European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:953–962
https://doi.org/10.1007/s00259-021-05551-5

ORIGINAL ARTICLE

[^{18}F]FDG PET-CT in patients with DLBCL treated with CAR-T cell therapy: a practical approach of reporting pre- and post-treatment studies

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Received: 24 July 2021 / Accepted: 29 August 2021 / Published online: 4 September 2021

Abstract

Purpose The introduction of CD19-specific chimeric antigen receptor T-cell therapy (CAR-T) for treatment of relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL) gives hope to patients with otherwise dismal prognosis. Therapy outcomes, however, depend upon selection of patients and accurate early identification of non-responders. Patients treated with CAR-T usually undergo [^{18}F]FDG PET-CT at time of decision (TD), time of CAR-T transfusion (TT), 1 month (M1), and 3 months (M3) post-therapy. The purpose of the current study was to identify the specific parameters that should be addressed when reporting PET-CT studies in the clinical setting of CAR-T therapy.

Methods A total of 138 PET-CT scans (30 TD, 42 TT, 44 M1, 22 M3) of 48 patients treated with CAR-T were included. SUVmax, TMTV, and TLG were calculated in all scans. Response was assessed using the Deauville scale and ΔSUVmax method. Overall survival (OS) was the primary endpoint. Median follow-up was 12.8 (IQR 6.4–16.0) months from CAR-T infusion.

Results In a univariate analysis, TD-SUVmax > 17.1 and TT-SUVmax > 12.1 were associated with shorter OS ($Pv < 0.05$). In a multivariate analysis, three factors were significantly associated with shorter OS: TD-SUVmax > 17.1 (HR 10.3; $Pv < 0.01$), LDH > 450 U/l (HR 7.7; $Pv < 0.01$), and ECOG score > 1 (HR 5.5; $Pv = 0.04$). Data from TD and TT PET-CT scans were not predictive of toxicity. On M1-PET-CT, patients with a Deauville score > 3 had significantly shorter OS (median 7.9 months, versus not reached, $Pv < 0.01$). ΔSUVmax ≤ 66% on M1-PET-CT predicted shorter OS when M1-SUVmax was compared to TD-SUVmax ($Pv = 0.02$) but not to TT-SUVmax ($Pv = 0.38$).

Conclusion Pre-treatment SUVmax may guide patient selection for CAR-T therapy. On M1-PET-CT, Deauville score and ΔSUVmax from TD may identify early therapy failure. These parameters are easy to obtain and should be included in the PET-CT report.

Keywords CAR-T · DLBCL · PET-CT · Deauville · SUVmax

Abbreviations

R/R DLBCL	Relapsed/refractory diffuse large B-cell lymphoma
CD19	Cluster of differentiation 19
CAR-T	Chimeric antigen receptor T-cell
CRS	Cytokine release syndrome
ICANS	Immune effector cell-associated neurotoxicity syndrome
ECOG	Eastern Cooperative Oncology Group
GCB	Germinal center B-cell like
COO	Cell of origin
[^{18}F]FDG	^{18}F-fluorodeoxyglucose
PET-CT	Positron emission tomography-computed tomography

This article is part of the Topical Collection on Hematology

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TD	Time of decision
TT	Time of transfusion
M1	1 Month
M3	3 Months
SUVmax	Maximum standardized uptake value
SUVmean	Mean standardized uptake value
TMTV	Total metabolic tumor volume
TLG	Total lesion glycolysis
OS	Overall survival
PFS	Progression-free survival
IQR	Interquartile range
Pv	*P*-Value
CI	Confidence interval
HR	Hazard ratio

Introduction

Overall survival (OS) of patients with relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL) who failed at least two treatment regimens is estimated as being only 4.4–6.3 months [1, 2]. This group of patients had limited treatment options prior to the recent approval of two commercially available CD19-specific chimeric antigen receptor T-cell (CAR-T) therapies, axicabtagene ciloleucel (axi-cel), and tisagenlecleucel (tisa-cel) [3–5].

Data from pivotal trials suggest durable remission in 30 to 40% of patients with R/R DLBCL treated with CAR-T therapy [4, 5]. However, this therapy is also associated with toxicity, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which can be life-threatening [6–8]. Benefit from CAR-T relies on selection of patients and reduction of toxicity associated with the therapy. Non-responders should be identified as early as possible after CAR-T infusion so that alteration of the treatment approach may be considered.

^{18}F-Fluorodeoxyglucose positron emission tomography-computed tomography ([^{18}F]FDG PET-CT) plays a key role in the management of patients with DLBCL and has been shown to predict outcome at specific time points in the earlier course of the disease [9–18]. In the clinical setting of CAR-T therapy, patients usually undergo [^{18}F]FDG PET-CT at four relevant time points. Two scans are performed before CAR-T infusion: time of decision (TD) PET-CT, based upon which the clinician selects CAR-T as the next therapy, and time of transfusion (TT) PET-CT, performed immediately prior to the infusion of CAR-T. Post-therapy, two PET-CT scans are performed to monitor response to therapy: 1 month (M1) PET-CT and 3 months (M3) PET-CT.

Several previous studies focused on the role of PET-CT in the mentioned time points [19–23]. In a model built by Vercellino et al. for prediction of early progression, total metabolic tumor volume (TMTV) was the only PET parameter assessed. That model identified high TMTV values obtained on TD and TT scans as risk factors for disease progression within 1 month after therapy [24]. Wang et al. found an association between TT-TMTV and severe CRS [20], while in a recent study by Iacoboni et al., higher TT-TMTV showed no association with CRS but was associated with a lower progression-free survival (PFS) [21].

In a busy clinical setting, TMTV is not routinely calculated or included in PET-CT reports. Monitoring the response to first-line therapy in DLBCL on [^{18}F]FDG PET-CT is assisted by using more practical methods: the Deauville 5-point scale or measurement of ΔSUVmax. The Deauville 5-point scale is based on a visual comparison between the uptake of lymphoma tissue and that of the liver and mediastinum, with a cut-off for the definition of an unfavorable response as an uptake greater than that of the liver [24]. Using the ΔSUVmax method, the maximum standardized uptake value (SUVmax) of the "hottest" tumor lesion is compared between two PET studies. An unfavorable response is defined when the SUVmax reduction is less than or equal to 66%, a cut-off that has been confirmed in several studies [25–28]. The role of both methods has not yet been determined in R/R DLBCL patients treated with CAR-T.

In the current study, we aimed to provide a practical guide for the interpretation of [^{18}F]FDG PET-CT performed before and after CAR-T therapy. Specifically, we aimed to identify pre-CAR-T PET-CT parameters that may assist in patient selection and post-CAR-T PET-CT parameters that may assist in identifying early CAR-T failure.

Methods

Patient population

After receiving the consent of the institutional ethical committee, we retrospectively screened the medical records of all patients that met the following inclusion criteria: (i) over 18 years old (ii) treated with CD19-targeted CAR-T for R/R DLBCL (iii) clinically evaluated at the hematology institute at Tel-Aviv Sourasky Medical Center and (iv) underwent whole-body [^{18}F]FDG PET-CT in our department before and/or after CAR-T transfusion.

A total of 138 PET-CT studies performed in the nuclear medicine department at Tel-Aviv Sourasky Medical Center were identified and included in the study. The studies were of 48 patients treated with CAR-T therapy between April 2019 and April 2021 and included 30 TD, 42 TT, 44 M1, and 22 M3 PET-CT scans. Fourteen patients had all 4 scans each (TD, TT, M1, and M3) done in our department. Twenty patients had 3 scans each (15 patients had TD, TT, and M1 scans, and 5 patients had TT, M1, and M3 scans). Eight

patients had 2 scans each (5 patients had TT and M1 scans, 2 patients had M1 and M3 scans, and 1 patient had TD and TT scans). Six patients had 1 scan each (3 M1, 2 TT, and 1 M3 scans).

Thirty-nine of the study patients received bridging therapy between TD and TT (27 received systemic and radiation therapy, 6 received systemic therapy, and 6 received radiation therapy). M1 and M3 scans were included only if no other anti-lymphoma treatment had been added since CAR-T infusion. The median interval between the TD and TT studies was 1.4 (IQR 1.3–2) months. The median interval between the TT study and CAR-T transfusion was 0.5 (IQR 0.3–1.2) months. The median time interval between CAR-T transfusion and the ensuing PET-CT studies were 1 (IQR 0.9–1.1) and 3 (IQR 2.8–3.3) months for the M1 and M3 scans, respectively.

Imaging

[^{18}F]FDG PET-CT studies were performed on PET-CT scanners (GE Healthcare; Discovery 690 and Discovery MI; 7 to 8 frames; frame time 1.5–3 min), according to our standard protocol, with the administration of a diluted oral contrast agent and injection of 3.7 MBq/kg [^{18}F]FDG approximately 60 min prior to the study.

For all 138 included studies, SUVmax, TMTV, and total lesion glycolysis (TLG) values were documented. SUVmax was measured in the "hottest" nodal or extranodal lymphoma site. The spleen was considered involved if there were focal uptake or diffuse uptake > 150% of the liver uptake. Bone marrow was considered only in case of focal uptake. TMTV was obtained with the 41% SUVmax threshold method as recommended by the European Association of Nuclear Medicine [29], by summing the metabolic volumes of all local nodal and extranodal lesions using Q.Volumetrix AI (GE Healthcare). The TLG value was computed as the product of the measured SUVmean and MTV.

Response assessment was done by means of two methods: the Deauville 5-point scale (1, no uptake; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, moderately increased uptake compared to the liver; 5, markedly increased uptake compared to the liver and/or new lesions) [9] and the ΔSUVmax method (calculation of ΔSUVmax as the percentage change in SUVmax between PET studies) [18]. A Deauville score ≤ 3 and ΔSUVmax > 66% were considered favorable response criteria [9, 18].

For response assessment, we recorded the Deauville score in all 42 TT, 44 M1, and 22 M3 PET-CT scans. The ΔSUVmax method, however, requires two available studies performed in our department. Thus, for response assessment at TT, ΔSUVmax (TD → TT) was calculated in 30 patients who underwent PET-CT in our department at TD and TT. Similarly, for response assessment at M1, ΔSUVmax (TT → M1) was calculated in 39 patients, and ΔSUVmax (TD → M1) was calculated in 29 patients. For response assessment at M3, ΔSUVmax (M1 → M3), ΔSUVmax (TT → M3), and ΔSUVmax (TD → M3) were calculated in 21, 19, and 14 patients, respectively.

Table 1 summarizes the clinical data and PET-CT findings on TD and TT scans done prior to CAR-T infusion.

Outcome variables

The primary endpoint of the study was overall survival (OS), defined as time from CAR-T transfusion to death from any cause. Imaging data both before and after CAR-T transfusion were evaluated for their role in predicting OS. For imaging data before CAR-T transfusion, secondary endpoints included toxicity (CRS and ICANS, graded according to the American Society for Transplantation and Cellular Therapy criteria [8]) and progression-free survival (PFS), defined as the time from CAR-T transfusion to disease progression as defined by Lugano criteria [9] or to death from any cause.

Statistical analysis

Categorical data were described with contingency tables that included frequency and percent. Continuous variables were evaluated for normal distribution and reported as median and interquartile range (IQR). Medians of continuous variables were used as cutoffs for defining dichotomous variables (i.e., values above the median were taken as positive). The median length of follow-up was measured using reverse censoring method. The median survival time and the probabilities of OS and PFS were estimated with the Kaplan–Meier method. Log-rank test and univariate cox regression were applied to study the crude association between the studied predictors and OS and PFS. Pearson's χ^2 test, Fisher's exact test, and univariate Cox regression were used to study the crude association between the studied predictors and toxicity outcomes. The Mann–Whitney U test was used to compare medians of continuous variables between two groups. A multivariate cox regression analysis was performed using a backward method ($P > 0.1$ was used as a criterion for removal) in order to identify independent predictors for OS. A two-sided P value of < 0.05 was considered statistically significant. Variables with a trend or a significant association to OS and PFS, as well as those known to be of important clinical significance, were tested in the multivariate model. SPSS software (IBM SPSS Statistics for Windows, version 27, IBM corp., Armonk, NY, USA, 2017) was used for statistical analyses. Survival curves were generated using the open-source statistics software R (version 4.0.5, R Foundation for Statistical Computing).

Table 1 Patient characteristics prior to CAR-T infusion

	Variable (units)		Value
Clinical characteristics	Age (years)	(median, IQR)	68 (61–76)
	Age (years)	(> 70, *N*, %)	22/48 (46%)
	Gender	(Male, *N*, %)	25/48 (52%)
	Serum LDH (U/l)	(median, IQR)	445 (356–575)
	Serum LDH (U/l)	(> 450, *N*, %)	22/46 (48%)
	ECOG performance	(score > 1, *N*, %)	25/47 (53%)
	De novo vs transformed	(De novo, *N*, %)	14/47 (30%)
	COO	(GCB, *N*, %)	20/48 (42%)
	Number of prior lines	(median, range)	2 (2–4)
	Number of prior lines	(> 2, *N*, %)	13/47 (28%)
	Bridging therapy	(yes, *N*, %)	39/46 (85%)
	CAR-T product	(Axi-cel, *N*, %)	34/47 (72%)
TD-PET parameters[a]	TD-SUVmax	(median, IQR)	17.1 (11.5–23.5)
	TD-TMTV (ml)	(median, IQR)	17.4 (7.3–46.3)
	TD-TLG (g)	(median, IQR)	216.8 (51.1–432.7)
	TD-Deauville	(score > 3, *N*, %)	30/30 (100%)
TT-PET parameters[b]	TT-SUVmax	(median, IQR)	12.1 (7.5–19.5)
	TT-TMTV (ml)	(median, IQR)	13.5 (2.6–61.9)
	TT-TLG (g)	(median, IQR)	70.5 (19.3–493.6)
	TT-Deauville	(score > 3, *N*, %)	35/42 (83%)
	ΔSUVmax (TD → TT)[c]	(Δ > 66%, *N*, %)	28/30 (93%)

TD-PET time of decision PET, the scan based on which CAR-T was selected as the next line of therapy; *TT-PET* time of transfusion PET, the scan performed immediately prior to CAR-T transfusion; *LDH* lactate dehydrogenase; *ECOG* Eastern Cooperative Oncology Group; *Transformed*, DLBCL transformed from another lymphoma; *COO* cell of origin; *GCB* germinal center B-cell like; *Bridging therapy*, anti-lymphoma treatment given between TD and TT; *CAR-T product*, chimeric antigen receptor T-cell product (Axi-cel or Tisa-cel); *SUVmax* maximum standardized uptake value; *TMTV* total metabolic tumor volume; *TLG* total lesion glycolysis

[a]TD-PET was performed in our department and therefore parameters were available in 30 patients

[b]TT-PET was performed in our department and therefore parameters were available in 42 patients

[c]ΔSUVmax (TD → TT) could be calculated in 30 patients who underwent both TD-PET and TT-PET in our department

Results

At the time of the analysis, the included patients had a median follow-up of 12.8 (IQR 6.4–16.0) months from CAR-T infusion. The median OS was not reached. The 6-month and 1-year survival rates were 70.7% and 52.4%, respectively.

Prediction of survival and toxicity prior to CAR-T infusion

In the univariate Cox regression analysis shown in Table 2, several PET and clinical parameters were found to be significantly predictive of OS and PFS prior to infusion of CAR-T. Patients with TD-SUVmax > 17.1 and those with TT-SUVmax > 12.1 had significantly shorter OS and PFS (see Fig. 1). A higher TT-TMTV and a higher TT-TLG were also identified as risk factors for poor OS. Patients with elevated LDH and an ECOG performance score > 1 had significantly shorter OS and PFS.

In a multivariate Cox regression analysis (Table 3) for OS that included age, sex, LDH, ECOG score, TD-SUVmax, TT-SUVmax, TT-TMTV, and TT-TLG as dichotomous variables, three independent prognostic factors were identified: TD-SUVmax > 17.1 (HR 10.3; 95% CI, 2.2–47.7; $Pv < 0.01$), serum LDH > 450 U/l (HR 7.7; 95% CI, 1.9–32.0; $Pv < 0.01$), and an ECOG score > 1 (HR 5.5; 95% CI, 1.1–31.0; $Pv = 0.04$).

Figure 2 illustrates the results of the multivariate analysis. We assigned a score between 0 and 3 to each of the study patients, based on the number of known independent risk factors they had before CAR-T transfusion (TD-SUVmax > 17.1, LDH > 450 U/l, ECOG score > 1). The OS curves of patients with different scores are presented in the figure. The patients in our data that met all of the

Table 2 Univariate analysis of pre-CAR-T clinical and PET factors for overall survival (OS) and for progression-free survival (PFS)

		OS		PFS	
		Pv	HR (95% CI)	*Pv*	HR (95% CI)
Clinical data	Age	0.89		0.67	
	Age > 70 years	0.99		0.94	
	Gender: male (vs female)	0.10		0.66	
	Serum LDH	< 0.01*	1.001 (1.001–1.002)	< 0.01*	1.001 (1.000–1.001)
	Serum LDH > 450 U/l	< 0.01*	8.5 (2.6–27.2)	< 0.01*	3.3 (1.5–7.5)
	ECOG performance score > 1	0.01*	5.1 (1.5–17.8)	0.03*	2.5 (1.1–5.8)
	De novo (vs transformed)	0.42		0.10	
	COO: GCB (vs non-GCB)	0.87		0.19	
	Number of prior lines > 2	0.37		0.64	
	Bridging therapy (vs no)	0.72		0.30	
	CAR-T product: Axi-cel (vs Tisa-cel)	0.27		0.44	
TD-PET data[a]	TD-SUVmax	0.06		0.07	
	TD-SUVmax > 17.1	0.02*	4.8 (1.3–18.1)	0.04*	2.5 (1.1–6.1)
	TD-TMTV	0.84		0.61	
	TD-TMTV > 17.4 (ml)	0.63		0.12	
	TD-TLG	0.84		0.83	
	TD-TLG > 216.8 (g)	0.19		0.14	
TT-PET data[b]	TT-SUVmax	0.02*	1.062 (1.010–1.116)	0.01*	1.058 (1.016–1.102)
	TT-SUVmax > 12.1	0.02*	3.7 (1.3–11.3)	0.01*	3.1 (1.4–7.1)
	TT-TMTV	0.02*	1.001 (1.000–1.002)	0.33	
	TT-TMTV > 13.5 (ml)	0.07		0.06	
	TT-TLG	0.01*	1.000 (1.000–1.000)	0.13	
	TT-TLG > 70.5 (g)	0.07		0.06	
Response criteria[c]	TT-Deauville > 3	0.25		0.33	
	ΔSUVmax (TD → TT) > 66%	0.39		0.21	

Each clinical and PET parameter known before CAR-T infusion was analyzed on a univariate Cox regression for OS and for PFS. Continuous variables were also analyzed as dichotomous variables, applying commonly used previously defined cut-offs (age > 70 years, LDH > 450 U/l) or medians as cut-offs. The hazard ratio (HR) with 95% confidence interval (CI) is presented for variables found significantly associated ($Pv < 0.05$) with overall survival (OS) or with progression-free survival (PFS)

[a]The statistical analysis included 30 patients who underwent TD-PET in our department, and therefore, PET parameters were available

[b]The statistical analysis included 42 patients who underwent TT-PET in our department, and therefore, PET parameters were available

[c]The statistical analysis for the Deauville score included 42 patients whose TT-PET was performed in our department. The statistical analysis for ΔSUVmax (TD → TT) included 30 patients who underwent both TD-PET and TT-PET in our department

three criteria (assigned a score of 3) had a median OS of 2.6 (95% CI, 1.1–4.0) months.

Response to bridging therapy, as evaluated on the TT scan, was not significantly associated with PFS or OS as assessed by both the Deauville 5-point scale (analysis of 42 patients) and the ΔSUVmax method (analysis of 30 patients). Only the minority of patients met the favorable response criteria: 7 patients (7/42, 16.7%) had a Deauville score ≤ 3, and 2 patients (2/30, 6.7%) had a ΔSUVmax > 66% on their TT scan.

Among the patients that underwent PET-CT prior to CAR-T transfusion, the post-therapy incidences of any grade CRS, grades 3–4 CRS, and ICANS were 76.2% (32/42 patients), 11.9% (5/42 patients), and 21.4% (9/42 patients), respectively. No statistically significant association was found between TD or TT PET variables and CRS or ICANS in this cohort.

Imaging interpretation of post-CAR-T PET-CT

Response to CAR-T therapy as evaluated on the M1-PET-CT scan was significantly associated with OS using the Deauville 5-point scale. While patients with a Deauville score > 3 had a median survival of 7.9 (95% CI, 3.8–12.0) months, the median survival of those with a Deauville score ≤ 3 was not reached ($Pv < 0.01$). While the 1-year OS for patients with a favorable response was 94%, it was 20% for those with a poor response based upon the Deauville scale (Fig. 3A).

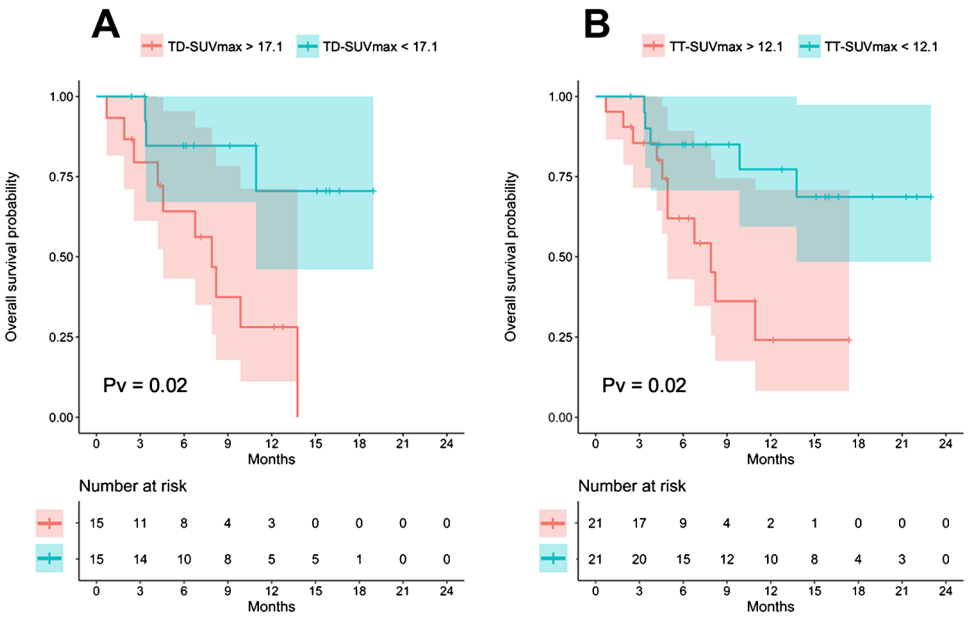

Fig. 1 OS prediction based on TD-SUVmax and TT-SUVmax. Note the significantly shorter OS of patients with a higher TD-SUVmax (**A**) and those with a higher TT-SUVmax (**B**)

Using the ΔSUVmax method, response assessment to CAR-T therapy on M1-PET-CT scans was not associated with OS when the reference baseline SUVmax had been obtained from the TT-PET scan ($Pv = 0.38$), but it was significantly associated with OS when the TD-SUVmax was used as the baseline SUVmax ($Pv = 0.02$). Using the ΔSUVmax method with TD-SUVmax as reference, the median survival of patients who met the favorable criterion had not been reached, and those categorized as having a poor response had a median survival of 8.2 (95% CI, 1.3–15.1) months ($Pv = 0.02$) (Fig. 3B, C).

In the group of patients who had a PET-CT scan 3 months post-CAR-T infusion and were not given any other anti-lymphoma therapy since the CAR-T infusion, response to therapy on the M3 scan was significantly associated with OS using the Deauville 5-point scale ($Pv < 0.01$, Fig. 4A). The ΔSUVmax method could significantly predict OS when the baseline SUVmax was obtained from the TD or TT scan ($Pv = 0.02$ for both, Fig. 4) but not from the M1 scan ($Pv = 0.25$).

Table 3 Multivariate analysis for overall survival (OS) – a model for patient selection for CAR-T therapy

Variables	HR (95% CI)	*Pv*
Serum LDH > 450 U/l	7.7 (1.9–32.0)	< 0.01
ECOG performance score > 1	5.5 (1.1–31.0)	0.04
TD-SUVmax > 17.1	10.3 (2.2–47.7)	< 0.01

On a multivariate Cox regression for OS, the presented dichotomous variables were identified as independent risk factors for shorter OS. Their hazard ratio (HR) with 95% confidence interval (CI) is presented

In multivariate analysis that included the response assessment criteria that were significantly associated with OS on M1 and M3 PET-CT scans, a Deauville score > 3 on M1-PET was the only factor significantly associated with OS (HR 7.2; 95% CI, 1.5–34.6; $Pv = 0.01$).

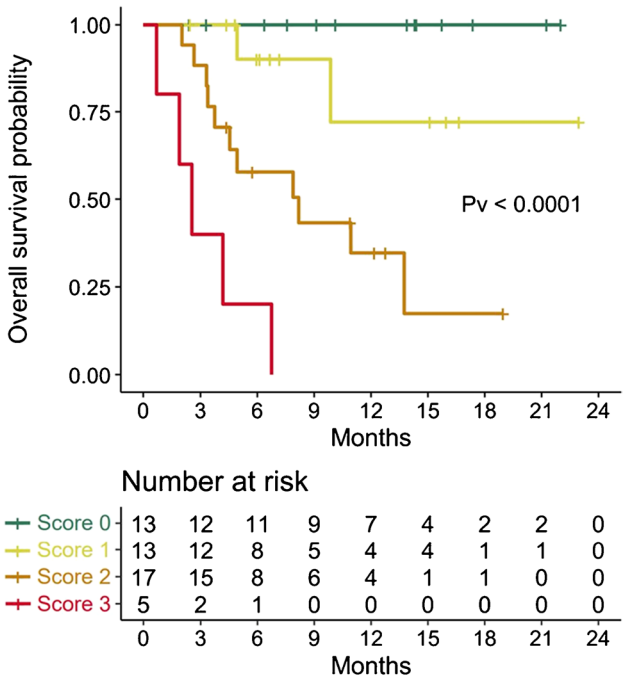

Fig. 2 OS prediction based on the model for patient selection presented in Table 3. The study patients were each assigned a score between 0 and 3 according to the number of known independent risk factors they had before CAR-T transfusion (TD-SUVmax > 17.1, LDH > 450 U/l and ECOG performance-score > 1). Note the different OS probability curves between patients with different scores and the short OS of those meeting all three criteria (red curve)

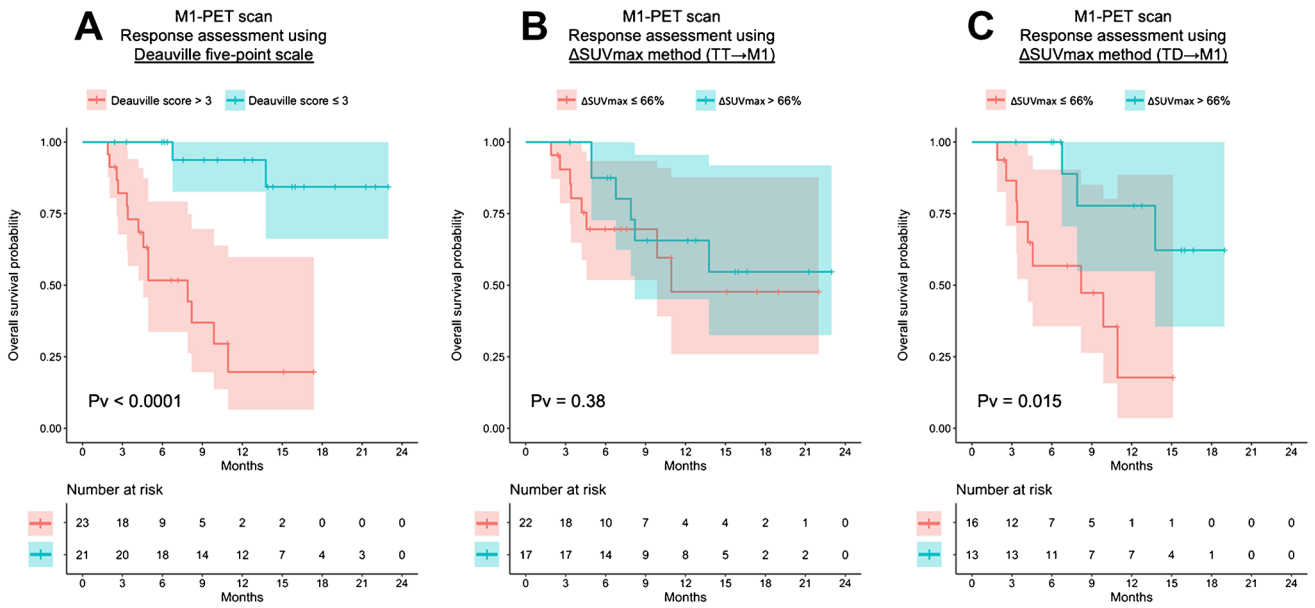

Fig. 3 OS prediction based on different response assessment criteria on M1-PET. Note the significantly short OS of patients with a Deauville score > 3 on M1-PET (**A**). Using the ΔSUV method, when TT-SUVmax was used as the baseline value, the criterion of ΔSUVmax < 66% failed to predict OS in our cohort (**B**). However, when TD-SUVmax was used as the baseline value, those with ΔSUVmax < 66% had a significantly shorter OS (**C**), and this method could early define CAR-T failure

Discussion

The introduction of CAR-T therapy into the clinical practice of R/R DLBCL patients provides a promising approach. However, this novel technology requires an infrastructure, it involves complicated logistics, it may be associated with severe toxicity, and the therapeutic response is variable. Thus, it should be considered only in selected patients that are likely to benefit from this therapy. Moreover, once CAR-T has been infused, failure should be identified as early as possible to enable change in treatment.

Serial [^{18}F]FDG PET-CT scans have been included in the imaging algorithm of patients with DLBCL, including a

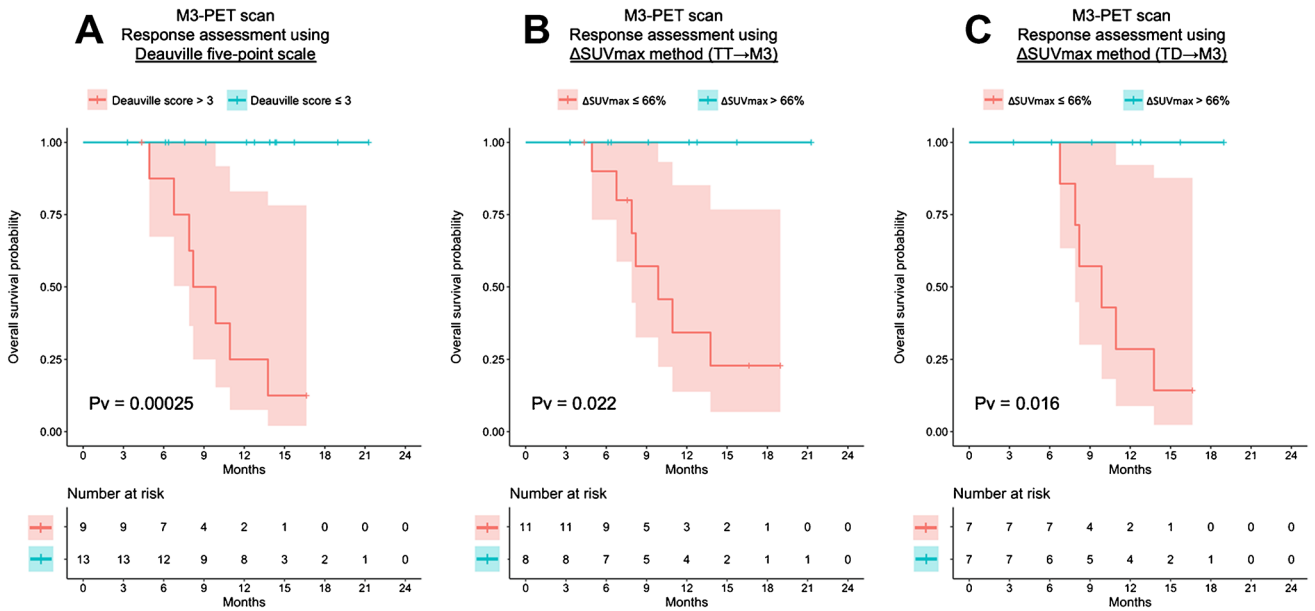

Fig. 4 OS prediction based on different response assessment criteria on M3-PET. A Deauville score ≤ 3 (**A**), ΔSUVmax (TT → M3) > 66% (**B**), and ΔSUVmax (TT → M3) > 66% (**C**) could all identify patients with significantly longer OS

baseline scan performed at diagnosis, scans during and after first-line treatment, as well as when recurrence is suspected [9]. When a PET-CT scan identifies viable R/R DLBCL and the clinician decides that CAR-T is indicated, this study is referred as TD scan. Immediately prior to CAR-T infusion, a TT PET-CT is usually performed. Some patients receive bridging therapy between TD and TT. For monitoring response to CAR-T therapy, PET-CT is usually performed early (M1 scan) and later (M3 scan). In the current study, we retrospectively investigated the role of PET-CT performed before CAR-T infusion in predicting outcome, thus assisting in the selection of patients that may benefit from CAR-T, as well as the application of post-treatment PET-CT in identifying therapy failure. Our medical center is a tertiary referral center that provides special medical services, such as CAR-T therapy, to patients living all over the country. The majority but not all PET-CT scans of the patients included in this study were performed in our department. In this retrospective study, the statistical analysis included scans performed in our facilities only.

Several PET parameters can be used in clinical practice for reporting PET-CT scans of DLBCL patients. Measurement of SUVmax, comparison of SUVmax between different time points (as done with the ΔSUVmax method), and application of the Deauville 5-point scale are usually easily performed. Calculation of TMTV and TLG are somewhat more time-consuming. In the current study, we investigated all of the latter parameters on TD, TT, M1, and M3 PET-CT scans.

Our multivariate analysis revealed that the only pre-CAR-T PET parameter found to be an independent risk factor for shorter OS was TD-SUVmax > 17.1. If a patient meets this criterion on TD PET-CT, it appears that already at this point the clinician may suspect that CAR-T might have a lower chance of success. Two pre-treatment clinical parameters were also found to independently predict shorter OS: serum LDH > 450 U/l (a risk factor identified earlier by Hirayama et al. [30]) and an ECOG performance score > 1. In practice, the patients included in our study with all of the three mentioned risk factors had very short OS and probably did not benefit from CAR-T therapy.

Data from recent studies suggested that TMTV measured on TT-PET may be associated with disease progression [19, 20]. This finding was also validated in the current study on a longer follow-up period. We also found that reporting TT-SUVmax, which is obtained more easily than TT-TMTV, is enough and provides an alternative practical tool for prediction of survival.

The response to bridging therapy given between TD and TT PET-CT scans, as assessed by both the Deauville scale and the ΔSUVmax method, did not predict post-CAR-T survival. This result again emphasizes that reporting TD-SUVmax and TT-SUVmax should be included in pre-treatment PET-CT reports rather than focusing on response assessment to the bridging therapy. This result that patients with a favorable response to the bridging therapy did not have significantly longer OS in our study call into question the prognostic role of the bridging therapy before CAR-T infusion. Still, one should keep in mind that several bridging protocols were given to the included patients in our cohort, that bridging therapy may be indicated to prevent toxicity, and that large prospective studies will be needed to define the optimal protocols and the true role of bridging therapy.

Unlike other small studies that found an association between TT-PET and CRS [20, 23], we did not find associations between PET variables at TD or TT and toxicity, possibly because of the high prevalence of CRS and the small numbers of high-grade CRS and ICANS.

Monitoring response to CAR-T therapy is essential in order to identify CAR-T failure as early as possible. A practical tool that correctly differentiates between responders with longer predicted OS and non-responders with shorter predicted OS is of great importance. A Deauville score > 3 on M1-PET-CT scans was found as the strongest predictor of short OS in the current study. ΔSUVmax measurement on M1-PET was also found to be of predictive value when comparing M1-SUVmax to TD-SUVmax (and not to TT-SUVmax). Either of these parameters on an M1-PET-CT report may provide critical information to clinicians and guide clinical decisions.

On M3-PET-CT scan, our findings suggest that response assessment correctly identified patients with a favorable response and longer OS using both the Deauville scale and the ΔSUVmax method (with TD-SUVmax or TT-SUVmax, but not M1-SUVmax as baseline values). In the current study, using either method, none of the patients that had been identified as having a favorable response on M3-PET-CT died during their follow-up. The number of patients included in this analysis was small, and their follow-up time was limited since we included only those patients that had not been given any anti-lymphoma treatment between CAR-T infusion and the M3-PET-CT scan. This limitation applies for this study in general, and further validation of our results on larger cohorts with longer follow-up is needed.

Conclusions

Our results suggest that measurement of SUVmax of the "hottest" lymphoma site on pre-treatment PET-CT, mainly in combination with serum LDH levels and evaluation of ECOG performance status, may differentiate between R/R DLBCL patients that may benefit from CAR-T therapy and those with poor prognosis for whom this treatment is less

valuable. Post-CAR-T PET-CT may identify early therapy failure. One month after CAR-T infusion, both the Deauville score and the ΔSUVmax measurement with TD-SUVmax as the reference for comparison can be used for differentiating between responders and non-responders.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate 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. All included data were collected as part of a retrospective study protocol approved by the local institutional ethics committee, which waived written informed consent (Reference ID 0503–20-TLV).

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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