Prognostic Value of ^{18}F-FDG PET/CT in Diffuse Large B-Cell Lymphoma Treated with a Risk-Adapted Immunochemotherapy Regimen

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Early identification of patients with diffuse large B-cell lymphoma (DLBCL) who are likely to experience disease recurrence or refractory disease after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) would be useful for improving risk-adapted treatment strategies. We aimed to assess the prognostic value of ^{18}F-FDG PET/CT parameters at baseline, interim, and end of treatment (EOT). **Methods:** We analyzed the prognostic impact of ^{18}F-FDG PET/CT in 166 patients with DLBCL treated with a risk-adapted immunochemotherapy regimen. Scans were obtained at baseline, after 4 cycles of R-CHOP or 3 cycles of RR-CHOP (double dose of R) and 1 cycle of CHOP alone (interim) and 6 wk after completing therapy (EOT). Progression-free survival (PFS) and overall survival (OS) were estimated using Kaplan–Meier and the impact of clinical/PET factors assessed with Cox models. We also assessed the predictive ability of the recently proposed International Metabolic Prognostic Index (IMPI). **Results:** The median follow-up was 7.9 y. International Prognostic Index (IPI), baseline metabolic tumor volume (MTV), and change in maximum SUV (ΔSUV_{max}) at interim scans were statistically significant predictors for OS. Baseline MTV, interim ΔSUV_{max}, and EOT Deauville score were statistically significant predictors of PFS. Combining interim PET parameters demonstrated that patients with Deauville 4–5 and positive $\Delta SUV_{max} \leq 70\%$ at restaging (~10% of the cohort) had extremely poor prognosis. The IMPI had limited discrimination and slightly overestimated the event rate in our cohort. **Conclusion:** Baseline MTV and interim ΔSUV_{max} predicted both PFS and OS with this sequential immunochemotherapy program. Combining interim Deauville score with interim ΔSUV_{max} may identify an extremely high-risk DLBCL population.

Key Words: ^{18}F-FDG PET/CT; diffuse large B-cell lymphoma; metabolic tumor volume; δ-SUV_{max}; Deauville score

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Diffuse large B-cell lymphoma (DLBCL) is a common and aggressive lymphoma subtype. The treatment regimen of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) is considered the standard first-line DLBCL treatment, with a long-term remission rate of 60%–70% (*1*). However, patients who do not respond to R-CHOP have a poor prognosis, and pretreatment prognostic models such as the International Prognostic Index (IPI) that are used to predict survival (*2*) fail to identify these high-risk patients. Several studies have evaluated more aggressive first-line treatments using risk-adapted strategies for patients with good versus poor prognosis (*3,4*). Hence, early identification of patients who are likely to experience disease recurrence or refractory disease after R-CHOP is important for improving stratification to modified and innovative regimens.

^{18}F-FDG PET/CT scans at baseline have proven to be highly sensitive in determining sites of disease for DLBCL (*5,6*). Furthermore, PET/CT scans at the end of treatment (EOT) have demonstrated high prognostic value for assessing long-term remission (*6*). However, there is still no consensus on the predictive value of interim PET/CT scans in the management of patients with DLBCL. Evidence that changing treatment strategy based on interim PET/CT scans improves outcome remains to be confirmed (*4,6,7*).

Imaging biomarkers have often been evaluated separately. Parameters calculated from PET/CT, such as metabolic tumor volume (MTV) at baseline and change in maximum SUV between baseline and interim scans (ΔSUV_{max}), were demonstrated to be prognostic in DLBCL (*1,3,7–12*) and may prove useful for risk stratification. Recently, a simple prognostic model, the International Metabolic Prognostic Index (IMPI), which combines baseline MTV, age, and stage, was shown to predict outcomes in DLBCL with higher accuracy than the IPI (*13*). Against this background, we aimed to assess the prognostic value of baseline, interim, and EOT ^{18}F-FDG PET/CT scans and validate IMPI in patients with DLBCL who were uniformly treated with a risk-adapted immunochemotherapy regimen.

MATERIALS AND METHODS

Study Population

Two risk-adapted studies treating patients with advanced-stage large cell lymphomas were approved by Memorial Sloan Kettering Cancer Center (MSK)'s institutional review board. From March 2002 to November 2006, 98 patients were enrolled onto protocol 01-142 (NCT00039195) and from July 2008 to May 2013, 99 patients were enrolled onto 08-026 (NCT00712582). All patients provided written informed consent. From November 2006 through September 2010, 26 patients were treated at MSK with a non–cross-reactive chemotherapeutic program consistent with that of 01-142 but performed off-protocol since 01-142 was closed at the time.

Patients were treated with R-CHOP ×4 or RR-CHOP (double dose of R) ×3 + CHOP ×1 induction, and either 3 cycles of ifosfamide, carboplatin, and etoposide (ICE), ICE ×2 + rituximab-ICE (R-ICE) ×1,

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or augmented R-ICE ×2 consolidation chemotherapy. Those with both an interim ^{18}F-FDG PET–positive result and confirmatory positive biopsy of the ^{18}F-FDG–positive site went on to receive high-dose therapy and autologous stem cell rescue.

The 223 patients had similar pretreatment characteristics and similar outcome after a median follow-up of 7.7 y (95% CI, 7.0–8.7), which justified combining the 3 cohorts. From the total cohort of 223 patients, 166 patients with baseline, interim, or EOT PET/CT scans available in MSK's PACS were included in this analysis. A consort diagram of evaluable patients is shown in Supplemental Figure 1 (supplemental materials are available at http://jnm.snmjournals.org). No clinical (Supplemental Table 1) or follow-up (Supplemental Figure 2) differences were observed between the 166 patients in the PET/CT cohort analyzed in this paper and the 57 patients who were excluded. Only a sex difference was observed (Supplemental Table 1).

^{18}F-FDG PET/CT Imaging and Analysis

^{18}F-FDG PET/CT scans were obtained at baseline, after 4 cycles of R-CHOP (interim), and 6 wk after completing immunochemotherapy (EOT). Patients fasted for 6 h before injection of 444 ± 44 MBq of ^{18}F-FDG. PET/CT scans from midskull to upper thighs were obtained on Discovery scanners (GE Healthcare) after a standardized uptake time of approximately 60 min.

Baseline, interim, and EOT PET/CT scans were interpreted by an experienced nuclear medicine physician masked to patient outcome. Mediastinal blood pool and normal liver were used as reference regions for background activity. Sites of abnormal ^{18}F-FDG uptake, defined as intensity greater than surrounding local background, were recorded. The intensity of ^{18}F-FDG uptake was measured using the SUV_{max}, defined as the highest SUV recorded among all lesions for each scan. Focal bone uptake corresponded to bone metastasis. Diffuse marrow uptake was defined visually and may represent lymphoma involvement or reactive hyperplasia. The SUV_{max} of diffuse uptake was not recorded.

All measurable lesions were identified at baseline. Volumetric regions of interest were placed over all sites of abnormal uptake in lymph nodes, soft-tissue organs, or focal bone lesions. Metabolic tumor volume (MTV) was measured using the semiautomatic software Beth Israel plugin for Fiji and applying a 41% SUV_{max} threshold (*14*). Total MTV was obtained by summing the metabolic volumes of all measurable lesions. Furthermore, focal bone involvement and diffuse marrow uptake were recorded. The IMPI score, which represents the probability of being progression free at 36 mo, was calculated for each patient on the basis of age, stage, and baseline MTV as described by Mikhaeel et al. (*13*).

The visual Deauville/Lugano 5-point scale was applied to the interim and EOT scans, with scores of 1–3 (indicating uptake ≤ that of the liver) considered negative and scores 4–5 (indicating uptake > the liver) considered positive. To measure metabolic change after induction therapy, ΔSUV_{max} was assessed using the most intense tumor in any region or organ at the interim scan—even if the location differed from the original tumor at baseline—calculated as follows: ΔSUV_{max} = (baseline SUV_{max} − interim SUV_{max})/baseline SUV_{max} (*15*). Patients with $\Delta SUV_{max} \leq 70\%$ were considered positive and patients with $\Delta SUV_{max} > 70\%$ were considered negative. The 70% threshold was chosen for this series based on the previously identified optimal cutoff to predict progression or death for ΔSUV_{max} after 4 cycles in the LNH2007-3B trial (*16*). As outlined by Meignan et al. based on the PETAL trial (NCT00554164), LNH2007-3B (NCT00498043), and International validation studies (*17*), patients with low baseline SUV_{max} (<10) or high interim SUV_{max} (>5) were deemed unsuitable for ΔSUV_{max} calculations. Visual assessment was used for these patients.

Statistical Analysis

Progression-free survival (PFS) and overall survival (OS) were used to evaluate the prognostic value of clinical and PET/CT parameters. PFS was defined as the time from the start of treatment to the date of disease progression/relapse or death from any cause. Patients without progression/relapse or death were censored at their last follow-up. OS was defined as the time from the start of treatment to the date of death from any cause. Surviving patients were censored at their last follow-up. To assess the prognostic value of parameters measured at interim or EOT, landmark analyses were used where PFS and OS were defined

TABLE 1
Patient Characteristics (n = 166)

Clinical characteristic	*n*
Median age (y)	50 (range, 20–71)
Ann Arbor stage	
II	34 (20%)
III–IV	132 (80%)
Median LDH	332 (range, 130–1,925)
KPS	
≤70	49 (30%)
>70	117 (70%)
Standard IPI score	
0	33 (20%)
1	39 (23%)
2	53 (32%)
3	41 (25%)
Baseline PET	166
Focal bone uptake	55 (33%)
Diffuse marrow uptake	20 (12%)
Median liver SUV_{max}	2.42 (range, 0.81–7.20)
Unknown	2
Median SUV_{max}	24.35 (range, 6.30–60.36)
Median TMTV	297.82 (range, 6–5,145.85)
≤510 mL	117 (70%)
>510 mL	49 (30%)
Interim PET	157
ΔSUV_{max}	
Median	0.90 (range, −0.33–0.98)
Negative	140 (89%)
Positive	17 (11%)
Deauville score	
1–3	118 (75%)
4	36 (23%)
5	3 (2%)
EOT PET	151
Deauville score	
1–3	124 (82%)
4	19 (13%)
5	8 (5%)

LDH = lactate dehydrogenase; KPS = Karnofsky performance scale; TMTV = total metabolic tumor volume; ΔSUV_{max} = change in SUV_{max}; EOT = end of treatment.

TABLE 2
Univariable Cox Regression Analyses

Clinical characteristic	OS			PFS		
	HR	95% CI	*P*	HR	95% CI	*P*
Standard IPI score			0.015			0.13
0	—	—		—	—	
1	0.91	0.23, 3.65		0.71	0.26, 1.97	
2	1.12	0.33, 3.82		1.00	0.42, 2.39	
3	3.35	1.12, 10.0		1.81	0.79, 4.14	
Baseline PET						
Focal bone uptake	0.88	0.42, 1.88	0.75	0.73	0.39, 1.36	0.31
Diffuse marrow uptake	1.52	0.58, 3.98	0.41	1.12	0.47, 2.64	0.81
SUV_{max} (per 5 units)	1.07	0.88, 1.30	0.53	0.92	0.79, 1.09	0.34
TMTV (dichotomized)			0.011			0.004
≤510 mL	—	—		—	—	
>510 mL	2.54	1.25, 5.13		2.33	1.32, 4.12	
Interim PET (landmark)						
ΔSUV_{max} (continuous)	0.03	0.01, 0.14	<0.001	0.08	0.02, 0.32	0.007
ΔSUV_{max} (dichotomized)			0.007			0.015
Negative	—	—		—	—	
Positive	3.75	1.60, 8.80		2.91	1.35, 6.29	
Deauville score			0.15			0.21
1–3	—	—		—	—	
4–5	1.79	0.83, 3.84		1.54	0.80, 2.95	
EOT PET (landmark)						
Deauville score			0.092			0.010
1–3	—	—		—	—	
4–5	2.24	0.93, 5.41		2.72	1.34, 5.51	

HR = hazard ratio; TMTV = total metabolic tumor volume; ΔSUV_{max} = change in SUV_{max}; EOT = end of treatment.

from the interim or EOT, respectively. Patients with the events of interest before the landmark time or without the corresponding PET/CT scans were excluded.

IPI, baseline PET/CT parameters (SUV_{max}, MTV, focal bone uptake, diffuse marrow uptake), interim PET/CT parameters (ΔSUV_{max} [positive vs. negative or continuous], Deauville scores [1–3 vs. 4–5]), and EOT PET/CT parameters (Deauville scores [1–3 vs. 4–5]) were evaluated as prognostic factors. We used 510 mL as the optimal cutoff for MTV as proposed by Meignan et al. (*18*), which we validated for PFS and OS in our cohort (Supplemental Fig. 3). PFS and OS rates were estimated using a Kaplan–Meier estimator. The impact of candidate factors on survival were assessed using univariable and multivariable Cox proportional hazards models. The median follow-up was estimated using the reverse Kaplan–Meier method. The comparison between the patients included and excluded from the cohorts was done using the Wilcoxon rank-sum test for continuous variables and the Fisher exact test for categoric variables. A 2-sided P value < 0.05 was considered statistically significant.

To assess the predictive ability of IMPI (probability of being progression free at 36 mo), its complement, cIMPI (probability of a progression event by 36 mo), was analyzed using 3 methods: measures of discrimination (Harrell's c-index), prediction error (Brier score), and calibration (calibration plot). Analyses were performed using R (version 4.1.0; R Foundation).

RESULTS

The median follow-up for the 166 patients included in this analysis was 7.9 y (95% CI, 6.7–8.8). Clinical characteristics and quantitative PET parameters are summarized in Table 1. Of the total, 48 patients experienced a progression event and 31 died (2 of these deaths were unrelated to cancer). The 5-y PFS and OS rates were 76% and 85%, respectively. The 10-y rates were 69% and 80%, respectively.

All 166 patients underwent baseline PET/CT scans. The median SUV_{max} was 24.35 (range, 6.30–60.36). Median MTV was 297.82 mL (range, 6.45–5,145.85 mL) and average MTV was 522.32 mL. Fifty-five patients had ^{18}F-FDG–positive focal bone lesions, and 20 patients had diffuse marrow uptake; among these, 5 patients had mixed focal bone lesions and diffuse uptake. Of the total, 157 patients underwent interim PET/CT after R-CHOP. For the remaining 9 patients, interim PET/CT was either not performed or not available (Supplemental Fig. 5). One patient progressed before interim scanning and was

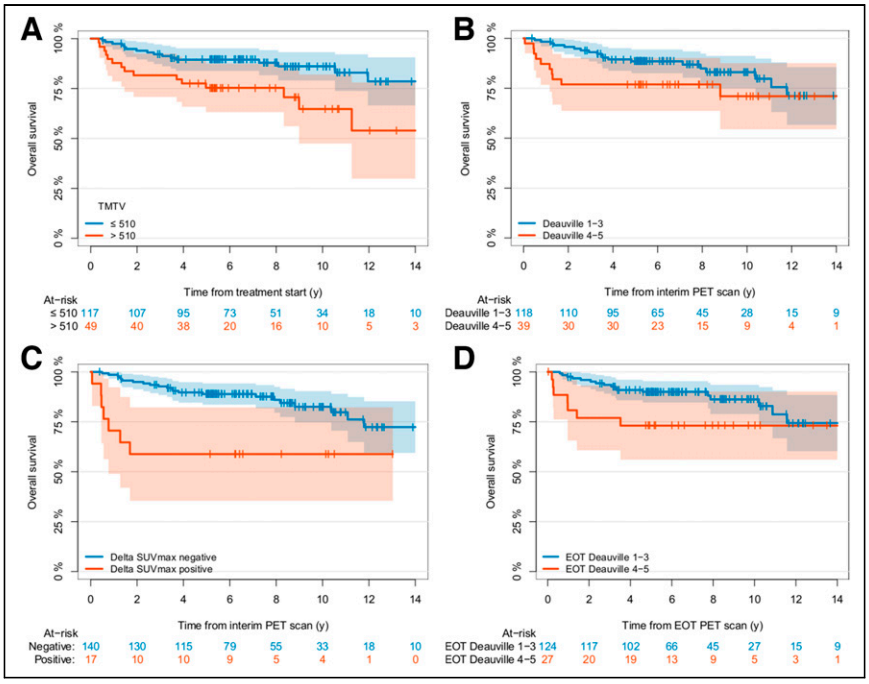

FIGURE 1. OS stratified by baseline total metabolic tumor volume (TMTV) (A), interim Deauville score (B), interim ΔSUV_{max} (C), and end-of-treatment (EOT) Deauville score (D).

excluded in PFS landmark analysis. By visual Deauville/Lugano classification, there were 39 interim PET/CT-positive patients (25%) and 118 interim PET/CT-negative patients (75%). The median ΔSUV_{max} was 0.90% (−0.33%–0.98%). When ΔSUV_{max} criteria was used, 17 patients were classified as positive (11%) and 140 patients were classified as negative (89%) at interim. Among them, 23 had initial $SUV_{max} < 10$ (6 patients) or interim $SUV_{max} > 5$ (17 patients); Deauville scores were used to classify them as positive or negative. All but 15 patients, for whom imaging was not performed or not available, were analyzed for EOT PET/CT (Supplemental Fig. 5). Three patients progressed before or on the day of EOT scan and were excluded in PFS landmark analysis. Visual Deauville/Lugano assessment was positive for 27 patients (17 of 27 also had a positive interim PET/CT result per Deauville/Lugano response criteria) and 124 were considered negative at EOT.

IPI, baseline MTV, and interim ΔSUV_{max} were statistically significant predictors of OS (Table 2; Fig. 1). IPI ($P = 0.059$) and baseline MTV ($P = 0.066$) were independent prognostic factors of OS in a multivariable model with borderline significance. Baseline MTV, interim ΔSUV_{max}, and EOT Deauville score were statistically significant predictors of PFS (Table 2; Fig. 2). Casasnovas et al. showed that combining visual (International Harmonization Project criteria) and quantitative (ΔSUV_{max}) PET assessments after 4 cycles of induction treatment identified patients at extremely high risk of induction failure or early relapse (*16*). We performed a similar analysis looking at the prognostic relevance of interim PET parameters (Deauville score and ΔSUV_{max}) to outcome by combining these 2 interim response criteria. This Kaplan–Meier analysis demonstrated that patients with Deauville of 4–5 and positive ΔSUV_{max} at restaging (~10% of the cohort) had extremely poor prognosis (Fig. 3). Among these, 9 patients also had high initial MTV.

The IMPI was calculated for all patients as a probability of being progression free at 36 mo. The predicted event rate was compared with the actual event rate (Supplemental Fig. 4), and we found that the IMPI overestimated the event rate.

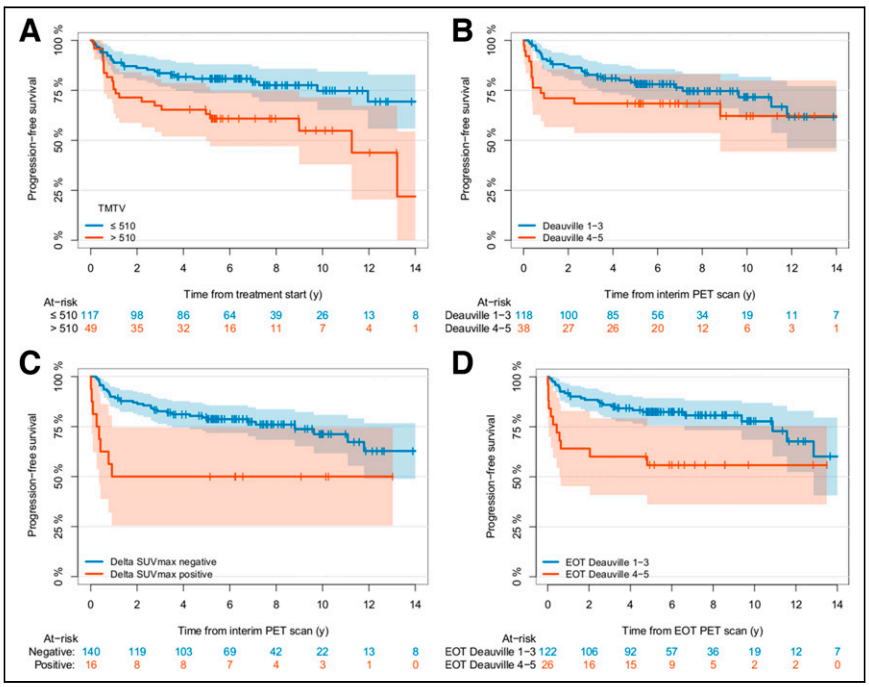

FIGURE 2. PFS stratified by baseline total metabolic tumor volume (TMTV) (A), interim Deauville score (B), interim ΔSUV_{max} (C), and end-of-treatment (EOT) Deauville score (D). One patient progressed before interim scan and was excluded from landmark analysis (B and C), 3 patients progressed before or on the day of EOT scan and were excluded from landmark analysis (D).

DISCUSSION

Early prediction of poor prognosis during the course of DLBCL therapy would be helpful for improving long-term outcome. Although assessing early response to treatment using PET/CT scans has identified potential prognostic factors, there is currently no consensus on how to adapt treatment strategies based on molecular imaging parameters. For example, studies with large DLBCL cohorts have identified baseline MTV as a significant predictor for PFS and OS (*9,12,19*). Other studies showed ΔSUV_{max} on interim PET to be associated with both PFS and OS (*3,10,20*).

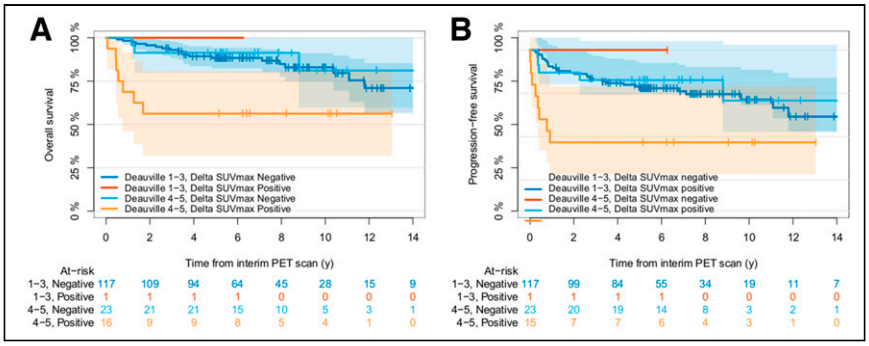

FIGURE 3. OS (A) and PFS (B) stratified by combination of interim Deauville score and interim ΔSUV_{max}. 1 patient progressed before interim scan and was excluded from landmark analysis (B).

Data reported by Casasnovas et al. also suggest that interim ΔSUV_{max} is more discriminant of outcome after 4 cycles of treatment than after 2 cycles (*3*). However, another large prospective trial reported interim PET/CT having limited prognostic relevance. Mamot et al. demonstrated that when interim PET/CT after 2 cycles was already positive, PET scans after 4 cycles of chemotherapy provided no additional predictive value compared with 2 cycles, and that only scans at EOT identified a significant difference in outcome (*7*).

To explore the prognostic value of PET/CT in DLBCL, we looked at the prognostic value of several PET/CT parameters in a group of 166 patients uniformly treated with a risk-adapted immunochemotherapy regimen. Our results showed that baseline MTV and interim ΔSUV_{max} were significant predictors of PFS and OS. We also found that EOT Deauville score was prognostic for PFS. To note, EOT PET demonstrated less prognostic value in our study than what was reported by Mamot et al. (*7*). This difference may be because of the risk-adapted treatment regimen as well as the longer follow-up in our series.

The recently proposed IMPI (*13*), which combines baseline MTV and age as continuous variables to predict patient outcome in DLBCL, is potentially useful for identifying patients with worse prognosis who might benefit from more aggressive or investigational treatment. We sought to validate this model in our cohort. In our series, the IMPI predictions overestimated the event rate. There are several potential explanations for the lower predictive accuracy in our population. Our patients were treated with R-CHOP followed by ICE/RICE, whereas Mikhaeel et al. used clinical data from patients treated with R-CHOP alone. Second, baseline MTV was calculated using different software. Finally, MTV was measured by including tumor with different SUV cutoffs (current analysis used the 41% SUV_{max} threshold method, whereas Mikhaeel et al. used $SUV_{max} \geq 4.0$). Nevertheless, the median MTV in the current study was similar to theirs (298 vs. 308 mL).

In our series, combining interim PET parameters Deauville score and ΔSUV_{max} demonstrated that patients with Deauville scores of 4–5 and positive ΔSUV_{max} (10% of the cohort) had extremely poor prognosis. These results combining visual and quantitative assessments are similar to those previously reported in an independent cohort after 4 cycles of induction treatment (*16*). Thus, it appears that adding ΔSUV_{max} to visual analysis may be a robust and reproducible tool for identifying high-risk patients with DLBCL. Combining the 2 interim PET parameters identifies patients who have a poor outcome with standard chemoimmunotherapy and may help define a cohort of patients for evaluation of alternative therapeutic approaches, such as CAR T-cell therapy. ZUMA-12 attempted to identify patients with a poor prognosis for early intervention with axicabtagene ciloleucel (*21*); however, that trial has been criticized for the means of selecting the poor risk cohort. The interim PET evaluation described herein could potentially identify a more uniform group of patients with a poor outcome. A prospective trial could randomize these high-risk patients to CAR T-cell versus second-line therapy followed by high-dose therapy and autologous stem cell rescue, similar to the ZUMA-7 (*22*) and TRANSFORM (*23*) clinical trials. Other studies evaluating the role of PET/CT metrics for treatment guidance in DLBCL have reported other parameter combinations to be relevant. Cottereau et al. demonstrated that baseline MTV and standardized Dmax (the largest distance between 2 lesions) complement each other in characterizing tumor burden and disease spread (*11*), whereas Vercellino et al. combined baseline MTV with the Eastern Cooperative Oncology Group performance status to identify a very-high-risk DLBCL subgroup (*12*). Recently, Eertink et al., on behalf of PETRA investigators, demonstrated in 217 patients that MTV, $Dmax_{bulk}$, SUV_{peak}, World Health Organization performance score, and age identify patients at risk of relapse at baseline (*24*).

To determine the optimal combination of PET/CT parameters and prognostic indices to improve the prediction of outcome in clinical practice, standardized methods of measurement are needed across all PET/CT centers internationally. Some examples include whether interim PET/CT scans should be acquired after 2 versus 4 cycles, standardized definitions of ΔSUV_{max}, and methods for determination of MTV (*25*). Once a robust set of parameters or score is determined, multiple large studies would need to validate the results for a consensus to be reached. Standardization is potentially complicated by different initial regimens. For the results to be applicable across studies, the parameters would ideally be independent of treatment. To move from being a prognostic tool to a predictive tool, well-designed clinical trials need to evaluate new treatment strategies for the high-risk DLBCL patient and show improved outcome.

CONCLUSION

Our study confirmed the prognostic value of baseline MTV and interim ΔSUV_{max} in DLBCL. Combining interim Deauville score with interim ΔSUV_{max} could improve risk stratification for patients with extremely poor prognosis. These results warrant large multicenter studies to develop standardized practices and refine existing prognostic indices in DLBCL.

DISCLOSURE

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KEY POINTS

QUESTION: Do baseline MTV, alone or in combination with ΔSUV, and the recently proposed IMPI score predict outcome in patients with DLBCL treated with the RCHOP-ICE drug regimen?

PERTINENT FINDINGS: Baseline MTV and ΔSUV_{max} at interim predict OS. Patients with Deauville scores of 4–5 and positive $\Delta SUV_{max} \leq 70\%$ at interim (~10% of the cohort) had extremely poor prognosis. The new IMPI score had limited discrimination and slightly overestimated the event rate in our cohort.

IMPLICATIONS FOR PATIENT CARE: Combining interim Deauville scores with interim ΔSUV_{max} could improve risk stratification for DLBCL patients with extremely poor prognosis.

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