European Journal of Nuclear Medicine and Molecular Imaging (2022) 49:1311–1321
https://doi.org/10.1007/s00259-021-05581-z

ORIGINAL ARTICLE

The prognostic value of end-of-treatment FDG-PET/CT in diffuse large B cell lymphoma: comparison of visual Deauville criteria and a lesion-to-liver SUV_{max} ratio-based evaluation system

Ying-He Li[1,2] · Yu-Mo Zhao[1,2] · Yong-Luo Jiang[1,2] · Si Tang[1,2] · Mei-Ting Chen[1,3] · Zi-Zheng Xiao[1,2] · Wei Fan[1,2] · Ying-Ying Hu[1,2] · Xu Zhang[1,2]

Received: 13 April 2021 / Accepted: 3 October 2021 / Published online: 15 October 2021

Abstract

Purpose The aim of this study was to determine a better criterion for end-of-treatment PET (EoT-PET) assessment and prognostic evaluation of patients with diffuse large B cell lymphoma (DLBCL).

Method EoT-PET scans were assessed using the visual Deauville 5-point scale (5PS) and LLR, the maximum standard uptake value ratio between the lesion and the liver. The cutoff value of LLR was obtained by receiver operator characteristic curve analysis. Patient outcomes were compared using Kaplan–Meier survival analysis. Prognostic indexes of different criteria were compared. Multivariate Cox regression analysis was performed to evaluate the prognostic factors.

Results Four hundred forty-nine newly diagnosed DLBCL patients who received rituximab-based immunochemotherapy were included, and the median follow-up duration was 41.4 months. Patients with Deauville score (DS) 4 displayed significantly longer PFS and OS compared with patients with DS 5 (both $p < 0.001$), and they had significantly shorter PFS ($p < 0.01$) but similar OS ($p = 0.057$) compared with patients with DS 1–3. The differences in PFS and OS between groups were all significant whether positive EoT-PET was defined as DS 4–5 or DS 5 (all $p < 0.001$). The optimal cutoff of LLR was 1.83, and both PFS and OS were significantly different between EoT-PET-positive and EoT-PET-negative patients as defined by the cutoff (both $p < 0.001$). LLR-based criterion displayed higher specificity, positive predictive value, and accuracy than 5PS-based criterion in the prediction of disease progression and death events. In the multivariate analysis, positive EoT-PET (as defined by LLR) was related to unfavorable PFS and OS (both $p < 0.001$). Additional treatment was not correlated with outcomes of EoT-PET-negative patients either defined by LLR or 5PS or EoT-PET-positive patients classified by 5PS, but it was the only beneficial factor for OS ($p < 0.05$) in EoT-PET-positive patients with LLR ≥ 1.83.

Conclusion The optimal cutoff of LLR may be superior to Deauville criteria in identifying low-risk DLBCL patients with negative EoT-PET after the first-line immunochemotherapy and sparing them the cost and toxicity of additional treatment.

Keywords Diffuse large B cell lymphoma · End-of-treatment PET/CT · Evaluation criterion · Prognostic value

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common type of aggressive non-Hodgkin lymphoma (NHL), representing 30% of lymphomas in developed regions and 43% in developing regions [1, 2]. Given the 18-fluorodeoxyglucose (^{18}F-FDG) avidity of 97% in patients with DLBCL [3], positron emission tomography with computed tomography (PET/CT) has been proposed for initial staging and end-of-treatment (EoT) evaluation of this disease [4–6]. The therapeutic purpose of EoT-PET is the early detection of residual disease that warrants additional therapy [4, 7, 8]. Additional treatment such as consolidative adjuvant

This article is part of the Topical Collection on Hematology

Ying-He Li, Yu-Mo Zhao and Yong-Luo Jiang contributed equally to this work.

✉ Wei Fan
fanwei@sysucc.org.cn

✉ Ying-Ying Hu
huyy@sysucc.org.cn

✉ Xu Zhang
zhangx2@sysucc.org.cn

Extended author information available on the last page of the article

radiotherapy following first-line immunochemotherapy remains controversial for EoT-PET-negative patients [9–11].

The prognostic value of EoT-PET has been less extensively studied than that of interim PET in patients with DLBCL [8, 12–14]. As with interim PET, the negative predictive value of EoT-PET is reassuringly high, but the positive predictive value varies [8, 13, 14]. The cutoff for PET positive was increased from the level of mediastinal blood pool in the Cheson 2007 criteria to that of the liver background in the Lugano 2014 criteria [15]. The visual Deauville 5-point scale (5PS) has been adopted as the major criterion for PET evaluation [15–17], where a Deauville scores of 1 (DS 1) to DS 3 are deemed to indicate complete metabolic response and DS 4 to DS 5 are taken to indicate incomplete metabolic response [4, 7, 15].

However, in practical applications, there exist ambiguities in the definition of DS 4 and DS 5. The consensus of the International Conference on Malignant Lymphoma recommended that DS 5 be defined as a lesion uptake two or three times that of the liver [7]. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines defined DS 5 as an uptake greater than that of the liver with new disease sites [4]. In addition, the interobserver agreement of positive reads using 5PS was only 74–76% [18]. To improve the 5PS scale, studies have tested the optimal ratio of lesion uptake to liver uptake as the threshold for PET positive, and the predictive values achieved in this way were superior to that of the conventional 5PS [19–21]. In calling for personalized and precision medicine, strong tools are needed in DLBCL care to accurately predict relapse of disease and potentially to improve stratification for treatment regimens.

This study retrospectively assessed the predictive value of EoT-PET under two criteria, 5PS and a system based on the ratio of maximum standard uptake value (SUV_{max}) between the lesion and the liver (lesion-to-liver SUV_{max} ratio, abbreviated as LLR), for PFS and OS in patients with DLBCL who received a full course of rituximab-based immunochemotherapy. We aimed to establish criteria that could outperform the 5PS criteria in predicting outcomes of patients with PET-negative and PET-positive scans.

Methods

Patients

This single-center study was approved by the institutional review board at the Sun Yat-Sen University Cancer Center (SYSUCC). Newly diagnosed DLBCL patients admitted to SYSUCC between April 2007 and October 2018 were retrospectively enrolled. The inclusion criteria were newly diagnosed and biopsy-verified DLBCL; age ≥ 18 years; six or eight cycles of rituximab-based standard immunochemotherapy as recommended by the NCCN guidelines [4]; ^{18}F-FDG avid lesion verified by pretherapeutic PET/CT; EoT-PET performed within 8 weeks after the last dose of immunochemotherapy [4, 7, 22] before any additional treatment; and a minimum follow-up period of 24 months for patients alive. The exclusion criteria were primary-mediastinal B-cell lymphoma or central nervous system involvement at diagnosis; history of other cancer; and incomplete data.

For the included patients, clinical data including age, gender, lactate dehydrogenase (LDH) level, sites of extranodal involvement, performance status evaluated by the Eastern Cooperative Oncology Group (ECOG), Ann Arbor stage, B symptoms (fever, night sweats, weight loss, and other systemic symptoms), pathological subtype (germinal center B-cell-like, abbreviated as GCB, versus non-GCB, abbreviated as NGCB), and bulky disease (one or more involved sites with a maximum diameter ≥ 10 cm) were collected. The International Prognostic Index (IPI) was calculated based on 5 clinical factors (age > 60 years, LDH > normal, Ann Arbor stage III or IV, ECOG ≥ 2, extranodal involvement > 1 site) [7, 23]. Treatment results and follow-up were obtained from the SYSUCC database, including the date of first-line immunochemotherapy, PET/CT scan, disease progression, relapse or death, last follow-up, and additional treatment following first-line immunochemotherapy. Disease progression was confirmed by pathological or imaging examination.

PET/CT imaging

Baseline ^{18}F-FDG-PET was performed before the start of treatment. EoT-PET was performed within 8 weeks after the last cycle of immunochemotherapy. The baseline PET and EoT-PET of any given patient were performed with the same PET/CT scanner.

All patients fasted for 5 to 6 h prior to ^{18}F-FDG administration, and their blood glucose levels were stable and lower than 200 mg/dL (11.1 mmol/L). PET/CT scans were performed with integrated PET/CT scanners (Discovery ST, GE Healthcare, Waukesha, Wisc., USA, or Biograph mCT, Siemens Healthcare, Henkestr, Germany). Imaging data were acquired 60 ± 10 min after the ^{18}F-FDG injection (3.7 ± 0.37 MBq [0.1 ± 0.01 mCi]/kg body weight). CT scans were obtained in an arm-up position with a Discovery ST (automatic tube current modulation, tube voltage 140 kV, rotation time 0.8 s, pitch 1.0, field of view 50 cm, collimation 16 × 1.25 mm, slice thickness 3.75 mm) or Biograph mCT apparatus (tube current 80–200 mAs, voltage 120 kV, rotation time 0.5 s, pitch 1.0, field of view 50 cm, collimation 32 × 1.25 mm, slice thickness 3 mm), and both scans were reconstructed in a 512 × 512 matrix. Whole-body imaging from the skull to the mid-thigh was performed in 6–8 bed positions (3 min/bed with the Discovery ST and

1.5–2 min/bed with the Biograph mCT). The PET images were reconstructed with a slice thickness of 3.25 mm (2D) in a 128 × 128 matrix or 2 mm (3D) in a 200 × 200 matrix using the ordered subsets expectation maximization (OSEM) iterative image reconstruction method. PET, CT, and fused PET/CT images were generated for review on a Xeleris computer workstation (GE Medical Systems).

PET/CT analyses

Archived PET results were assessed using two methods: the visual 5PS and a method based on LLR. For the 5PS, three nuclear physicians evaluated the retrieved PET results independently and while blinded to patient outcomes. The 5PS comprises five categories, which are defined as follows: DS 1, no residual uptake; 2, residual uptake not exceeding mediastinal uptake; 3, residual uptake above mediastinal but not exceeding liver uptake; 4, residual uptake moderately above liver uptake; 5, residual uptake markedly above liver uptake and/or new lesions; and X, newly emerged uptake unlikely to be related to lymphoma [7, 16]. The DS of each scan was recorded when ≥ 2 physicians reached an agreement. For the LLR-based scale, the SUV_{max} of the liver was obtained by measuring the SUV_{max} of a spherical volume of interest (VOI) of diameter 3 cm in the right upper lobe of the liver (avoided the edge and vessels). The SUV_{max} of the lesion was measured on the most intense focus when the residuals were presented on EoT-PET, and the SUV_{max} was considered equal to the SUV of the background if no lesion was visible. LLR was calculated by dividing the SUV_{max} of the lesion by the SUV_{max} of the liver. Three nuclear physicians measured the liver SUV_{max} and lesion SUV_{max} separately, and the final LLR was the average value of the three LLRs got by these physicians.

Statistical analysis

Progression-free survival (PFS) and overall survival (OS) were chosen as end points. PFS was defined as the time from the first cycle of chemotherapy to the first evidence of progression or relapse or to death. OS was defined as the time from the first cycle of chemotherapy until death of any cause. Data were censored if patients were alive with no progression or relapse at the last follow-up. Interobserver agreement was tested with Kendall's W test (for categorical variable) or intraclass correlation coefficient (ICC, for continuous variable). Survival probability was estimated using Kaplan–Meier (K-M) analysis, and differences between groups were tested with the log-rank test. Receiver operator characteristic (ROC) curve analyses were performed to determine the optimal cutoff value of LLR. Multivariate Cox proportional hazards analyses were used to examine the prognostic impact of EoT-PET. The proportional hazards (PH) assumption was tested, and independent variables were screened by stepwise logistic regression. Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, USA) or R (version 3.6.1), and graph plotting was performed using Prism 7.0 (GraphPad, San Diego, USA). A p value of less than 0.05 indicated statistical significance.

Results

Patients

A total of 449 patients with newly diagnosed DLBCL were included in this study, 57% of whom presented with stage III–IV disease. The median age at diagnosis was 51 years (range 18–85), and the ratio of males to females was 55/45. The majority of patients (95.3%) were treated with 6 cycles of chemotherapy, and the rest (4.7%) of the patients were given 8 cycles. A total of 386 (86%) patients were given a standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy regimen. The median follow-up duration was 41.4 months (range 5.6–150.2 months). A total of 101 (22.5%) patients progressed or relapsed, and 62 (13.8%) patients died (3 of them died of non-DLBCL-related causes). Detailed clinical characteristics are shown in Table 1. A flow diagram to summarize the EoT-PET results, treatments, and outcomes of patients is presented in Fig. 1.

Survival analysis based on the visual 5PS

The interobserver agreement of the 5PS-based scores was perfect, with a Kendall coefficient of 0.988 ($p < 0.001$). Among the EoT-PETs of the 449 included patients, 221 (49.2%) were assigned DS 1, 77 (17.1%) DS 2, 61 (13.6%) DS 3, 50 (11.1%) DS 4, and 40 (8.9%) DS 5. The main area of disagreement was the score level of 4. Of the 50 EoT-PETs given DS 4, 7 (14%) were given DS 5 by one physician, and 14 (28%) were given DS 3 by one physician.

Figure 2 shows K-M survival curves depicting the PFS and OS of patients. When the patients were categorize as three groups, including DS 1–3, DS 4, and DS 5 using the 5PS, DS 5 was associated with significantly worse outcomes than DS 4 (PFS, $p < 0.001$; OS, $p < 0.001$), and DS 4 was associated with significantly shorter PFS than DS 1–3 ($p < 0.01$). However, OS did not differ significantly between DS 1–3 and DS 4 ($p = 0.057$). The 5-year PFS was 82.1% (95% confidence interval (CI) 77.4–87.1%), 67.6% (95% CI 55.7–82.1%), and 20.0% (95% CI 10.8–37.2) for DS 1–3, DS 4, and DS 5, respectively; the 5-year OS was 89.8% (95% CI 86.2–93.6%), 84.0% (95% CI 74.4–94.8%), and 39.7% (95% CI 27.0–58.3) for DS 1–3, DS 4, and DS 5, respectively (Table 2). When patients were categorized

Table 1 Baseline characteristics of patients

		n = 449 (%)
Age at diagnosis*	≤ 60 y	325 (72)
	> 60 y	124 (28)
Gender	Male	249 (55)
	Female	200 (45)
Ann Arbor stage	I and II	192 (43)
	III and IV	257 (57)
B symptoms	Yes	131 (29)
	No	318 (71)
LDH level	Normal	258 (57)
	Elevated	191 (43)
Extranodal involvement	≤ 1 site	301 (67)
	> 1 site	148 (33)
ECOG performance status	< 2	317 (71)
	≥ 2	133 (29)
IPI group	0–1	187 (42)
	2	109 (24)
	3	85 (19)
	4–5	68 (15)
Bulky disease	No	378 (84)
	Yes	71 (16)
Pathology subtype	GCB	164 (37)
	Non-GCB	281 (63)
	Uncertain	4 (< 1)
First-line therapy	R-CHOP	386 (86)
	R-CDOP	24 (5)
	R-EPOCH	15 (3)
	R-CEOP	13 (3)
Additional treatment	Yes	200 (45)
	No	249 (55)

*There were 11 patients ≥ 75 years old

LDH lactate dehydrogenase, *ECOG* Eastern Cooperative Oncology Group, *IPI* International Prognostic Index, *GCB* germinal center B-cell-like

as PET positive or PET negative, PET-positive results were always associated with worse outcomes when either DS 4 was included in the positive group (PET-negative DS 1–3 vs. PET-positive DS 4–5, noted as $DS_{1-3/4-5}$; PFS, $p < 0.001$; OS, $p < 0.001$) or the negative group (PET-negative DS 1–4 vs. PET-positive DS 5, noted as $DS_{1-4/5}$; PFS, $p < 0.001$; OS, $p < 0.001$).

The outcome predictive values of EoT-PET are shown in Table 3. Compared to a $DS_{1-4/5}$, $DS_{1-3/4-5}$ showed superior sensitivity and negative predictive value (NPV) but inferior specificity and positive predictive value (PPV). $DS_{1-4/5}$ showed better accuracy in predicting disease progression or death than $DS_{1-3/4-5}$ (disease progression, $DS_{1-3/4-5}$ vs. $DS_{1-4/5}$ 78.8% vs. 82.9%; death, $DS_{1-3/4-5}$ vs. $DS_{1-4/5}$ 80.4% vs. 88.0%).

Survival analysis based on LLR

The interobserver agreement of LLR was perfect, with an ICC of 0.9997 ($p < 0.001$). The 449 patients had median, minimum, and maximum LLR values of 0.41, 0.03, and 17.63, respectively. The descriptive statistics of LLR of all patients and of different Deauville categories were shown in Table 4 and Fig. 3. The descriptive statistics of EoT-PET liver SUV_{max} and residual SUV_{max} were also shown in the supplementary material (Table S1). Two hundred twenty-eight patients evaluated as DS 2–5 (with visible residuals) were tested with ROC analysis, and disease progression was taken as state variable. The optimal cutoff of LLR was 1.83, and the area under the curve (AUC) showed a prognostic accuracy of 0.738 (95% CI 0.660–0.815, $p < 0.001$) (Fig. 4a).

Applying LLR = 1.83 as cutoff, 68% (34/50) of patients evaluated as DS 4 were categorized as PET negative, while 32% (16/50) of patients evaluated as DS 4 and 100% (40/40) of patients evaluated as DS 5 were PET positive, where PET positive was significantly associated with poor PFS ($p < 0.001$) and poor OS ($p < 0.001$) (Fig. 4b and c). The 5-year PFS was 81.2% (95% CI 76.6–86.0%) for LLR < 1.83 and 30.4% (95% CI 20.4–45.1%) for LLR ≥ 1.83, respectively. And the 5-year OS was 89.4% (95% CI 85.9–93.0%) for LLR < 1.83 and 51.2% (95% CI 39.6–66.4%) for LLR ≥ 1.83, respectively (Table 2). Compared to 5PS criteria using DS 4 as cutoff, LLR using 1.83 as cutoff showed a lower sensitivity (disease progression, LLR vs. $DS_{1-3/4-5}$ 38.6% vs. 47.5%; death, LLR vs. $DS_{1-3/4-5}$ 43.5% vs. 51.6%) but higher specificity (disease progression, LLR vs. $DS_{1-3/4-5}$ 95.1% vs. 87.9%; death, LLR vs. $DS_{1-3/4-5}$ 92.5% vs. 85.0%), PPV (disease progression, LLR vs. $DS_{1-3/4-5}$ 69.6% vs. 53.3%; death, LLR vs. $DS_{1-3/4-5}$ 48.2% vs. 35.6%), and accuracy (disease progression, LLR vs. $DS_{1-3/4-5}$ 82.4% vs. 78.8%; death, LLR vs. $DS_{1-3/4-5}$ 85.7% vs. 80.4%)(Table 3).

Multivariate analysis

The multivariate analysis included the EoT-PET result-relevant variable (positive or negative) as classified by LLR or by 5PS; baseline variables including the IPI score (low risk, scores 0–1; medium to high risk, score 2–5), pathological subtype (GCB or non-GCB), B symptoms (yes or no), and bulky disease (yes or no); and a treatment-relevant variable, the use of additional treatment after first-line therapy (yes or no). EoT-PET results classified by LLR in the analysis of PFS and EoT-PET results classified by 5PS in the analysis of PFS and OS were time-dependent variables. Other variables met the proportional hazards assumption.

As listed in Table S2, when EoT-PET positive was defined as LLR ≥ 1.83, positive EoT-PET (HR (0–36 months) 5.280, 95% CI 3.079–9.056, $p < 0.001$), IPI scores 2–5 (HR 2.234, 95% CI 1.322–3.775, $p < 0.01$), and NGCB subtype

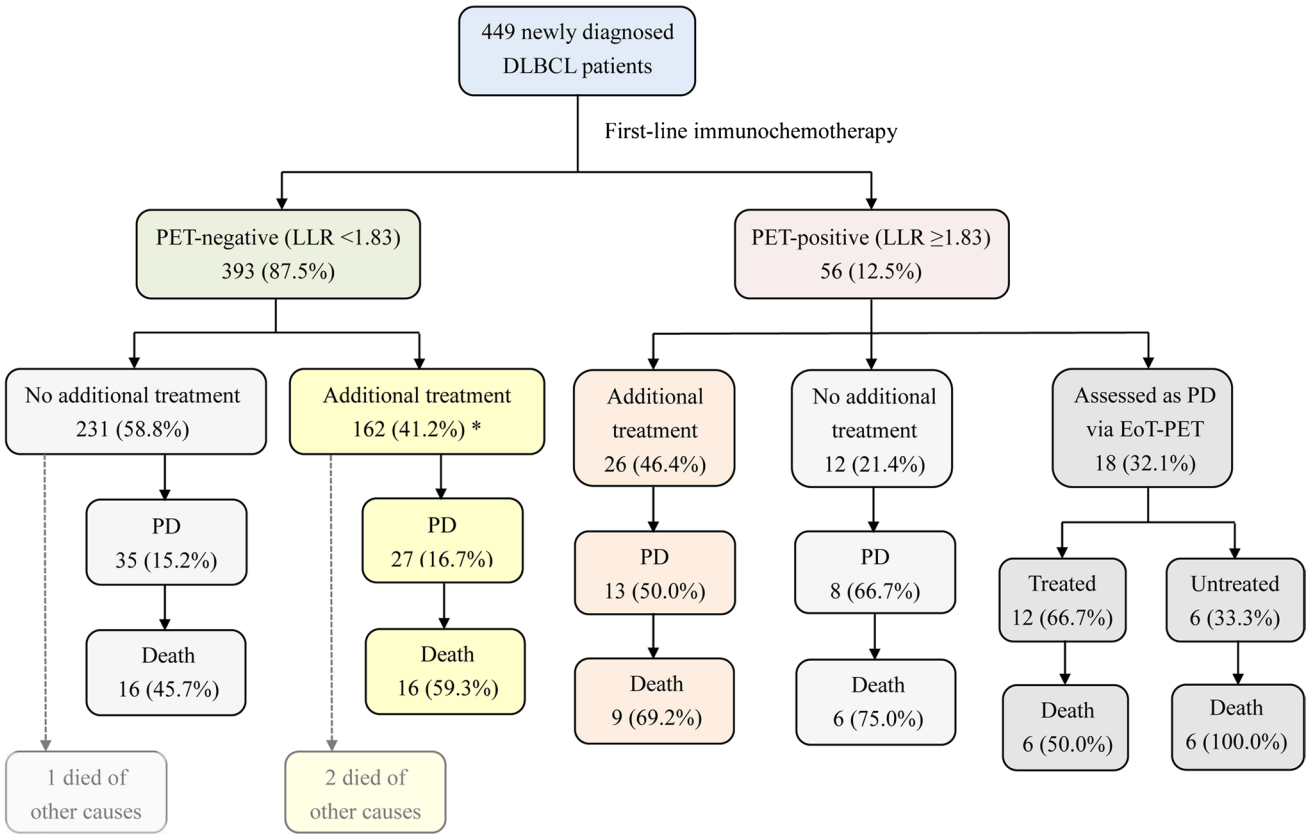
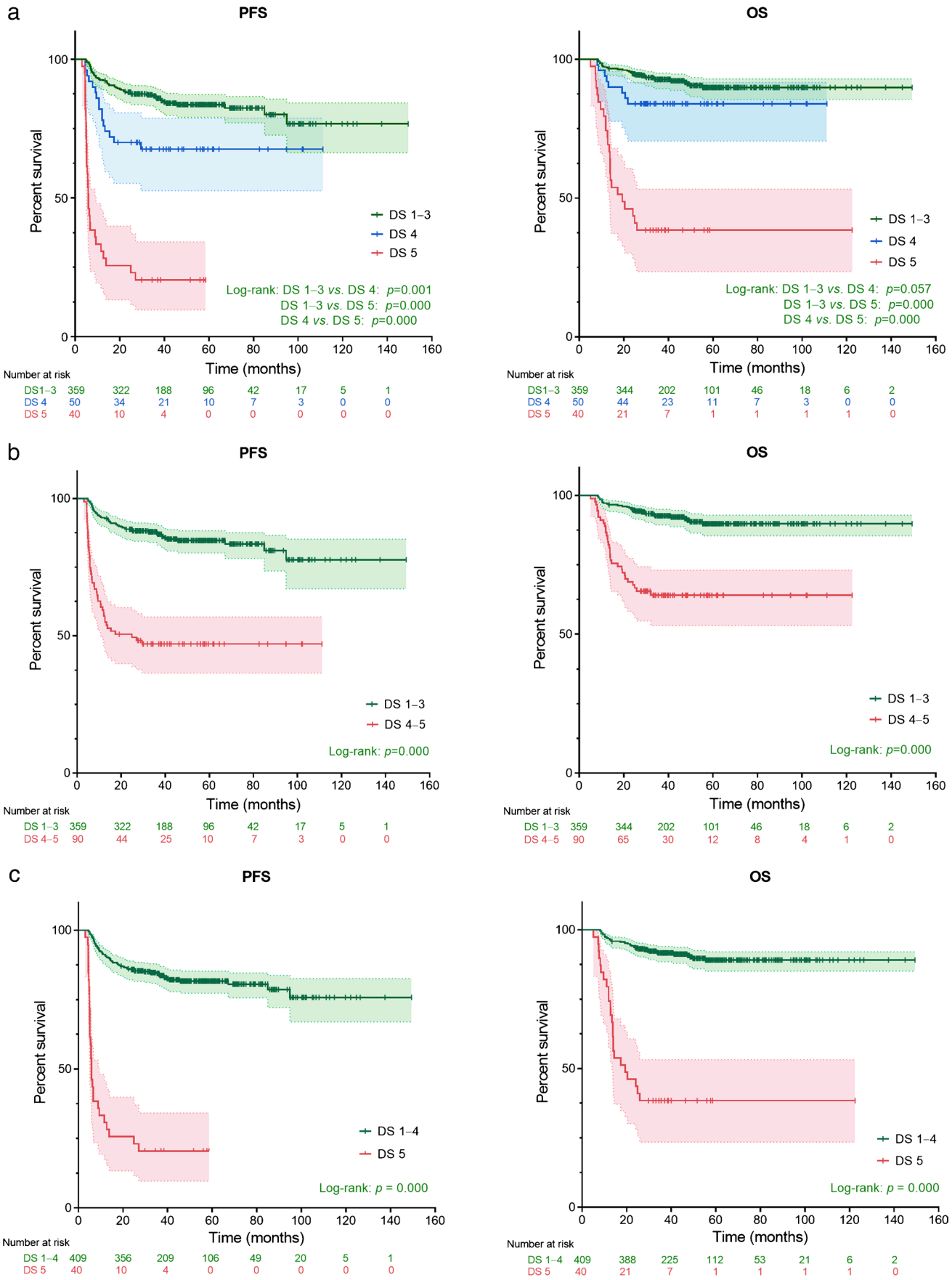


Fig. 1 Patient outcome flow chart. The cutoff of LLR was used to classify PET-positive and PET-negative patients. *Among the 162 PET-negative patients receiving additional treatment, 120 underwent adjuvant radiotherapy with or without additional chemotherapy (of whom 20 relapsed/progressed and 12 died), 30 received additional chemotherapy (of whom 7 relapsed/progressed and 5 died), 3 underwent surgery (of whom 0 relapsed and 1 died), and 4 underwent autologous stem cell transplantation (of whom 0 relapsed and 0 died). PD, progressive disease

(HR 1.917, 95% CI 1.154–3.184, $p<0.05$) were associated with inferior PFS; positive EoT-PET (HR 7.391, 95% CI 4.287–12.743, $p<0.001$), IPI scores 2–5 (HR 3.124, 95% CI 1.602–6.090, $p<0.01$), and NGCB subtype (HR 1.786, 95% CI 1.006–3.170, $p<0.05$) were associated with reduced OS. When EoT-PET positive was defined as DS ≥ 4, positive EoT-PET (HR (0–36 months) 3.659, 95% CI 2.247–5.956, $p<0.001$), IPI scores 2–5 (HR 2.203, 95% CI 1.301–3.728, $p<0.01$), and NGCB subtype (HR 1.799, 95% CI 1.081–2.994, $p<0.05$) were associated with inferior PFS; positive EoT-PET (HR (0–36 months) 5.554, 95% CI 3.201–9.638, $p<0.001$) and IPI scores 2–5 (HR 2.962, 95% CI 1.514–5.795, $p<0.01$) were associated with reduced OS. No matter the EoT-PET results were classified by the LLR or the 5PS, additional treatments, B symptoms, and bulky disease had no apparent impact on outcomes ($p>0.05$).

As listed in Table S3, multivariate analysis in EoT-PET-negative patients classified by LLR (<1.83) showed that IPI scores of 2–5 were associated with reduced PFS (HR 3.134, 95% CI 1.699–5.781, $p<0.001$) and reduced OS (HR 4.337, 95% CI 1.770–10.627, $p<0.01$); NGCB subtype was associated with inferior PFS (HR 2.000, 95% CI 1.094–3.656, $p<0.05$) but did not show a significant effect on OS. Additional treatment had no apparent impact on either PFS or OS ($p=0.682$ and $p=0.157$, respectively). In EoT-PET-negative patients classified by 5PS (DS 1–3), only IPI scores of 2–5 was associated with reduced PFS (HR 2.648, 95% CI 1.410–4.971, $p<0.01$) and OS (HR 3.858, 95% CI 1.548–9.618, $p<0.01$), while additional treatment had no significant influence ($p=0.571$ for PFS and $p=0.095$ for OS, respectively). In EoT-PET-positive patients classified by LLR (≥1.83), additional treatment was the only factor related to longer OS ($p=0.019$), though it did not related to longer PFS ($p=0.302$). In EoT-PET-positive patients classified by 5PS (DS 4–5), additional treatment did not show a significant effect on either PFS ($p=0.518$) or OS ($p=0.096$) (Table S4).


a
PFS
Percent survival
Time (months)
DS 1–3
DS 4
DS 5
Log-rank: DS 1–3 vs. DS 4: p=0.001
DS 1–3 vs. DS 5: p=0.000
DS 4 vs. DS 5: p=0.000
Number at risk
DS1–3 359 322 188 96 42 17 5 1
DS 4 50 34 21 10 7 3 0 0
DS 5 40 10 4 0 0 0 0 0
OS
Log-rank: DS 1–3 vs. DS 4: p=0.057
DS 1–3 vs. DS 5: p=0.000
DS 4 vs. DS 5: p=0.000
DS1–3 359 344 202 101 46 18 6 2
DS 4 50 44 23 11 7 3 0 0
DS 5 40 21 7 1 1 1 1 0
b
PFS
DS 1–3
DS 4–5
Log-rank: p=0.000
DS 1–3 359 322 188 96 42 17 5 1
DS 4–5 90 44 25 10 7 3 0 0
OS
DS 1–3 359 344 202 101 46 18 6 2
DS 4–5 90 65 30 12 8 4 1 0
c
PFS
DS 1–4
DS 5
Log-rank: p = 0.000
DS 1–4 409 356 209 106 49 20 5 1
DS 5 40 10 4 0 0 0 0 0
OS
DS 1–4 409 388 225 112 53 21 6 2
DS 5 40 21 7 1 1 1 1 0

◂**Fig. 2** K-M survival analysis of PFS and OS according to EoT-PET status using the Deauville 5PS. **a** Patients categorized as DS 1–3, DS 4, and DS 5. **b** Patients categorized as DS 1–3 and DS 4–5. **c** Patients categorized as DS 1–4 and DS 5

Discussion

PET/CT has been recommended for response assessment in DLBCL, and the 5PS has been widely applied in the evaluation of PET results [4, 7, 15]. After first-line immunochemotherapy, patients with an EoT-PET evaluation of DS 4–5 are generally considered PET positive, and those with DS 1–3 are considered PET negative [4, 7, 15]. A number of studies have confirmed that positive EoT-PET defined by DS ≥ 4 is associated with inferior outcomes in DLBCL [8, 11, 19–21, 24, 25]. However, the ambiguities exist in the definition of DS 4 and DS 5, and the assessment can be easily influenced by subjective factors. Recently, PET/CT-derived semiquantitative or quantitative parameters have been investigated as a means of improving prognostic accuracy. Zhang et al., Toledano et al., and Annunziata et al. reported that a lesion-to-liver uptake ratio exhibited better interobserver agreement than DS and may improve the predictive performance of the visual 5PS criteria with a cutoff of DS ≥ 4 as the threshold for PET positive [19–21].

In this study, we compared the prognostic value of the 5PS and the LLR method in EoT-PET evaluation. When using the 5PS-based criterion, we found that the outcome of DS 4 was significantly different from that of DS 1–3 or DS 5 in terms of PFS, and it was even comparable to the outcome of DS 1–3 in terms of OS. In the subsequent survival analysis, whether we categorized DS 4 and DS 1–3 together as the PET-negative group or categorized DS 4 and DS 5 together as the PET-positive group, the differences in PFS and OS between groups were all significant. It appears that patients with DS 4 should not be classified unconditionally as PET positive or PET negative. Therefore, we attempted to use 1.83, the optimal LLR cutoff to reclassify the patients, and EoT-PET-positive patients with LLR ≥ 1.83 had significantly lower PFS and OS than EoT-PET-negative patients. Compared to the commonly used 5PS-based evaluation criterion that classifies DS 4–5 as PET positive, LLR had a higher specificity, PPV, and accuracy. In the multivariate analysis, both LLR-based positive EoT-PET and 5PS-based positive EoT-PET were statistically significant risk factors of PFS and OS, and the former displayed an HR higher than the latter, indicating a stronger relevance between LLR-based positive EoT-PET and survival outcomes.

An LLR cutoff value of 1.83 obtained in this study was higher than a cutoff value of 1.4 reported by Toledano et al. [20]. The difference in the type of patients included in the ROC analysis may be one cause of this discrepancy. Toledano et al. used DS 3 and 4 to determine the optimal cutoff [20], whereas our study included patients with scores of 2–5 because we needed an LLR cutoff value useful for all the ranges of residual uptake. We reanalyzed our data using 1.4 as the cutoff, and the outcomes of PET-positive (≥ 1.4) and PET-negative (< 1.4) groups differed significantly in the K-M survival analysis (Table S5, Figure S1). However, the cutoff value of 1.4 did not increase the sensitivity of 1.83 but reduced the specificity, PPV, and accuracy of the latter (Table S6). In addition to LLR, Schöder et al. also reported that 66% ΔSUV_{max} (equals to $(SUV_{baseline} - SUV_{treated}) \div SUV_{baseline} \times 100\%$) showed better prognostic value than 5PS in the evaluation of EoT-PET [26]. ΔSUV_{max} was studied widely in interim PET, and 66% was a cutoff of ΔSUV_{max} recommended by a serious of studies [27]. However, few studies detected the prognostic value of ΔSUV_{max} in EoT-PET [19, 26]. We also reanalyzed our data using the 66% ΔSUV_{max} as cutoff (Figure S2, Table S5 and S6), but it exhibited a prognostic value inferior to LLR that all of its prognostic indexes were lower than those of LLR. Using ROC analysis, we found a new cutoff value of 77.7% ΔSUV_{max} (Figure S3, Table S5 and S6). This cutoff had a lower sensitivity compared to DS 4 without obviously increasing the specificity and PPV of the latter, and its specificity, PPV, and accuracy were lower than that of the LLR cutoff, 1.83.

There is ongoing debate over the benefit of additional treatment, especially adjuvant radiotherapy after first-line therapy [28]. Some retrospective studies reported that additional radiotherapy after first-line immunochemotherapy improved the prognosis of DLBCL in the early Ann Arbor stages [29, 30], and others concluded that additional radiotherapy did not confer a survival benefit in patients with early-stage DLBCL [31] or patients with initial bulky disease [32]. A prospective study including 723 patients reported that 517 EoT-PET-negative patients had good outcomes in the absence of radiotherapy [11]. In our study, according to the multivariate analysis, additional treatment is not beneficial in patients with a negative EoT-PET when either defined as LLR < 1.83 or DS 1–3. For patients with positive EoT-PET classified by LLR (but not by 5PS), additional treatment is the only beneficial factor of OS. Under such circumstance, a higher specificity would be preferred to select more true-negative patients and avoid long-term side effect brought by overtreatment in these patients. A higher PPV may also be preferred to exclude more true-negative patients from the positive group. According to this study, LLR taking 1.83 as cutoff exhibited higher specificity and PPV compared to $DS_{1–3/4–5}$ (as well as compared to LLR with a cutoff value of 1.4 and ΔSUV_{max} with a cutoff value of 66% or 77.7%), indicating that it may be superior to other criteria in identifying patients who will not develop disease progression after the first-line therapy and potentially minimizing the long-term side effects of radiotherapy, prolonged

Table 2 Five-year survival rate of patients categorized by the Deauville 5PS and LLR

5-year survival rate (95%CI)			*p* value			
	For PFS	For OS	Group 1	Group 2	PFS	OS
DS 1–3	82.1% (77.4–87.1%)	89.8% (86.2–93.6%)	DS 1–3	DS 4	0.042	0.291
DS 1–4	80.3% (75.9–85.1%)	89.1% (85.7–92.6%)		DS 5	0.000	0.000
DS 4	67.6% (55.7–82.1%)	84.0% (74.4–94.8%)		DS 4–5	0.000	0.000
DS 5	20.0% (10.8–37.2%)	39.7% (27.0–58.3%)	DS 1–4	DS 5	0.000	0.000
DS 4–5	46.4% (37.1–58.0%)	64.1% (54.8–74.9%)	DS 4	DS 5	0.000	0.000
LLR < 1.83	81.2% (76.6–86.0%)	89.4% (85.9–93.0%)	LLR ≥ 1.83	LLR < 1.83	0.000	0.000
LLR ≥ 1.83	30.4% (20.4–45.1%)	51.2% (39.6–66.4%)				

DS Deauville score, *LLR* lesion-to-liver ratio calculated as SUV_{max} of the residual divided by SUV_{max} of the liver, *PFS* progression-free survival, *OS* overall survival

Table 3 The predictive performance of different EoT-PET classification methods

	Sensitivity	Specificity	PPV	NPV	Accuracy
Relapse/progression					
$DS_{1–3/4–5}$	47.5%	87.9%	53.3%	85.2%	78.8%
$DS_{1–4/5}$	31.7%	97.7%	80.0%	83.1%	82.9%
$LLR_{1.83}$	38.6%	95.1%	69.6%	84.2%	82.4%
Survival					
$DS_{1–3/4–5}$	51.6%	85.0%	35.6%	91.6%	80.4%
$DS_{1–4/5}$	38.7%	95.9%	60.0%	90.7%	88.0%
$LLR_{1.83}$	43.5%	92.5%	48.2%	91.1%	85.7%

EoT end of treatment, *PPV* positive predictive value, *NPV* negative predictive value, *DS* Deauville score, *LLR* lesion-to-liver ratio calculated as SUV_{max} of the residual divided by SUV_{max} of the liver

Table 4 The descriptive statistics of LLR

	Median	IQR	Minimum value	Maximum value
All patients	0.41	0.50	0.03	17.63
DS 1	0.25	0.15	0.03	0.52
DS 2	0.47	0.10	0.30	0.77
DS 3	0.70	0.16	0.48	1.01
DS 4	1.33	0.85	0.95	2.91
DS 5	5.23	3.07	3.14	17.63

DS Deauville score, *IQR* interquartile range

chemotherapy, or surgery. Therefore, we posit that the optimal cutoff of LLR is a promising tool for EoT-PET evaluation and for better guidance of additional treatment after the first-line immunochemotherapy.

This study was limited by its single-center and retrospective nature; accordingly, there is a possibility of selection bias. In our study, patients with age > 60 only composed 28% of all patients, which was lower than 34–35% reported by other studies about Chinese population [19, 33, 34]. One cause of this bias was that part of old patients could not tolerate the first-line chemotherapy and were excluded from our study. According to the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov), a 5-year survival rate declines with an increase in age, and the survival rate of patients in our study may be higher than reality. Besides, repeated PET scans may have resulted in the preferential inclusion of patients with better compliance and financial health. Additionally, the sample size of patients evaluated as EoT-PET positive was limited. In the future, the prognostic power of the LLR-based evaluation system for EoT-PET should be further tested with prospective research in a larger patient population.

Conclusion

This study found that, when the visual Deauville 5PS was used to evaluate treatment response in DLBCL patients, EoT-PET scans rated as DS 4 should not be unconditionally classified as PET positive or PET negative. Additional treatment did not improve the outcomes of the PET-negative patients identified either by the optimal cutoff of LLR or 5PS but improved the OS in PET-positive patients grouped by the cutoff of LLR, suggesting that the LLR-based evaluation system with a higher specificity and PPV may be superior to 5PS in identifying low-risk patients and thus sparing them the cost and toxicity of additional treatment. The evaluation based on LLR may hold promise as an accurate means of EoT-PET evaluation and a source of guidance for additional treatment after first-line immunochemotherapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00259-021-05581-z.

Author contribution Conceptualization, Xu Zhang, Ying-Ying Hu, and Ying-He Li; methodology, Ying-He Li, Yu-Mo Zhao, Mei-Ting Chen, and Zi-Zheng Xiao; formal analysis and investigation, Ying-He Li, Zi-Zheng Xiao, Yong-Luo Jiang, Mei-Ting Chen, Si Tang, Yu-Mo Zhao, Ying-Ying Hu, and Xu Zhang; writing (original draft preparation), Ying-He Li; writing (review and editing), Ying-He Li, Yu-Mo Zhao, and Yong-Luo Jiang; resources, Wei Fan; supervision, Xu Zhang,

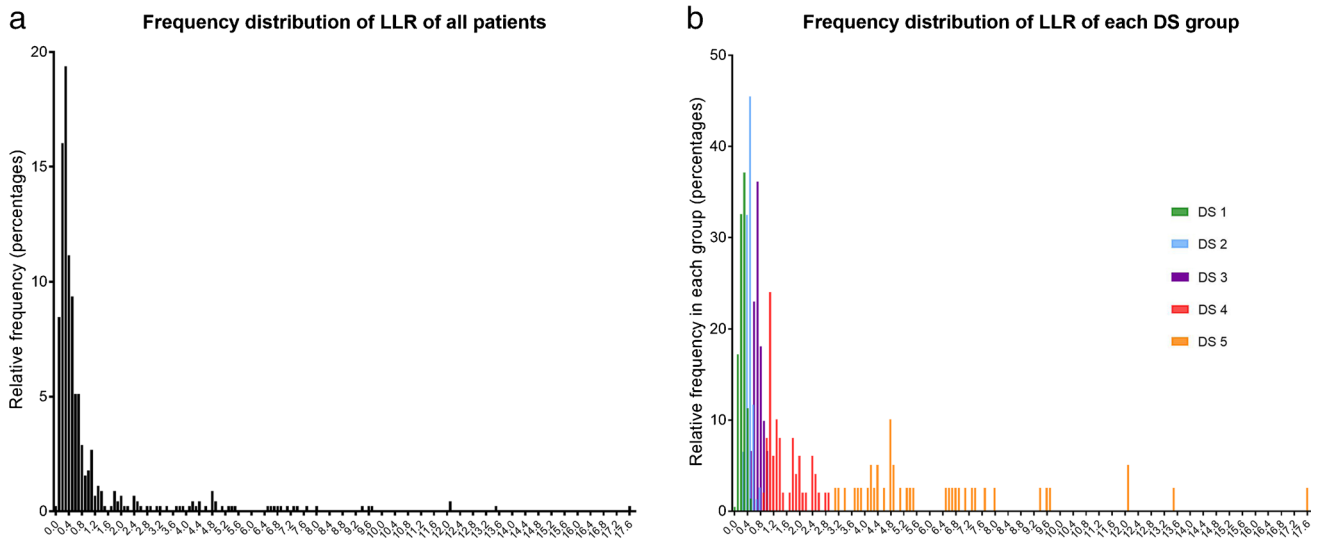


Fig. 3 Frequency distribution of LLR. **a** LLR of all 449 patients. **b** LLR of patients in different Deauville categories

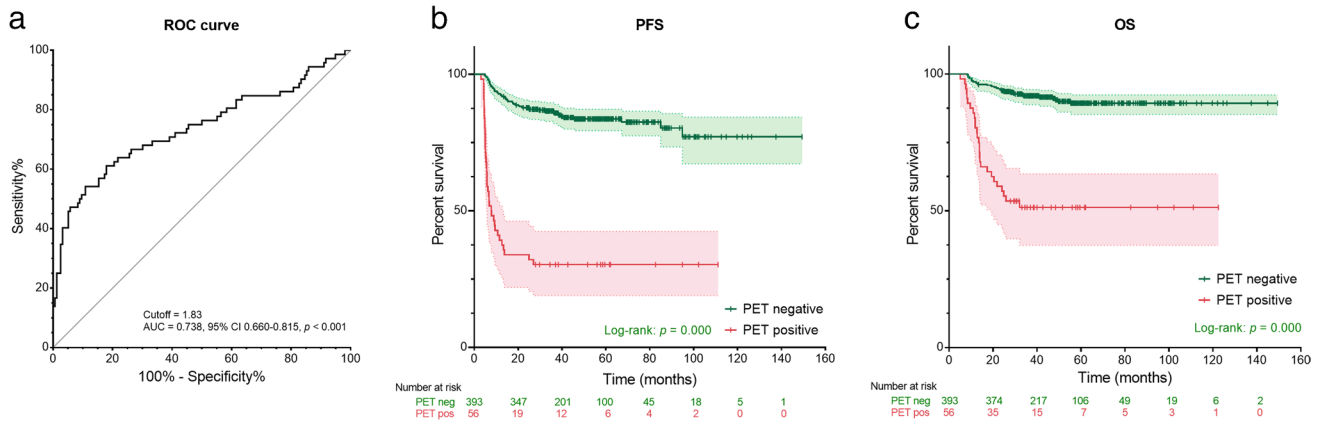


Fig. 4 ROC curves and K-M survival analysis of LLR-based PET status. **a** ROC curves for disease progression/relapse. **b**–**c** K-M survival curves of PFS (**b**) and OS (**c**) according to PET status (positive or negative) derived from the LLR

Ying-Ying Hu, and Wei Fan. All authors read and approved the final manuscript.

Funding This work was supported by grants from the Medical Science and Technology Foundation of Guangdong Province (A2018077).

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

Code availability Not applicable.

Declarations

Ethics approval 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. Ethical approval was also obtained from the Ethics Committee of Sun Yat-Sen University Cancer Center (approval number: B2021-189–01).

Consent to participate This retrospective study was performed with the Ethics Committee approval and a waiver of the requirement for patients' informed consent.

Consent for publication Additional informed consent was obtained from all legal guardians for whom identifying information is included in this article.

Conflict of interest The authors declare no competing interests.

References

1. Al-Hamadani M, Habermann TM, Cerhan JR, Macon WR, Maurer MJ, Go RS. Non-Hodgkin lymphoma subtype distribution,

geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. Am J Hematol. 2015;90:790–5. https://doi.org/10.1002/ajh.24086.
2. Perry AM, Diebold J, Nathwani BN, Maclennan KA, Müller-Hermelink HK, Bast M, et al. Non-Hodgkin lymphoma in the developing world: review of 4539 cases from the International Non-Hodgkin Lymphoma Classification Project. Haematologica. 2016;101:1244–50. https://doi.org/10.3324/haematol.2016.148809.
3. Weiler-Sagie M, Bushelev O, Epelbaum R, Dann EJ, Haim N, Avivi I, et al. 18F-FDG avidity in lymphoma readdressed: a study of 766 patients. J Nuc Med. 2010;51:25–30. https://doi.org/10.2967/jnumed.109.067892.
4. Zelenetz AD, Gordon LI, Wierda WG, Abramson JS, Advani RH, Andreadis CB, et al. Diffuse large B-cell lymphoma version 1.2016. J Natl Compr Canc Netw. 2016;14:196–231. https://doi.org/10.6004/jnccn.2016.0023.
5. Zelenetz AD, Gordon LI, Abramson JS, Advani RH, Bartlett NL, Caimi PF, et al. NCCN guidelines insights: B-cell lymphomas, Version 3.2019. J Natl Compr Canc Netw. 2019;17:650–61. https://doi.org/10.6004/jnccn.2019.0029.
6. Tilly H, Gomes da Silva M, Vitolo U, Jack A, Meignan M, Lopez-Guillermo A, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26 Suppl 5:v116–25. https://doi.org/10.1093/annonc/mdv304.
7. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Müeller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the international conference on malignant lymphomas imaging working group. J Clin Oncol. 2014;32:3048–58. https://doi.org/10.1200/JCO.2013.53.5229.
8. Kostakoglu L, Nowakowski GS. End-of-treatment PET/computed tomography response in diffuse large B-cell lymphoma. PET clinics. 2019;14:307–15. https://doi.org/10.1016/j.cpet.2019.03.001.
9. Kobe C, Dietlein M, Hellwig D. PET/CT for lymphoma post-therapy response assessment in Hodgkin lymphoma and diffuse large B-cell lymphoma. Semin Nucl Med. 2018;48:28–36. https://doi.org/10.1053/j.semnuclmed.2017.09.003.
10. Melani C, Advani R, Roschewski M, Walters KM, Chen CC, Baratto L, et al. End-of-treatment and serial PET imaging in primary mediastinal B-cell lymphoma following dose-adjusted EPOCH-R: a paradigm shift in clinical decision making. Haematologica. 2018;103:1337–44. https://doi.org/10.3324/haematol.2018.192492.
11. Freeman CL, Savage KJ, Villa DR, Scott DW, Srour L, Gerrie AS, et al. Long-term results of PET-guided radiation in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2021;137:929–38. https://doi.org/10.1182/blood.2020005846.
12. Adams HJA, Kwee TC. Systematic review on the value of end-of-treatment FDG-PET in improving overall survival of lymphoma patients. Ann Hematol. 2020;99:1–5. https://doi.org/10.1007/s00277-019-03881-x.
13. Adams HJA, Nievelstein RAJ, Kwee TC. Prognostic value of complete remission status at end-of-treatment FDG-PET in R-CHOP-treated diffuse large B-cell lymphoma: systematic review and meta-analysis. Br J Haematol. 2015;170:185–91. https://doi.org/10.1111/bjh.13420.
14. Kostakoglu L, Martelli M, Sehn LH, Belada D, Carella AM, Chua N, et al. End-of-treatment PET/CT predicts PFS and OS in DLBCL after first-line treatment: results from GOYA. Blood Adv. 2021;5:1283–90. https://doi.org/10.1182/bloodadvances.2020002690.
15. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: The Lugano classification. J Clin Oncol. 2014;32:3059–67. https://doi.org/10.1200/JCO.2013.54.8800.
16. Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on interim-PET scan in lymphoma. Leuk Lymphoma. 2009;50:1257–60. https://doi.org/10.1080/10428190903040048.
17. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. Lancet. 2017;390:298–310. https://doi.org/10.1016/s0140-6736(16)32407-2.
18. Burggraaff CN, Cornelisse AC, Hoekstra OS, Lugtenburg PJ, De Keizer B, Arens AIJ, et al. Interobserver agreement of interim and end-of-treatment18F-FDG PET/CT in diffuse large B-cell lymphoma: Impact on clinical practice and trials. J Nuc Med. 2018;59:1831–6. https://doi.org/10.2967/jnumed.118.210807.
19. Zhang Y, Fan Y, Ying Z, Song Y, Zhu J, Yang Z, et al. Can the LLR-based interpretation improve prognostic accuracy of interim and posttreatment 18F-FDG PET/CT in patients with diffuse large B-cell lymphoma? Leuk Lymphoma. 2018;59:660–9. https://doi.org/10.1080/10428194.2017.1357171.
20. Toledano MN, Vera P, Tilly H, Jardin F, Becker S. Comparison of therapeutic evaluation criteria in FDG-PET/CT in patients with diffuse large-cell B-cell lymphoma: prognostic impact of tumor/liver ratio. PLoS ONE. 2019;14. https://doi.org/10.1371/journal.pone.0211649.
21. Annunziata S, Pelliccioni A, Hohaus S, Maiolo E, Cuccaro A, Giordano A. The prognostic role of end-of-treatment FDG-PET/CT in diffuse large B cell lymphoma: a pilot study application of neural networks to predict time-to-event. Ann Nucl Med. 2021;35:102–10. https://doi.org/10.1007/s12149-020-01542-y.
22. Juweid ME, Stroobants S, Hoekstra OS, Mottaghy FM, Dietlein M, Guermazi A, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the imaging subcommittee of international harmonization project in lymphoma. J Clin Oncol. 2007;25:571–8. https://doi.org/10.1200/JCO.2006.08.2305.
23. Project IN-HsLPF. A predictive model for aggressive non-Hodgkin's lymphoma. N Engl J Med. 1993;329:987–94. https://doi.org/10.1056/nejm199309303291402.
24. Lee JW, Oh D, Eom KY, Kim JH, Kim WC, Chung MJ, et al. The prognostic value of PET/CT evaluation with Deauville score on the recurrence and survival in diffuse large B-cell lymphoma: a multi-institutional study of KROG 17–02. Clin Exp Metastasis. 2020;37:125–31. https://doi.org/10.1007/s10585-019-09992-z.
25. Del Puig Cózar-Santiago M, García-Garzón JR, Moragas-Freixa M, Soler-Peter M, Bassa Massanas P, Sánchez-Delgado M, et al. Optimisation of metabolic criteria in the prognostic assessment in patients with lymphoma. A multicentre study. Rev Esp Med Nucl Imagen Mol. 2017;36:304–11. https://doi.org/10.1016/j.remn.2017.03.003.
26. Schöder H, Polley MC, Knopp MV, Hall N, Kostakoglu L, Zhang J, et al. Prognostic value of interim FDG-PET in diffuse large cell lymphoma: results from the CALGB 50303 Clinical Trial. Blood. 2020;135:2224–34. https://doi.org/10.1182/blood.2019003277.
27. Meignan M, Gallamini A, Itti E, Barrington S, Haioun C, Polliack A. Report on the Third International Workshop on Interim Positron Emission Tomography in Lymphoma held in Menton, France, 26–27 September 2011 and Menton 2011 consensus. Leuk Lymphoma. 2012;53:1876–81. https://doi.org/10.3109/10428194.2012.677535.
28. Specht L. Does radiation have a role in advanced stage Hodgkin's or non-Hodgkin lymphoma? Curr Treat Options Oncol. 2016;17:4. https://doi.org/10.1007/s11864-015-0377-x.
29. Ballonoff A, Rusthoven KE, Schwer A, McCammon R, Kavanagh B, Bassetti M, et al. Outcomes and effect of radiotherapy in patients with stage I or II diffuse large B-cell lymphoma: a

surveillance, epidemiology, and end results analysis. Int J Radiat Oncol Biol Phys. 2008;72:1465–71. https://doi.org/10.1016/j.ijrobp.2008.02.068.
30. Vargo JA, Gill BS, Balasubramani GK, Beriwal S. Treatment selection and survival outcomes in early-stage diffuse large B-cell lymphoma: do we still need consolidative radiotherapy? J Clin Oncol. 2015;33:3710–7. https://doi.org/10.1200/jco.2015.61.7654.
31. Chung MJ, Cho WK, Oh D, Eom KY, Kim JH, Kim WC, et al. A multi-institutional and case-matched control study on treatment outcomes of consolidative radiotherapy after a full course of R-CHOP compared with R-CHOP alone in stage I-II diffuse large B-cell lymphoma (KROG 17–02). J Radiat Res. 2019;60:677–84. https://doi.org/10.1093/jrr/rrz043.
32. Tomita N, Kodama F, Motomura S, Itoh S, Ohshima R, Hyo R, et al. Adjuvant radiotherapy to an initial bulky mass in diffuse large B-cell lymphoma: lack of survival benefit. Int J Lab Hematol. 2008;30:53–7. https://doi.org/10.1111/j.1751-553X.2007.00900.x.
33. Shi Y, Han Y, Yang J, Liu P, He X, Zhang C, et al. Clinical features and outcomes of diffuse large B-cell lymphoma based on nodal or extranodal primary sites of origin: analysis of 1,085 WHO classified cases in a single institution in China. Chin J Cancer Res. 2019;31:152–61. https://doi.org/10.21147/j.issn.1000-9604.2019.01.10.
34. Li X, Xie X, Zhang L, Li X, Li L, Wang X, et al. Research on the midterm efficacy and prognosis of patients with diffuse large B-cell lymphoma by different evaluation methods in interim PET/CT. Eur J Radiol. 2020;133: 109301. https://doi.org/10.1016/j.ejrad.2020.109301.

Authors and Affiliations

Ying-He Li[1,2] · Yu-Mo Zhao[1,2] · Yong-Luo Jiang[1,2] · Si Tang[1,2] · Mei-Ting Chen[1,3] · Zi-Zheng Xiao[1,2] · Wei Fan[1,2] · Ying-Ying Hu[1,2] · Xu Zhang[1,2]

1 State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China

2 Department of Nuclear Medicine, Sun Yat-Sen University Cancer Center, 651 Dongfengdong Road, Guangzhou 510060, Guangdong, China

3 Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, Guangdong, China