Official title: Synergistic effect of $^{18}$F-FDG PET radiomics and International Prognostic Index on outcome prediction in diffuse large B-cell lymphoma

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Study Protocol and Statistical Analysis Plan

Background: Previous studies have shown that ¹⁸F-FDG PET radiomics is predictive of survival in DLBCL. However, to the best of the investigator's knowledge, a multi-feature radiomic signature for prognosis assessment of DLBCL has not yet been described. Furthermore, it remains unclear whether PET-based radiomics could add more prognostic values to the IPI in DLBCL.

Objectives: This study aims to develop ¹⁸F-FDG PET radiomic signatures, and investigate whether the RS could improve the prognostic value of the IPI in predicting progression-free survival (PFS) and overall survival (OS) in DLBCL.

Study design and methods:

Study population

We retrospectively included patients with newly-diagnosed DLBCL between July 2013 and July 2019 in our institution. The inclusion criteria were: 1) histopathologically confirmed DLBCL, 2) over 18 years old, 3) underwent pre-treatment ¹⁸F-FDG PET/CT, and 4) initial treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) or R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin). Patients were excluded if they had coexistent central nervous system lymphoma or second primary cancer, underwent surgical resection, or had an incomplete follow-up.

Clinical variables including gender, age at diagnosis, cell of origin, performance status, B symptoms, Ann Arbor stage, serum lactate dehydrogenase level, serum β2-microglobulin (β2-MG) level, extranodal involvement and treatment regimens of each patient were recorded. The IPI score was calculated.

Patient Treatment and Follow-up

Patients were initially treated with standard first-line chemotherapy every 21 days. Response to treatment was assessed according to the Lugano classification.
Follow-up was performed every 3 months after the completion of treatment, and ended in July 2021. The endpoints included OS (defined as the period from the initial diagnosis to the death from any cause) and PFS (defined as the period from the initial diagnosis to the progression, relapse or death from any cause).

**PET Image Segmentation and Feature Extraction**

PET images were analyzed by two experienced nuclear medicine physicians who were blind to the patients’ outcome. The volumes of interest (VOIs) were semiautomatically delineated using the LIFEx software (https://www.lifexsoft.org/index.php) with a fixed threshold of 41% SUVmax. A total of 1245 radiomic features were extracted via PyRadiomics software. The radiomics features consisted of four groups: (1) first-order statistics features; (2) shape descriptors features; (3) texture features calculated by gray level co-occurrence matrix (GLCM), gray level dependence matrix (GLDM), gray level run length matrix (GLRLM), and gray level size zone matrix (GLSZM); (4) filter and wavelet features obtained by filter and wavelet transformation of the original image, such as exponential, logarithm, square, square root and eight frequency band combinations (low-high-low [LHL], low-high-high [LHH], high-low-low [HLL], low-low-high [LLH], high-low-high [HLH], high-high-high [HHH], high-high-low [HHL] and low-low-low [LLL]).

**Radiomics feature selection**

First, intra-class correlation coefficients (ICCs) were used to evaluate the inter- and intra-observer agreement for 1248 features, including 3 conventional and 1245 radiomics features. Features with both inter- and intra-observer ICCs greater than 0.75 were retained. Then, the least absolute shrinkage and selection operator (LASSO) Cox regression algorithm with 10-fold cross-validation was applied to select the optimal features with non-zero coefficients in the training set. The radiomics signature was developed by linear combination of the selected features weighted by their respective coefficients. The cut-off value of the radiomics signature was identified by X-tile software. Based on the cut-off value of the R-signature, patients were divided into high-
and low-risk groups. Survival function of the R-signature was estimated by Kaplan-Meier analysis, and survival distributions were compared using log-rank test.

**Model construction**

Univariate Cox regression analysis was performed to investigate the prognostic value of the R-signature and clinical variables. Then, all significant variables were enrolled into a stepwise multivariate Cox regression to build an integrated radiomics-based model for PFS and OS prediction.

**Model performance assessment**

Time-dependent ROC curve analysis was conducted to investigate the predictive accuracy of the R-signature, clinical variables and the integrated radiomics-based model. The 95% confidence interval (CI) of the area under the curves (AUCs) were calculated by bootstrapping with 1000 resampling. The AUC between the radiomics-based model and clinical variables was compared by using the Delong's test. The calibration plots and the Hosmer-Lemeshow test were used to compare the predicted and observed probabilities of the radiomics-based model. The decision curve analysis (DCA) was applied to determine the clinical utility by quantifying the net benefits under different threshold probabilities in the whole cohort.

**Statistical analysis**

The chi-square test and independent t-test were performed using SPSS software (version 25.0, IBM). ICC, LASSO regression analysis, time-dependent ROC analysis, Delong’s test, calibration plots, Hosmer-Lemeshow test, DCA and Kaplan-Meier survival analysis were performed using R software (version 3.6.1, http://www.r-project.org). A two-sided P value of < 0.05 was considered statistically significant.