patients with DLBCL, AMC, ALC, and LMR all impact on survival outcomes. The evaluation of the discrimination power by C-Harrel shows that the AMC parameter is the one that best distinguishes the risk groups, especially if we consider the OS. Taking this one step further the results of the present study reported here demonstrate that by combining EOT-PET-CT results with the AMC at diagnosis, it is possible to clearly distinguish 4 risk -groups for treatment failure. It is indeed of interest that patients with negative EOT-PET-CT, but with AMC $>$ 630/mmc have a 3-years EFS of 72%, while those with negative EOT-CT-PET and AMC $\leq$ 630/mmc have a 3-years EFS of 84%. Furthermore, when considering patients with positive EOT-PET-CT, it is significant that patients with AMC $>$ 630/mmc have a 3-years EFS of 8%, while those with AMC $\leq$ 630/mmc have a far better EFS of 38%. Applying this information could be useful, not only for improved prognostic stratification, but also, in making an early decision when to employ a more aggressive therapeutic approach. We are fully aware of the fact that our study has some limitations as it is retrospective, includes a relatively small number of patients, and obviously still needs validation in a much larger group of patients. On the other hand, we also showed that by combining the current 'gold standard' used to evaluate response - EOT-PET-CT, with a simple, easily applied and inexpensive parameter, AMC at diagnosis, it is possible to further upgrade prognostication in the field of DLBCL. While waiting for more refined methods like those based on genomic investigation to be routinely available in common practice in the future, we proposed that this simple method could be a useful guide for physicians involved in the clinical practice of lymphoma in the 'real world' outside of larger medical centers.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article online at https://doi.org/10.1080/10428194.2018.1564049.

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