Journal of Hematology & Oncology

CORRESPONDENCE

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Conventional and novel [^{18}F]FDG PET/CT features as predictors of CAR-T cell therapy outcome in large B-cell lymphoma

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Abstract

Relapse and toxicity limit the effectiveness of chimeric antigen receptor T-cell (CAR-T) therapy for large B-cell lymphoma (LBCL), yet biomarkers that predict outcomes and toxicity are lacking. We examined radiomic features extracted from pre-CAR-T ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) scans ($n=341$) of 180 patients (121 male; median age, 66 years). Three conventional (maximum standardized uptake value [SUVmax], metabolic tumor volume [MTV], total lesion glycolysis [TLG]) and 116 novel radiomic features were assessed, along with inflammatory markers, toxicities, and outcomes. At both pre-apheresis and pre-infusion time points, conventional PET features of disease correlated with elevated inflammatory markers. At pre-infusion, MTV was associated with grade ≥ 2 cytokine release syndrome (odds ratio [OR] for 100 mL increase: 1.08 [95% confidence interval (CI), 1.01–1.20], $P=0.031$), and SUVmax was associated with failure to achieve complete response (CR) (OR 1.72 [95% CI, 1.24–2.43], $P<0.001$). Higher pre-apheresis and pre-infusion MTV values were associated with shorter progression-free survival (PFS) (HR for 10-unit increase: 1.11 [95% CI, 1.05–1.17], $P<0.001$; 1.04 [95% CI, 1.02–1.07], $P<0.001$) and shorter overall survival (HR for 100-unit increase: 1.14 [95% CI, 1.07–1.21], $P<0.001$; 1.04 [95% CI, 1.02–1.06], $P<0.001$). A combined MTV and LDH measure stratified patients into high and low PFS risk groups. Multiple pre-infusion novel radiomic features were associated with CR. These quantitative conventional [^{18}F]FDG PET/CT features obtained before CAR-T cell infusion, which were correlated with inflammation markers, may provide prognostic biomarkers for CAR-T therapy efficacy and toxicity. The use of conventional and novel radiomic features may thus help identify high-risk patients for earlier interventions.

Keywords Lymphoma, Positron emission tomography, Biomarker, Immunotherapy, CAR-T, Radiomics

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Among the emerging treatments for patients with large-B cell lymphoma (LBCL), CD19-directed chimeric antigen receptor T cell (CAR-T) therapy demonstrates potential for sustained disease remission [1, 2]. However, 60% of patients treated with CAR-T cells experience disease relapse or progression within 6 months [3, 4], and severe therapy-associated toxicities, such as cytokine release syndrome (CRS) and neurotoxicity, are common [5, 6]. Therefore, biomarkers that predict the risk of treatment failure, and could trigger early on-treatment interventions, are urgently needed. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) is the standard-of-care for staging and response assessment of LBCL [7], but its role in guiding CAR-T therapy is not fully explored. Prior to CAR-T therapy, patients may undergo PET/CT before leukapheresis, to assess treatment eligibility, disease extent, and the need for bridging therapy; and again before lymphodepletion and CAR-T cell infusion, as baseline for response assessment. Previous research suggested that these PET scans [8], as well as certain laboratory parameters [6, 9], may be prognostic for therapy outcomes and treatment-associated toxicities. In our study–the largest to-date on this topic– we investigated (1) whether conventional and novel radiomic [^{18}F]FDG PET/CT features could predict treatment response, survival, and treatment-related toxicities in patients with LBCL receiving CAR-T therapy; and (2) for the first time, whether laboratory markers of inflammation are correlated with PET features.

Findings

We retrospectively included 180 patients with LBCL who had undergone [^{18}F]FDG PET/CT at pre-apheresis (aph-PET) and/or pre-infusion (car-PET) time points before autologous CD19-directed CAR-T therapy at Memorial Sloan Kettering Cancer Center (axi-cel, $n=93$; tisa-cel, $n=52$; and liso-cel, $n=35$ patients; Additional Files 1 and 2). In total, 341 PET/CT scans (161 aph-PET and 180 car-PET scans) performed on different PET scanners were analyzed; some car-PETs were performed before apheresis and thus considered for two time points. Maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG), and 116 radiomic features capturing metabolic heterogeneity and lesion shape, were calculated for each PET/CT (Additional File 1). Markers of tumor burden and inflammation (LDH, CRP, IL-6, IL-10, TNF-α, ferritin, fibrinogen, D-dimer) were correlated with aph-PET and car-PET features (Additional Files 2 and 3). Following multivariable adjustment, car-PET MTV showed a significant association with CRS (OR 1.08 for 100-unit increase [95% CI, 1.01–1.20], $P=0.031$) (Additional File 4). Failure to achieve complete remission (CR) after CAR-T therapy was associated with higher car-PET SUVmax (OR 1.72 for 10-unit increase [95% CI, 1.24–2.43], $P<0.001$). Of 116 car-PET radiomic features, 47 differed significantly between patients with, and those without, day 100 best response CR (adjusted $P<0.05$) (Fig. 1). Higher aph-PET MTV (HR 1.11 for 10-unit increase [95% CI, 1.05–1.17], $P<0.001$) and car-PET MTV (HR 1.04 for 10-unit increase [95% CI, 1.02–1.07], $P<0.001$) were associated with shorter PFS. Similarly, higher aph-PET MTV (HR 1.14 for 100-unit increase [95% CI, 1.07–1.21], $P<0.001$) and car-PET MTV (HR 1.04 for 100-unit increase [95% CI, 1.02–1.06], $P<0.001$) were associated with shorter OS. The combination of MTV (calculated cutoff, 24 mL) and LDH, both significant outcome predictors on multivariable analysis, enabled separation of high and low PFS and OS risk groups, and two intermediate risk groups (Fig. 2).

Discussion

CAR-T cell response, survival, and toxicities are clinically relevant endpoints for which predictive biomarkers are currently lacking. Our data suggest that higher car-PET SUVmax may be associated with higher likelihood of non-CR to CAR-T cells. This finding, which has not been reported before, may be explained by the prior observation that SUV on [^{18}F]FDG-PET is linked to lymphoma aggressiveness. Moreover, we found significant differences in several car-PET radiomic features between patients achieving, and those not achieving, CR. These features quantitatively assess lesion heterogeneity and shape, and have previously shown correlations with tumor aggressiveness and clinical outcomes [10]. Our identification of MTV as a key parameter associated with poor PFS and OS in patients treated with CAR-T cells confirms the findings of prior smaller studies [8, 11]. With regard to toxicities–a major limiting factor for CAR-T therapy– we found that car-PET MTV may predict the development of CRS. We also observed associations between car-PET and aph-PET features and multiple inflammation markers that are linked to an immunosuppressive tumor microenvironment, and thus, probably also to toxicities and lower response rates to CAR-T therapy [9].

The present study has some limitations. First, radiomics is still an exploratory analytic technique whose results are influenced by multiple factors, such as acquisition parameters [12]. While radiomic feature extraction is relatively fast (approximately 5 min per PET/CT) and, per se, reproducible, interrater differences in terms of lesion delineation/segmentation are known to affect feature values [10]. Since we did not further evaluate our model performance by cross-validation or in a held-out cohort, the results of our radiomic analyses must be considered as preliminary and require external validation. Second, our risk classification model combines MTV and LDH, both

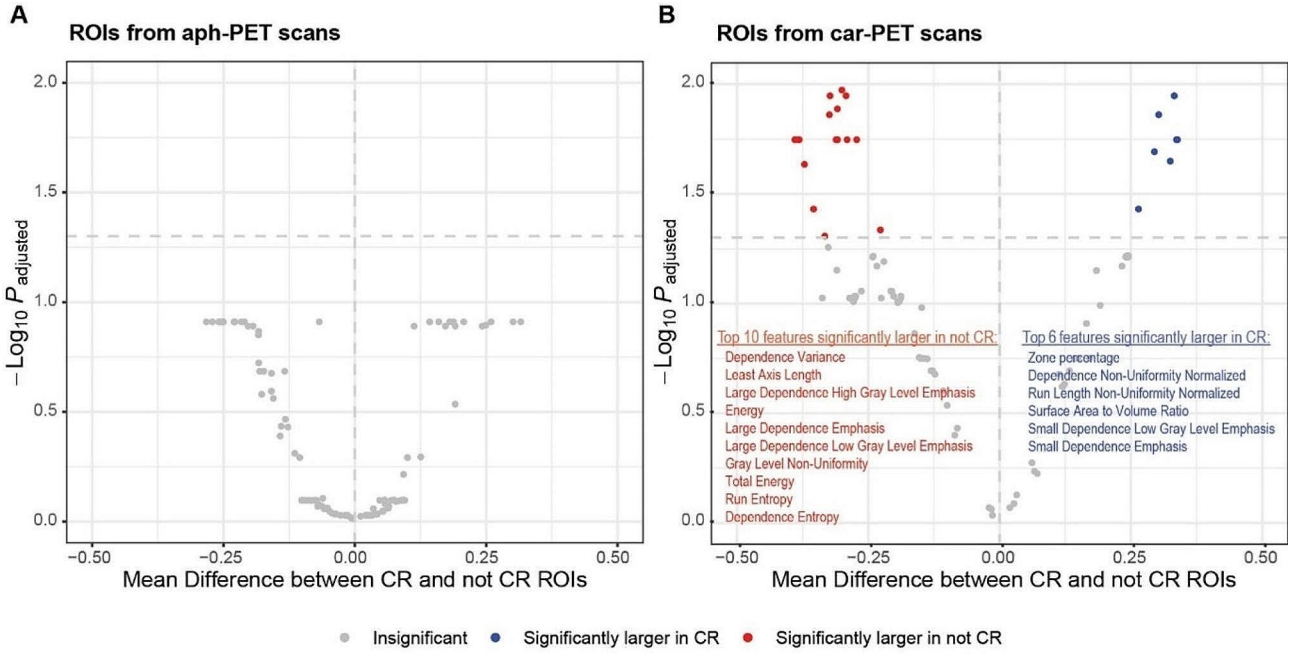

Fig. 1 Prognostic value of PET radiomic features. Volcano plots showing PET radiomic features from (**A**) aph-PET and (**B**) car-PET scans. Radiomic features extracted from aph-PET scans did not differ significantly between patients achieving complete remission (CR) or not. In contrast, several radiomic features extracted from lymphoma manifestations on car-PET scans, such as Energy and Zone Percentage, differed significantly ($P < 0.05$) between the two outcome groups (CR vs. non-CR). Abbreviations: Aph-PET = pre-leukapheresis PET scan; Car-PET = pre-CAR-T cell infusion PET scan; CR = complete response; ROI = region of interest

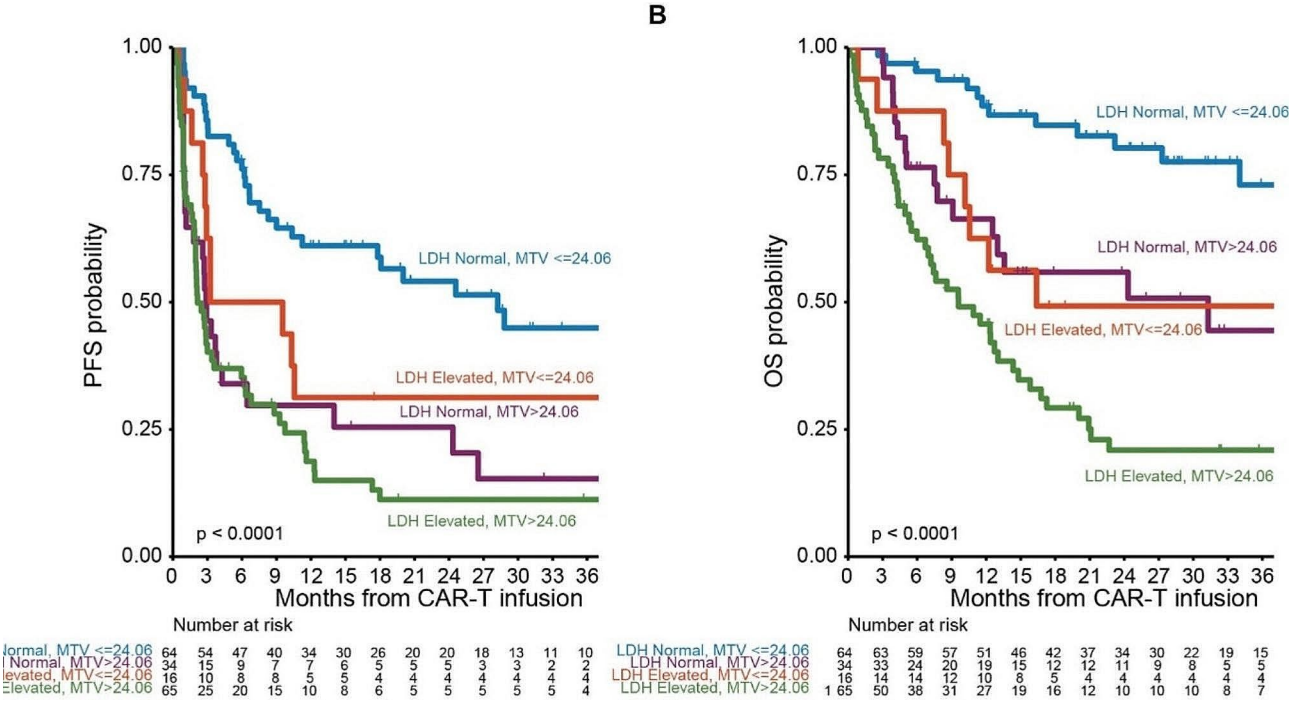

Fig. 2 Combined prognostic value of MTV and LDH. Kaplan-Meier curves show that the combination of car-PET MTV (based on a cutoff of 24.06) and LDH separate high and low (**A**) progression-free survival (PFS) and (**B**) overall survival (OS) risk groups. Abbreviations: LDH = lactate dehydrogenase; MTV = metabolic tumor volume

of which (directly or indirectly) reflect tumor volume; our model illustrates how MTV could further improve risk definition from LDH alone, and therefore the incremental utility of PET parameters. Third, data on extra-nodal involvement, which is a known risk factor in CAR-T cell therapy, was not available in this study and might be of interest in further analyses. Fourth, some car-PETs were considered for two time points, rendering our cohort more heterogeneous due to possible bridging therapies. In conclusion, for patients with LBCL undergoing CAR-T therapy, quantitative [^{18}F]FDG PET/CT features assessed immediately before CAR-T cell infusion are associated with clinical outcomes, treatment response, toxicity, and markers of inflammation. [^{18}F]FDG PET/CT features could therefore guide additional interventions in high-risk populations to increase the efficacy and safety of CAR-T therapy.

Abbreviations

Aph-PET	Last PET before leukapheresis
Car-PET	Last PET before lymphodepletion and CAR-T cell infusion
CAR-T	CD19-directed chimeric antigen receptor T cell
CR	Complete response
CRP	C-reactive protein
CRS	Cytokine release syndrome
IL-6	Interleukin 6
IL-10	Interleukin 10
LBCL	Large-B cell lymphoma
LDH	Lactate dehydrogenase
MTV	Metabolic tumor volume
OS	Overall survival
PET/CT	Positron emission tomography/computed tomography
PFS	Progression-free survival
SUV	Standardized uptake value
TLG	Total lesion glycolysis
TNF-α	Tumor necrosis factor alpha
[^{18}F]FDG	^{18}F-fluorodeoxyglucose

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-024-01540-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Acknowledgements
Editorial support in the preparation of this paper was provided by Hannah Rice, MA, ELS.

Author contributions
RS, HS, and DL designed the research study. MC, PBD, ALDA, IL, RJL, MS, GLS, and AAT collected research data. HS, RS, GS, and MAP provided financial resources and infrastructure for the study. DL, AB, DL, and LM performed the image analysis. JRF, SMD, AM, TF, SZ, JZ, and MEM performed the statistical analysis or data interpretation. DL, RS, HS, BSI, HH, MEM, MLP, MS, JHP, and GS contributed to drafting/writing of the paper. All authors read and approved the final manuscript.

Funding
This research was funded in part through the National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center Support Grant P30 CA008748. RS was supported by an NIH-NCI K-award (K08CA282987), the American Society of Hematology Fellow Scholar Award, a grant from the Long Island Sound Chapter, Swim Across America, the Robert Hirschhorn Award, and the Memorial Sloan Kettering Steven Greenberg Lymphoma Research Award. SZ was supported by the NIH grant R25CA272282. MC was supported by a grant from the Alfonso Martin Escudero Foundation. AL was supported by the Fundacion Espa?ola de Hematologia y Hemoterapia FEHH/2022 grant.

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

Declarations

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Memorial Sloan Kettering Cancer Center.

Consent for publication
All patients signed written informed consent for treatment, data collection and usage of data for clinical research in accordance with modified Declaration of Helsinki and Good Clinical Practice guidelines.

Competing interests
G.L.S. has research funding to the institution from Janssen, Amgen, BMS, Beyond Spring, and GPCR, and is on the DSMB for ArcellX. G.S. has received in the last 12 months financial compensations for participating in advisory boards: Abbvie, Beigene, BMS, Genentech/Roche, Genmab, Incyte, Ipsen, Janssen, Kite/Gilead, Loxo/Lilly, Merck, Novartis, Nurix; has received in the last 12 months financial compensations consulting from: Abbvie, Atbtherapeutics, Beigene, BMS, Debiopharm, Genentech/Roche, Genmab, Incyte, Ipsen, Kite/Gilead, Molecular Partners, Nordic Nanovector, Novartis, Orna; he is also a shareholder of: Owkin; received research support managed by his institution from Genentech, Janssen, Ipsen, Nurix. M.E.M. received speaker honoraria from Siemens, General Electric, and Bristol Myers Squibb. All other authors report no competing interests. M.L.P received honoraria and research funding from BMS, Cellectar, Ceramedix, Juno, Kite, MustangBio, Garuda Therapeutics, Novartis, Pluto Immunotherapeutics, Rheos, Seres Therapeutics, Smart Immune, Thymofox, Synthekine, June and Seres. M.S. served as paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc, and Omeros Corporation; received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, and Amgen, Inc.; served on ad hoc advisory boards for Kite– A Gilead Company; and received honoraria from i3Health, Medscape, and CancerNetwork for CME-related activitiy. M.A.P. reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Sanofi, Syncopation, VectivBio AG, and Vor Biopharma; serves on DSMBs for Cidara Therapeutics and Sellas Life Sciences, and the scientific advisory board of NexImmune; has ownership interests in NexImmune, Omeros and OrcaBio; has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis. All other authors declare that they have no competing interests.

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Received: 9 February 2024 / Accepted: 2 April 2024
Published online: 23 April 2024

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