Cancer Treatment and Research Communications 46 (2026) 101080

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.sciencedirect.com/journal/cancer-treatment-and-research-communications

Impact of spleen volume and volume change in non-Hodgkin lymphoma treated with chimeric antigen receptor t-cell therapy

Christina Quell [a,1], Wolfgang G. Kunz [a,c,f,1], Viktoria Blumenberg [b,c,d], Kai Rejeski [c,d,g], Veit L. Bücklein [b,c,d,f], Maria Ingenerf [a], Christian Schmidt [d], Gabriel T. Sheikh [e], Matthias Brendel [e,f], Jens Ricke [a,f], Michael von Bergwelt-Baildon [c,d,f], Marion Subklewe [b,c,d,f], Michael Winkelmann [a,c,f,*]

[a] Department of Radiology, University Hospital, LMU Munich, Munich, Germany
[b] Laboratory for Translational Cancer Immunology, Gene Center of the LMU Munich, Munich, Germany
[c] German Cancer Consortium (DKTK) and Bavarian Center for Cancer Research (BZKF), partner site Munich, Munich, Germany
[d] Department of Medicine III, University Hospital, LMU Munich, Munich, Germany
[e] Department of Nuclear Medicine, University Hospital, LMU Munich, Munich, Germany
[f] Comprehensive Cancer Center München-LMU ($CCCM^{LMU}$), LMU Munich, Munich, Germany
[g] Adult Bone Marrow Transplantation Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA

ARTICLE INFO

Keywords:
Spleen
CAR T-cell therapy
Non-Hodgkin-Lymphoma
Immunotherapy

ABSTRACT

Purpose: Chimeric antigen receptor T-cell (CART) therapy targeting CD19 is effective for relapsed/refractory (r/r) lymphoma. As part of the lymphatic system, the spleen might influence CART outcomes. We examined how spleen volume (SV) and its changes affect progression-free (PFS) and overall survival (OS).
Methods: Patients with baseline (BL) and 30-day follow-up (FU1) (PET)/CT scans were included. Spleens were 3D-segmented, and volume change (SVC) from BL to FU1 was calculated. Treatment response, overall response rate, and PFS were evaluated by Lugano criteria.
Results: Among 68 patients, responders had a significantly greater SVC decrease from BL to FU1 than non-responders ($p = 0.001$). Those with baseline splenic involvement (SI^{BL}) showed a smaller, non-significant $SVC^{BL\ to\ FU1}$ decrease ($p = 0.056$). Survival analysis showed significant differences in OS (167 vs. 390 days, $p = 0.040$) and PFS (79 vs. 327 days, $p = 0.008$) based on median $SVC^{BL\ to\ FU1}$. In combination with SI^{BL}, SVC was significantly associated with PFS ($p = 0.049$), but not OS.
Conclusion: This study demonstrated that the early change in SV is associated with PFS and OS, regardless of splenic involvement and should be explored as a potential novel dynamic biomarker in the context of lymphoma patients receiving CART.

Introduction

Chimeric antigen receptor T-cell therapy (CART) targeting the CD19 antigen is a powerful treatment option for the treatment of relapsed or refractory (r/r) large B-cell lymphoma (LBCL) [1–3], follicular lymphoma (FL) [2,3] and mantle-cell lymphoma (MCL) [4] with different available CAR T cell products. Compared to historical cohorts CART results in clinically significant improvements of both progression-free survival (PFS) and overall survival (OS). In clinical trials overall response rates (ORR) between 52 and 85 % were shown. Approximately 60 % of non-Hodgkin lymphoma (NHL) patients suffer progression or relapse within the first three months after reinfusion of CAR T-cells [1, 3–6]. There are many factors that have an impact on CART efficacy, such as age [7], the International Prognostic Index (IPI) [8] or tumor burden (TB) [9–11]. However, the mechanisms leading to CART resistance are not fully understood yet.

Novelty Statement: This study is the first to demonstrate that changes in spleen volume are significantly associated with progression-free and overall survival in lymphoma patients receiving CAR T-cell therapy, highlighting spleen volume dynamics as a potential novel biomarker for treatment response.

* Corresponding author at: Department of Radiology, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany.
E-mail address: michael.winkelmann@med.lmu.de (M. Winkelmann).

[1] Christina Quell and Wolfgang G. Kunz contributed equally to this work.

https://doi.org/10.1016/j.ctarc.2025.101080

Available online 18 December 2025
2468-2942/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Computed tomography (CT) and 18-F fluorodeoxyglucose positron emission tomography ([18F]-FDG PET)/CT are commonly used for baseline (BL) staging and response evaluation in NHL [12]. Besides detection of TB, lymphoma spread and extranodal manifestations, more recent studies show the benefit of dynamic changes in TB including the pre-baseline examinations [13,14]. The imaging based biomarkers can be used for risk stratification, response assessment, and early detection of relapse, helping to further personalize and optimize CART [15]. So far, previous studies on medical imaging biomarkers for CART have mainly assessed tumor lesions rather than the structure and behavior of individual organs during disease progression.

NHL most commonly affect lymph nodes with painless enlargement, as well as other lymphatic organs like the tonsils and the spleen [16]. Manifestations in the spleen can either be focal or diffuse with or without splenomegaly. The spleen, as part of the lymphatic system, is often involved in immune response processes [17]. These immunological mechanisms could also play a role in CART efficacy [18]. Therefore, imaging of lymphatic tissue (such as spleen and bone marrow) is of particular interest. One study detected that FDG uptake in bone marrow unaffected by tumor infiltration is a possible PET/MRI parameter for prediction of PFS and OS [19]. Another case series with a small population of seven patients investigated PET/CT imaging of lymphatic organs in LBCL patients. They were able to show that larger decreases in post-therapeutic FDG uptake in normal spleen and lymph nodes were associated with unfavorable outcome of CAR T-cell therapy [20].

Since there are few studies that shed light on the role of the spleen in the context of CART, further investigation of the influence of lymphoid tissue besides lymph nodes on the efficacy of CART is needed. In this study, we investigate the impact of SV and its dynamic change between BL and early follow-up imaging time points on PFS and OS in the context of CART.

Methods

Study design and population

The study population consists of patients of a prospective registry who were treated at the Comprehensive Cancer Center Munich of the Ludwig-Maximilian University Munich ($CCCM^{LMU}$) with commercialized CD19 specific CART products.

The following inclusion criteria were applied:

1. Patients with r/r lymphoma (LBCL, tFL and MCL)
2. CAR T-cell infusion between 01/2019 and 06/2022
3. Available CT or ^{18}F-FDG PET/CT imaging studies at BL (≤2 weeks before CART)
4. Available imaging at 30-day follow-up (FU1)

The following exclusion criteria were applied:

1. Any non-diagnostic imaging studies
2. No measurable disease on imaging according to Lugano criteria [12]
3. Absence of target lesions according to Lugano criteria at BL imaging

All medical records and imaging studies were reviewed with the approval of the LMU Munich Institutional Review Board (LMU Ethics Committee, project number 19–817) and informed patient consent was obtained from all individual participants included in the study.

Imaging and response assessment

The trial reporting software mintLesion 3.8 (mint Medical GmbH; Heidelberg, Germany) was used for all imaging analyses. To evaluate treatment response Lugano criteria [12] were applied with segmentation of up to six target lesions (TL). In addition to unidimensional measurement as requested by Lugano criteria, a 3D segmentation of the spleen was performed as described below. Responders were defined as patients who had complete response (CR) or partial response (PR) and non-responders were defined as patients who had a stable disease (SD) or progressive disease (PD) at the imaging time point FU1, according to Lugano criteria. All imaging analysis were approved in consensus reading of two board certified radiologists.

Definition of spleen volume (SV), spleen involvement (SI) and spleen volume change (SVC)

SV was measured at BL and FU1 by manual 3D segmentation. In addition, the dynamic changes in spleen volume (SVC) between these two timepoints were analyzed. Spleen involvement (SI) of lymphoma was evaluated at BL. SI was defined as focal or diffuse involvement or as both. Splenomegaly was determined according to Lugano criteria with enlargement >13 cm [12].

BL imaging was performed as the last imaging exam before CAR T-cell infusion (≤2 weeks before CART). Time windows have been defined to limit time bias in the calculation of SVC.

SVC was calculated using the following formula:

$$SVC^{BL\ to\ FU1}\ [\%] = \frac{SV_{FU1} - SV_{BL}\ [in\ cm^3]}{SV_{BL}\ [in\ cm^3]} * 100$$

Analysis of PFS and OS

PFS was defined from day one of CART to the day progression of lymphoma was detected on CT as defined by Lugano criteria and above. OS was defined from day one of CART to the day of any death related event (either lymphoma-treatment-related or any other cause).

Statistical analysis

All statistical analyses were performed using IBM SPSS statistics (version 29.0.0.0 (241)). The associated figures were created using R Project (version 4.3.0) including package survival (version 3.5–5).

Mann-Whitney U tests were used to investigate the significance of differences between responders and non-responders and between patients with or without SI^{BL}. ORR was calculated as the proportion of patients with CR and PR according to Lugano in % and corresponds to the group of responders at FU1.

For survival analysis, OS and PFS were visualized using Kaplan-Meier survival curves. Log-rank (Mantel-Cox) tests were performed to assess the significance of survival between the groups. For the various sub analyses of survival, the groups were formed either based on the median (for analysis of the influence of SV^{BL} and $SVC^{BL\ to\ FU1}$ on OS or PFS), and based on the presence or absence of SI (for analysis of the influence of SI^{BL} on OS or PFS). For all statistical tests an alpha level of 0.05 was used.

Results

Patient characteristics

Of the 78 patients treated during the inclusion period 68 patients met the inclusion criteria (median age: 64 years, 41.2 % female). 4 patients were excluded due to missing FU1 imaging and 6 patients due to missing measurable TL at BL (see Fig. 1).

Out of the 68 included patients 56 had a LBCL (82.4 %), 11 patients had a MCL (16.2 %), and 1 patient had a tFL (1.5 %). The patients' SV at BL ranges between 57.7 cm^3 and 5181.8 cm^3 (median SV 244.5 cm^3). Splenomegaly was present in 12 patients (15.4 %, all patients were male). Data is shown in patient characteristics in Table 1.

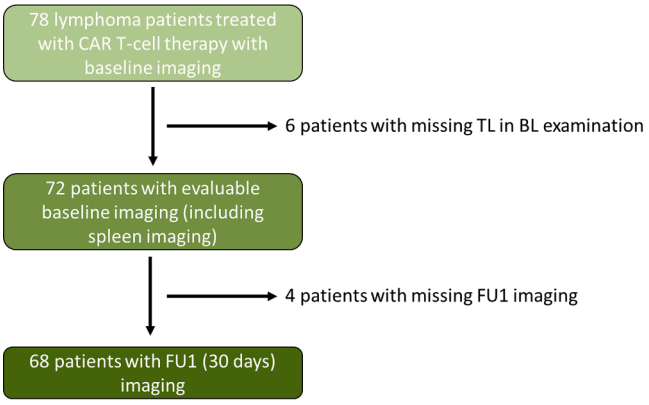

Fig. 1. Flow Chart. Illustrated is a flow chart for all 78 patients that were treated with CAR T-cell therapy Comprehensive Cancer Center Munich-Ludwig-Maximilian University Munich ($CCCM^{LMU}$) with CD19 specific CART products in between 01/2019 and 06/2022. 10 patients had to be excluded due to missing FU1 imaging or missing TL in BL examination.

Table 1
Patient Characteristics. BL: baseline; CAR: chimeric antigen receptor; CR: complete response; FL: follicular lymphoma; FU1: follow up 1; IPI: International Prognostic Index; LBCL: large B cell lymphoma; LDH: lactate dehydrogenase; MCL: mantle cell lymphoma; PD: progressive disease; PR: partial remission; SD: stable disease; SPD: sum of the product of diameters; SV: spleen volume; SVC: spleen volume change.

Age (median)		64
Gender	Female:	28 (41.2 %)
	Male:	40 (58.8 %)
Lymphoma Entity	LBCL:	56 (82.4 %)
	MCL:	11 (16.2 %)
	tFL:	1 (1.5 %)
Ann Arbor Stage	I:	12 (17.6 %)
	II:	14 (20.6 %)
	III:	10 (14.7 %)
	IV:	32 (47.1 %)
IPI	0:	1 (1.5 %)
	1:	15 (22.1 %)
	2:	17 (25.0 %)20 (29.4 %)
	3:	11 (16.2 %)
	4:	4 (5.9 %)
	5:	
CAR T Product	Tisagenlecleucel:	28 (41.2 %)
	Axicabtagene ciloleucel:	26 (38.2 %)
	Brexucabtagene autoleucel:	11 (16.2 %)
	Lisocabtagene maraleucel:	3 (4.4 %)
Bridging	Yes:	48 (70.6 %)
	No:	20 (29.4 %)
SPD (median)	BL:	4332.5 mm^2
	FU1:	1643.7 mm^2
LDH (median)	Apheresis:	319.5 U/L
	Prior Lymphodepletion:	281.0 U/L
Lugano Response FU1:	CR:	10 (14.7 %)
	PR:	27 (39.7 %)
	SD:	16 (23.5 %)
	PD:	15 (22.1 %)
SV (median)	BL:	244.5 cm^3
	FU1:	209.6 cm^3
SVC (median)	BL to FU1:	−8.85 cm^3
Splenomegaly at BL	Total:	12 (15.4 %)0 (0 %)
	Female:	12 (100 %)
	Male:	
Spleen Involvement	Yes:	16 (23.5 %)
	Diffuse:	13 (81.2 %)
	Focal:	1 (6.3 %)
	Both:	2 (12.5 %)
	No:	52 (76.5 %)

Association of $SVC^{BL\ to\ FU1}$ with treatment response and with spleen involvement at BL (SI^{BL})

At FU1, patients of the responder group showed a significant decrease in spleen volume ($SVC^{BL\ to\ FU1}$) compared to the non-responding group (median $SVC^{BL\ to\ FU1}$ responder: −16.2 %, median $SVC^{BL\ to\ FU1}$ non-responder: +1.4 %, $p = 0.001$; see Fig. 2A). For FU1, 37 of the included 68 patients were classified as responders and 31 as non-responders (ORR = 54.4 %). There was a difference in the ORR for patients with $SVC^{BL\ to\ FU1} \geq$ median (ORR = 41.2 %) and the ORR for patients with $SVC^{BL\ to\ FU1} <$ median (ORR = 76.5 %).

In a next analysis the differences between patients with and without baseline splenic involvement (SI^{BL}) were analysed. Here, we detected a small difference in $SVC^{BL\ to\ FU1}$, with patients with SI^{BL} showing a tendency towards decreasing spleen size compared to the patient group without SI^{BL}. However, this difference did not reach statistical significance (median $SVC^{BL\ to\ FU1}$ with SI^{BL}: −20.0 %, median $SVC^{BL\ to\ FU1}$ without SI^{BL}: −7.4 %, $p = 0.056$; see Fig. 2B).

Impact of SV^{BL} on survival

Next, we examined the association between absolute baseline splenic volume (SV^{BL}) and survival. Patients were grouped according to the median SV^{BL} of 244.5 cm^3 (interquartile range (IQR): 164.8 cm^3 to 378.5 cm^3). Median PFS was 91 days in patients with SV > median and 124 days in patients with SV < median (Fig. 3). Median OS was 243 days in patients with SV > median and 393 days in patients with SV < median. There were small differences for both PFS (Fig. 3A; $p = 0.376$) and OS (Fig. 3B; $p = 0.342$) that were not statistically significant.

Impact of $SVC^{BL\ to\ FU1}$ on survival

As there were differences in responding and non-responding patients in the change of splenic volume from baseline to first follow-up ($SVC^{BL\ to\ FU1}$, Fig. 2A), we next explored if $SVC^{BL\ to\ FU1}$ can also be used to stratify PFS and OS. Therefore, patients were split in two groups by median $SVC^{BL\ to\ FU1}$ of −8.9 cm^3 (IQR: −27.0 % to 6.1 %), which is shown in Fig. 4. Patients with a SVC < median exhibited significantly extended PFS compared to patients with values > median (327 vs. 79 days, $p = 0.008$). Similar differences were detected in OS (Fig. 4B) with patients ⟨ median having a median OS of 390 days compared to patients ⟩ median having a median OS of 167 days ($p = 0.040$).

Influence of SI^{BL} and $SVC^{BL\ to\ FU1}$ on survival

To exclude that splenic involvement at baseline (SI^{BL}) influences the prognostic value of $SVC^{BL\ to\ FU1}$ shown in Fig. 4*A+B* additional analyses were conducted. In a first step, survival analysis comparing the 16 (23.5 %) patients with SI^{BL} with the 52 (76.5 %) patients without SI^{BL} were performed (Fig. 4*C+D*). We detected no significant differences for PFS ($p = 0.550$) and OS ($p = 0.474$).

In a next step, we performed a subgroup analysis. Both patients with $SVC^{BL\ to\ FU1}$ higher and lower than median were split into subgroups depending on SI^{BL}. 23 patients (33.8 %) had a $SVC^{BL\ to\ FU1} <$ median without SI^{BL} (median PFS 153 days and median OS 386 days), 11 patients (16.2 %) had a $SVC^{BL\ to\ FU1} <$ median with SI^{BL} (median PFS 354 days and median OS 418 days), 29 patients (42.6 %) had a $SVC^{BL\ to\ FU1} \geq$ median without SI^{BL} (median PFS 87 days and median OS 169 days) and 5 patients (7.4 %) had a $SVC^{BL\ to\ FU1} \geq$ median with SI^{BL} (median PFS 33 days and median OS 93 days). There was a small significant difference between the groups for PFS ($p = 0.049$; Fig. 5A), while there was no significant difference regarding OS ($p = 0.175$; Fig. 5B).

Discussion

In this retrospective observational study, we report results from 68

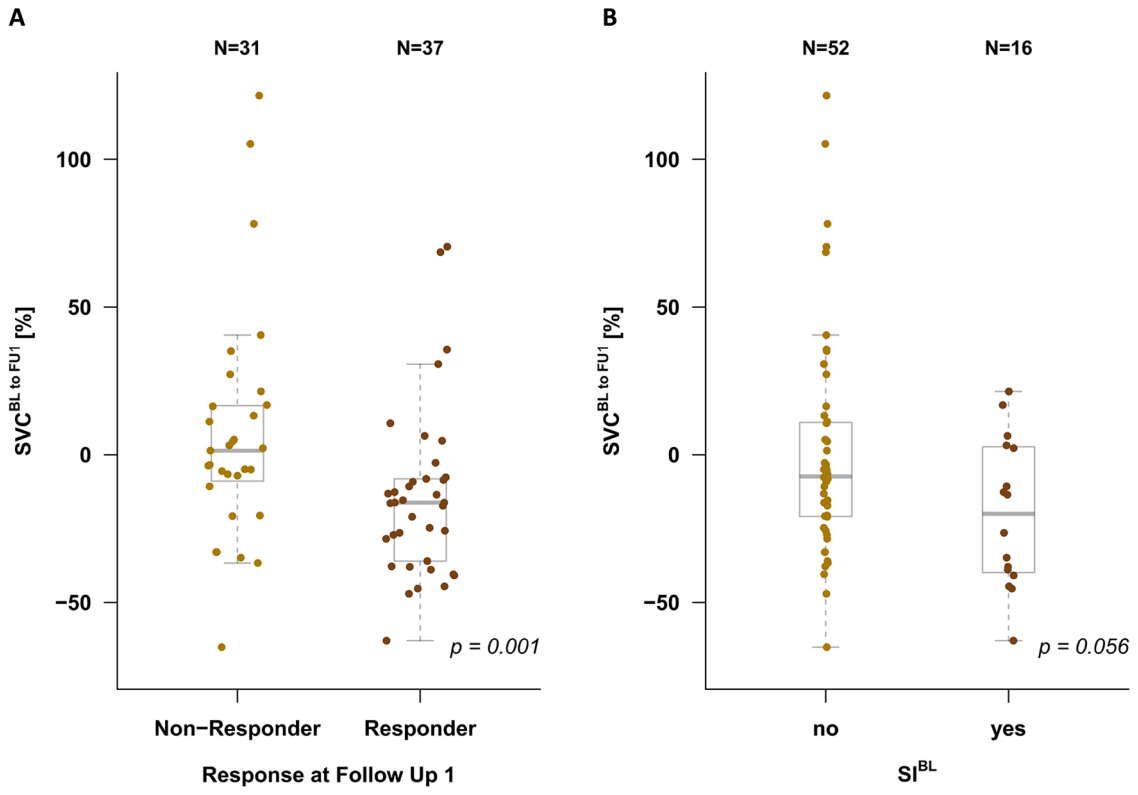

Fig. 2. $SVC^{BL\ to\ FU1}$ per Lugano Response at FU1 and per SI^{BL}. Analysis of differences in spleen volume change (SVC). **A** compares the SVC distribution between responding and non-responding patients in a boxplot analysis. Median $SVC^{BL\ to\ FU1}$ was −16.2 % (IQR: −36.9 % to −7.9 %) in responding and +1.4 % (IQR: −10.7 % to +16.8 %) in non-responding patients at FU1 ($p = 0.001$). **B** shows a boxplot for the analysis of SVC distribution by splitting the cohort according to their spleen involvement at BL (SI^{BL}). Median $SVC^{BL\ to\ FU1}$ was −20.0 % (IQR: −40.4 % to +2.9 %) in patients with SI^{BL} and −7.4 % (IQR: −20.9 % to 11.1 %) with no SI^{BL} ($p = 0.056$).

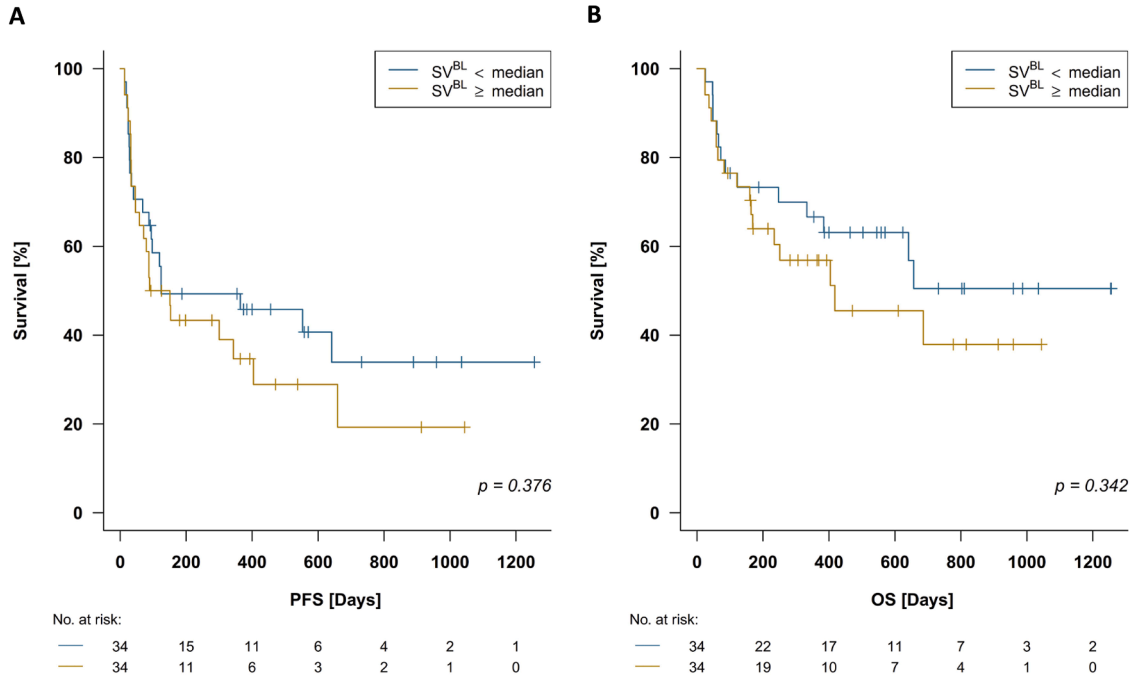

Fig. 3. Impact of SV^{BL} on PFS and OS. Analysis of progression-free survival (PFS) and overall survival (OS) for spleen volume (SV) categories. **A** depicts Kaplan-Meier curves for PFS for patients split by the median SV at baseline ($SV^{BL\ (median)}$). Median PFS was 91 days (IQR: 33 days to 348 days) in patients with volumes higher than median and 124 days (IQR: 32.75 days to 554.25 days) in patients with values smaller than median. The difference is statistically not significant ($p = 0.376$). **B** displays the survival analysis for OS for the same groups as in Fig. 3A. Median OS was 243 days (IQR: 90 days to 431 days) in patients with SVC^{BL} higher than median and 393 days (IQR: 91 days to 676 days) in patients with SVC^{BL} smaller than median. There was no significant difference between the two groups ($p = 0.342$). The group with SV^{BL} < median is labeled blue and the group with $SV^{BL} \geq$ median are labeled brown.

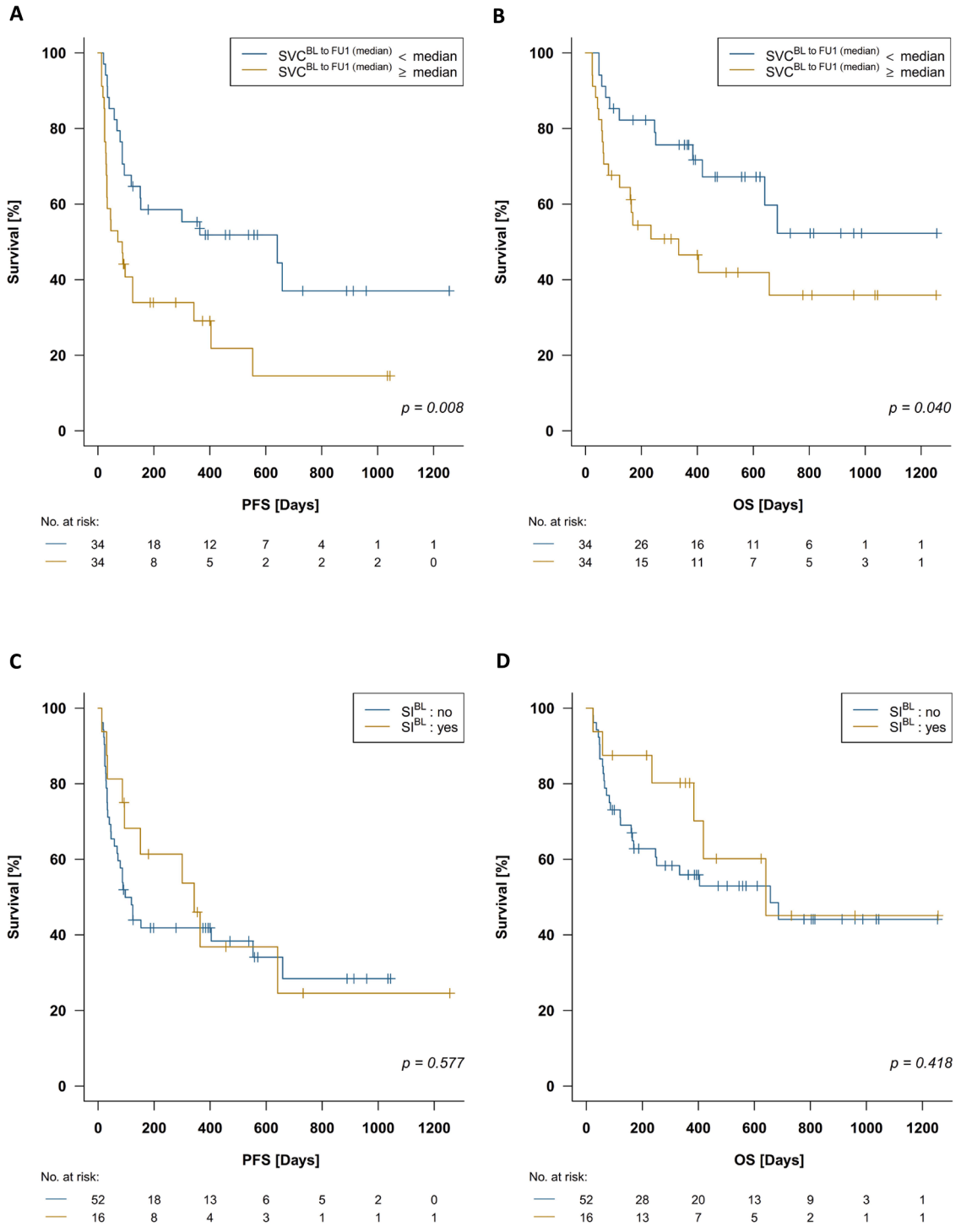

Fig. 4. Impact of $SVC^{BL\ to\ FU1}$ and SI^{BL} on PFS and OS. Analysis of progression-free survival (PFS) and overall survival (OS) for spleen volume change (SVC) and spleen involvement (SI) categories. **A** depicts Kaplan-Meier curves for PFS for patients with $SVC^{BL\ to\ FU1\ (median)}$ ($p = 0.008$) and **B** for OS for patients with $SVC^{BL\ to\ FU1\ (median)}$ ($p = 0.040$) with a SVC < median SVC labeled blue and a SVC ≥ median SVC labeled brown. Median PFS was 79 days (IQR: 27 days to 218 days) in patients with volumes higher than median and 327 days (IQR: 85 days to 561 days) in patients with values smaller than median. Median OS was 167 days (IQR: 62 days to 514 days) in patients with volumes higher than median and 390 days (IQR: 204 days to 652 days) in patients with values smaller than median. **C** depicts Kaplan-Meier curves for PFS for patients with/without SI^{BL} ($p = 0.577$) and **D** for OS for patients with/without SI^{BL} ($p = 0.418$) with none SI^{BL} labeled blue and patients with SI^{BL} labeled brown. Median PFS was 240 days (IQR: 89 days to 433 days) in patients with SI^{BL} and 94 days (IQR: 32 days to 398 days) in patients without SI^{BL}. Median OS was 377 days (IQR: 220 days to 637 days) in patients with SI^{BL} and 267 days (IQR: 83 days to 600 days) in patients without SI^{BL}.

patients with r/r lymphoma treated with CD19 specific CART products in a real-world setting. We demonstrate that the change in spleen volume between baseline and 30-day follow-up ($SVC^{BL\ to\ FU1}$) is associated with PFS and OS both for patients with and without involvement of the spleen at baseline (SI^{BL}). Therefore, $SVC^{BL\ to\ FU1}$ is a promising candidate to be used as an early survival and response predictor for lymphoma patients under CART.

SV has previously been shown to have a predictive value for

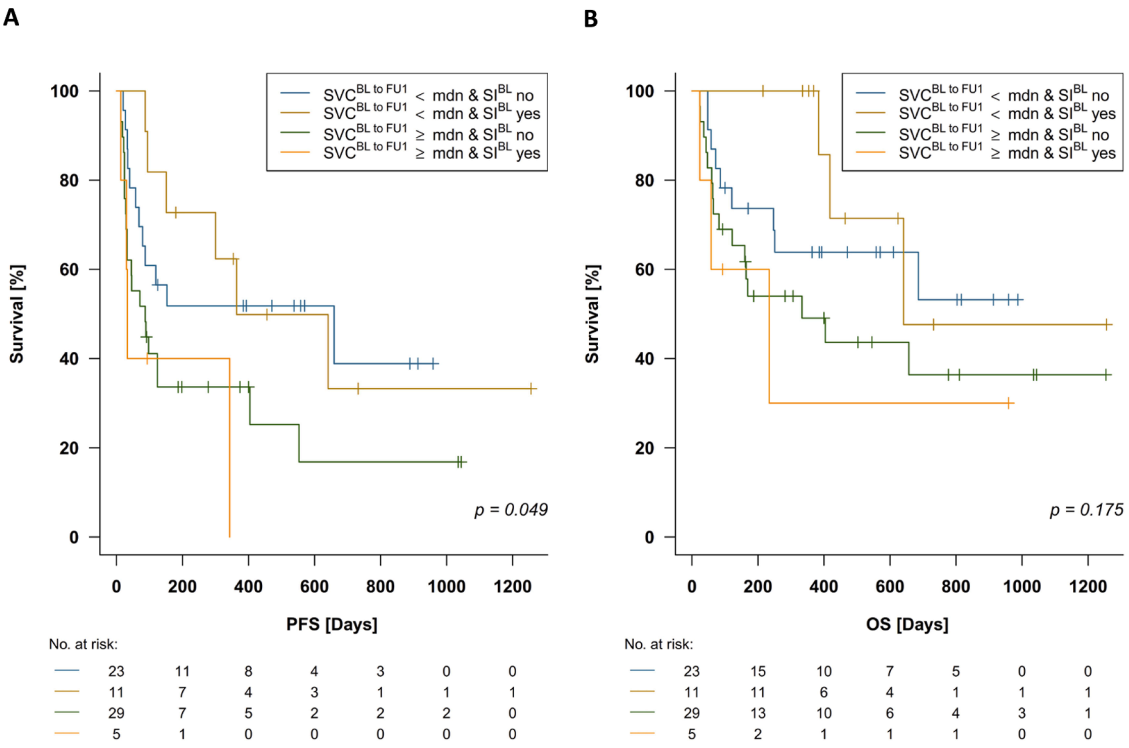

Fig. 5. Subgroup Survival analysis for $SVC^{BL\ to\ FU1\ (median)}$ and SI^{BL} on PFS and OS. Subgroup analysis of progression-free survival (PFS) and overall survival (OS) for spleen volume change (SVC) in combination with splenic involvement (SI) categories. **A** depicts Kaplan-Meier curves for PFS for patients with $SVC^{BL\ to\ FU1}$ in combination with SI^{BL} ($p = 0.049$) and **B** for OS for patients with $SVC^{BL\ to\ FU1}$ in combination with SI^{BL} ($p = 0.175$) with $SVC^{BL\ to\ FU1}$ < median (mdn) and no SI^{BL} labeled blue, $SVC^{BL\ to\ FU1}$ < mdn and SI^{BL} labeled brown, $SVC^{BL\ to\ FU1}$ ≥ mdn and no SI^{BL} labeled green and patients with $SVC^{BL\ to\ FU1}$ ≥ mdn and SI^{BL} labeled orange.

treatment response and treatment course in various studies in solid tumors, but had not yet been extensively investigated in patients with NHL receiving CART. Prassopoulos et al. and Harris et al. found, that SV of patients with solid tumors may be influenced by sex, age and underlying chronic inflammation [21,22]. Suzuki et al. investigated SV as a predictive factor for severe thrombocytopenia and possibly as a long-term prognostic indicator for patients with pancreatic cancer [23]. El Chediak et al. examined SV in relation to its ability as a predictor of oxaliplatin toxicity in patients with solid tumors. This study showed that an increase in SV could potentially lead to peripheral neuropathy and is therefore a possible marker for oxaliplatin-induced toxicity [24]. Other studies in lymphomas show that radiomic features also play a role and may even distinguish lymphoma subtypes [25].

In our study, we used the Lugano criteria, which are the most widely used criteria for response classification for lymphoma [12], to determine the tumor response and ORR, to divide patients into responder and non-responder groups and to determine PFS. According to Lugano criteria a 30-day ORR (FU1) of 54.4 % was found in our study. The ORR of the pivotal study for tisagenlecleucel (tisa-cel) was with 52 % in a similar range to that in our cohort [1], while the ORR of the pivotal studies for axicabtagene ciloleucel (axi-cel) [3,5], brexucabtagene autoleucel (brexu-cel) (ORR 85 %) [4] and lisocabtagene maraleucel (lisocel) (ORR 73 %) [6] was higher, but similar differences have already been shown comparing US and European cohorts [26]. By dividing our patient cohort into patients above and below the median, the ORR for patients with a SVC < median was even higher (ORR 76.5 %). In keeping with this, in our statistical comparison of responders and non-responders, a significantly lower $SVC^{BL\ to\ FU1}$ is observed in patients with a positive response to CART at FU1 (Fig. 2A). These results of our study correspond to the observations from a study of Daskalogiannaki et al., in which the spleen of patients with lymphoma showed a reduction in size when responding to therapy [27]. SI in lymphoma is common while the spleen is involved in 10 – 40 % of patients with NHL [28,29]. In our cohort, SI^{BL} was 23.5 %. When dividing our cohort into patients with and without SI^{BL}, there was a nonsignificant trend in which patients with SI^{BL} tended to have a lower $SVC^{BL\ to\ FU1}$, which means a higher decrease in volume (Fig. 2B). Since responders have a significantly lower $SVC^{BL\ to\ FU1}$, there could be a tendency for patients with SI^{BL} to show a better response to CART. Overall, our investigations show that an early decrease in spleen volume in the first 30 days post CART is associated with an improved response to CART and an improved ORR.

PFS and OS relating to SV^{BL} and $SVC^{BL\ to\ FU1}$ with and without SI^{BL} were analysed in different scenarios. We showed that there is no significant difference by grouping patients according to the absolute SV^{BL} in either PFS or OS. In contrast, grouping patients by the dynamic change spleen volume ($SVC^{BL\ to\ FU1}$) resulted in significant differences in PFS or OS. Zhu et al. and Batlevi et al. showed an association between imaging endpoint surrogates for survival in first-line treatment of lymphoma [30,31]. In line with this, in our study we investigated that the $SVC^{BL\ to\ FU1}$ had a significant influence in both PFS and OS. Patients with a greater decrease in $SVC^{BL\ to\ FU1}$ had hereby significantly longer PFS and OS. Derlin et al. examined in a small cohort the 18F FDG uptake in PET/CT in lymphoid organs from seven LBCL patients. Here it was shown that larger decreases in post therapeutic FDG uptake in normal spleen and lymph nodes were associated with an unfavorable outcome of CART [20].

Although our study design does not allow definitive mechanistic conclusions, several plausible explanations support why early spleen volume changes may correlate with PFS and OS. As a central immunologic organ, the spleen reflects systemic immune activity; early volume reductions may signal favorable CAR-T–related immune responses, including decreased lymphoma burden, shifts in immune cell populations, or dampened inflammation. Such changes have been linked to more effective CAR-T function and may serve as surrogate markers of early tumor control. A decrease from BL to FU1 may also indicate reduced splenic lymphoma involvement, consistent with previously reported associations with improved outcomes. More broadly, early spleen volume normalization may reflect lower systemic stress and cytokine

activity, conditions associated with optimal CAR-T expansion and durability. While these interpretations remain hypothesis-generating and require biological validation, they offer a mechanistic context for the observed associations between spleen volume change, PFS, and OS.

Since no significant differences were observed in either PFS or OS when dividing patients with and without SI^{BL}, we further considered more differentiated subgroups in combination of SI^{BL} with $SVC^{BL\ to\ FU1}$. There was a significant difference between the groups in PFS, but not in OS. In keeping with our initial analyzes of responders and non-responders and the difference in $SVC^{BL\ to\ FU1}$ in patients with and without SI^{BL}, the maximum PFS was shown here in the group of patients with an $SVC^{BL\ to\ FU1}$ smaller than the median and simultaneous SI^{BL}. The minimum PFS was found in patients with an $SVC^{BL\ to\ FU1}$ greater than the median, also with SI^{BL}.

To our knowledge, there are no previous studies analyzing the dynamic SVC in r/r NHL patients under CAR T-cell therapy. Our study is the first study to analyze SVC in patients undergoing CART, but it is limited by moderate patient numbers and its monocentric design. In the future, the generalizability of shown results (e.g., the association of $SVC^{BL\ to\ FU1}$ with PFS and OS) should be confirmed in an independent study. Furthermore, it is important to note that some patients had to be excluded from analysis as there was no measurable disease in the performed imaging. Since this issue also occurs in everyday clinical routine, it may limit the use of this imaging biomarker. Therefore, additional studies including different sites with various clinical backgrounds are warranted.

To conclude, we demonstrate that early volume change of the spleen ($SVC^{BL\ to\ FU1}$) is prognostic for tumor response, ORR, as well as PFS and OS. Here a $SVC^{BL\ to\ FU1}$ smaller than the median is associated with longer PFS and OS and could therefore be used as an early response predictor for lymphoma patients under CART. SI^{BL} does not have a significant impact on PFS and OS. A trend was seen for patients with SI^{BL} to have lower $SVC^{BL\ to\ FU1}$. Therefore, future studies should investigate SI and SVC in larger studies to better understand the impact of SI and SVC on treatment response, PFS, and OS in lymphoma patients receiving CART.

Glossary

BL = baseline
CART = chimeric antigen receptor T-cell therapy
CR = complete response
DoR = depth of response
FDG = fluorodeoxyglucose
FL = follicular lymphoma
FU= follow-up
IPI = International prognostic index
IQR = interquartile range
LBCL = large B-cell lymphoma
MCL = mantle-cell lymphoma
NHL = non-Hodgkin lymphoma
ORR = overall response rate
OS = overall survival
PET/CT = positron emission tomography-computed tomography
PD = progressive disease
PFS = progression-free survival
PR = partial response r/*r* = relapsed or refractory
SD = stable disease
SI = splenic involvement
SPD = sum of the product diameters
SV = spleen volume
SVC = spleen volume change
TB = tumor burden
TL = target lesion

Funding

The work was supported by funding from the research program "Förderung für Forschung und Lehre (FöFoLe) project number 1147″ of the Medical Faculty of Ludwig Maximilian University (LMU) Munich and the Bavarian Cancer Research Center (BZKF) to M.W.. The work was further supported by the Else-Kröner-Fresenius Stiftung (to V.B.) and the German Cancer Consortium DKTK (to V.B.).

Ethics approval

All medical records and imaging studies were reviewed with the approval of the LMU Munich Institutional Review Board (LMU Ethics Committee, project number 19–817).

Consent to participate

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

CRediT authorship contribution statement

Christina Quell: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Wolfgang G. Kunz:** Writing – review & editing, Validation, Supervision, Methodology, Data curation, Conceptualization. **Viktoria Blumenberg:** Writing – review & editing, Investigation, Formal analysis, Data curation. **Kai Rejeski:** Writing – review & editing, Formal analysis, Data curation. **Veit L. Bücklein:** Writing – review & editing, Data curation. **Maria Ingenerf:** Writing – review & editing, Data curation. **Christian Schmidt:** Writing – review & editing, Data curation. **Gabriel T. Sheikh:** Writing – review & editing, Data curation. **Matthias Brendel:** Writing – review & editing. **Jens Ricke:** Writing – review & editing. **Michael von Bergwelt-Baildon:** Writing – review & editing. **Marion Subklewe:** Writing – review & editing. **Michael Winkelmann:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

V.B.: BMS/Celgene: Research Funding; Kite/Gilead: Consultancy, Honoraria, Research Funding; Janssen: Research Funding, Honoraria; Novartis: Research Funding, Honoraria,; Roche: Research Funding; Takeda: Research Funding. **K.R.:** Kite/Gilead: Research Funding, Consultancy, Honoraria and travel support; Novartis: Honoraria; BMS/Celgene: Consultancy, Honoraria; Pierre-Fabre: travel support. **V.L.B.:** Amgen: Honoraria; Celgene/BMS: Research Funding; Kite/Gilead: Research Funding, Honoraria; Novartis: Honoraria; Pfizer: Honoraria. **C. S.:** Kite/Gilead: Travel Support. **M.v.B.:** Astellas: Consultancy, Research Funding and Honoraria; BMS: Consultancy, Research Funding and Honoraria; Kite/Gilead: Consultancy, Research Funding and Honoraria; Miltenyi: Consultancy, Research Funding and Honoraria; Mologen: Consultancy, Research Funding and Honoraria; MSD Sharp & Dohme: Consultancy, Research Funding and Honoraria; Novartis: Consultancy, Research Funding and Honoraria; Roche: Consultancy, Research Funding and Honoraria. **M.S.:** Amgen: Research Funding, Speakers Bureau; Astra Zeneca: Speakers Bureau; Aven Cell: Consultancy, BMS/Celgene: Research Funding, Speakers Bureau; CDR-Life: Consultancy, Gilead: Research Funding, Speakers Bureau; GSK: Speakers Bureau; Ichnos Sciences: Consultancy; Incyte Biosciences: Consultancy; Janssen: Research Funding, Consultancy, Speakers Bureau; Miltenyi Biotec: Research Funding, Consultancy; Morphosys: Research Funding; Molecular Partners: Consultancy; Novartis: Research Funding, Consultancy, Speakers Bureau; Pfizer: Consultancy, Speakers Bureau; Roche: Research Funding, Speakers Bureau; Seattle Genetics: Research Funding;

Takeda: Research Funding, Consultancy, Speakers Bureau. **W.G.K.**: Bristol Myers Squibb: Advisor; Boehringer Ingelheim: Advisor; mintMedical: Advisor, Need, Inc.: Advisor. The remaining authors declare no competing financial interests. None of the mentioned conflicts of interest were related to financing of the content of this manuscript.

References

[1] S.J. Schuster, et al., Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma, N. Engl. J. Med. 380 (1) (2018) 45–56, https://doi.org/10.1056/NEJMoa1804980.

[2] S.J. Schuster, et al., Chimeric antigen receptor T cells in refractory B-cell lymphomas, N. Engl. J. Med. 377 (26) (2017) 2545–2554, https://doi.org/10.1056/NEJMoa1708566.

[3] S.S. Neelapu, et al., Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma, N. Engl. J. Med. 377 (26) (2017) 2531–2544, https://doi.org/10.1056/NEJMoa1707447.

[4] M. Wang, et al., KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma, N. Engl. J. Med. 382 (14) (2020) 1331–1342, https://doi.org/10.1056/NEJMoa1914347.

[5] F.L. Locke, et al., Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial, Lancet Oncol. 20 (1) (2019) 31–42, https://doi.org/10.1016/S1470-2045(18)30864-7.

[6] J.S. Abramson, et al., Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study, Lancet 396 (10254) (2020) 839–852, https://doi.org/10.1016/S0140-6736(20)31366-0.

[7] W.A. Bethge, et al., GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany, Blood 140 (4) (2022) 349–358, https://doi.org/10.1182/blood.2021015209.

[8] M. Garcia-Recio, et al., The International prognostic index is associated with outcomes in diffuse large B cell lymphoma after chimeric antigen receptor T cell therapy, TransPlant Cell Ther. 27 (3) (2021) 233–240, https://doi.org/10.1016/j.jtct.2020.10.022.

[9] E.A. Dean, et al., High metabolic tumor volume is associated with decreased efficacy of axicabtagene ciloleucel in large B-cell lymphoma, Blood Adv. 4 (14) (2020) 3268–3276, https://doi.org/10.1182/bloodadvances.2020001900.

[10] G. Iacoboni, et al., Prognostic impact of total metabolic tumor volume in large B-cell lymphoma patients receiving CAR T-cell therapy, Ann. Hematol. 100 (9) (2021) 2303–2310, https://doi.org/10.1007/s00277-021-04560-6.

[11] M. Winkelmann, et al., Lymphoma tumor burden before chimeric antigen receptor T-cell treatment: RECIL vs. Lugano vs. metabolic tumor assessment, Front. Oncol. 12 (2022), https://doi.org/10.3389/fonc.2022.974029.

[12] B.D. Cheson, et al., Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification, J. Clin. Oncol. 32 (27) (2014) 3059–3068, https://doi.org/10.1200/JCO.2013.54.8800.

[13] M. Winkelmann, et al., Prognostic value of pre-infusion tumor growth rate for patients with lymphoma receiving chimeric antigen receptor T-cell therapy, Cytotherapy. 25 (9) (2023) 986–992, https://doi.org/10.1016/j.jcyt.2023.03.007.

[14] M. Winkelmann, et al., Modification of Lugano criteria by pre-infusion tumor kinetics improves early survival prediction for patients with lymphoma under chimeric antigen receptor T-cell therapy, J. Immunother. Cancer 11 (10) (2023), https://doi.org/10.1136/jitc-2022-006659.

[15] L. Vercellino, et al., Current and future role of medical imaging in guiding the management of patients with relapsed and refractory non-hodgkin lymphoma treated with CAR T-cell therapy, Front. Oncol. 11 (2021) 664688, https://doi.org/10.3389/fonc.2021.664688.

[16] M. Michl, BASICS Hämatologie, Elsevier, München, 2023, 6th ed.

[17] S.M. Lewis, A. Williams, S.C. Eisenbarth, Structure and function of the immune system in the spleen, Sci. Immunol. 4 (33) (2019), https://doi.org/10.1126/sciimmunol.aau6085.

[18] J. Cheng, et al., Understanding the mechanisms of resistance to CAR T-cell therapy in malignancies, Front. Oncol. 9 (2019) 1237, https://doi.org/10.3389/fonc.2019.01237.

[19] T. Sjöholm, et al., Whole body FDG PET/MR for progression free and overall survival prediction in patients with relapsed/refractory large B-cell lymphomas undergoing CAR T-cell therapy, Cancer Imaging 22 (1) (2022) 76, https://doi.org/10.1186/s40644-022-00513-y.

[20] T. Derlin, et al., (18)F-FDG PET/CT of off-target lymphoid organs in CD19-targeting chimeric antigen receptor T-cell therapy for relapsed or refractory diffuse large B-cell lymphoma, Ann. Nucl. Med. 35 (1) (2021) 132–138, https://doi.org/10.1007/s12149-020-01544-w.

[21] P. Prassopoulos, M. Daskalogiannaki, M. Raissaki, A. Hatjidakis, N. Gourtsoyiannis, Determination of normal splenic volume on computed tomography in relation to age, gender and body habitus, Eur. Radiol. 7 (2) (1997) 246–248, https://doi.org/10.1007/s003300050145.

[22] A. Harris, et al., Splenic volume measurements on computed tomography utilizing automatically contouring software and its relationship with age, gender, and anthropometric parameters, Eur. J. Radiol. 75 (1) (2010) e97–101, https://doi.org/10.1016/j.ejrad.2009.08.013.

[23] R. Suzuki, et al., Splenic volume as a prognostic indicator for unresectable pancreatic cancer, World Acad. Sci. J. 3 (1) (2021) 9, https://doi.org/10.3892/wasj.2020.80.

[24] A. El Chediak, et al., Increase in spleen volume as a predictor of oxaliplatin toxicity, Ther. Clin. Risk Manag. 14 (2018) 653–657, https://doi.org/10.2147/TCRM.S150968.

[25] J.S. Enke, et al., Radiomics features of the spleen as surrogates for CT-based lymphoma diagnosis and subtype differentiation, Cancers (Basel) 14 (3) (2022), https://doi.org/10.3390/cancers14030713.

[26] V. Bücklein, et al., Inferior outcomes of EU versus US patients treated with CD19 CAR-T for relapsed/refractory large B-cell lymphoma: association with differences in tumor burden, systemic inflammation, bridging therapy utilization, and CAR-T product use, Hemasphere 7 (8) (2023). Online]. Available: https://journals.lww.com/hemasphere/fulltext/2023/08000/inferior_outcomes_of_eu_versus_us_patients_treated.2.aspx.

[27] M. Daskalogiannaki, P. Prassopoulos, G. Katrinakis, I. Tritou, G. Eliopoulos, N. Gourtsoyiannis, Splenic involvement in lymphomas: evaluation on serial CT examinations, Acta Radiol. 42 (3) (2001) 326–332, https://doi.org/10.1080/028418501127346738.

[28] S.S. Saboo, et al., Spleen in haematological malignancies: spectrum of imaging findings, Br. J. Radiol. 85 (1009) (2012) 81–92, https://doi.org/10.1259/bjr/31542964.

[29] P.A. de Jong, et al., CT and 18F-FDG PET for noninvasive detection of splenic involvement in patients with malignant lymphoma, Am. J. Roentgenol. 192 (3) (2009) 745–753, https://doi.org/10.2214/AJR.08.1160.

[30] C.L. Batlevi, A. Younes, Surrogate end points in lymphoma, Ann. Oncol. 29 (8) (2018) 1622–1623, https://doi.org/10.1093/annonc/mdy219.

[31] J. Zhu, et al., Association of progression-free or event-free survival with overall survival in diffuse large B-cell lymphoma after immunochemotherapy: a systematic review, Leukemia 34 (10) (2020) 2576–2591, https://doi.org/10.1038/s41375-020-0963-1.