Clinical & Experimental Metastasis (2020) 37:125–131
https://doi.org/10.1007/s10585-019-09992-z

RESEARCH PAPER

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

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Received: 25 April 2019 / Accepted: 16 September 2019 / Published online: 25 September 2019

Abstract

The Korean Radiation Oncology Group (KROG) assessed the value of Deauville score (DS) on ^{18}F-fluorodeoxyglucose Positron emission tomography-computed tomography (FDG PET/CT) as a predictor of recurrence and survival after rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) chemotherapy in diffuse large B-cell lymphoma (DLBCL). A total of 512 patients with stage I–III DLBCL who received six cycles of R-CHOP with or without radiation therapy (RT) and obtained treatment responses according to PET-CT imagings after R-CHOP ± RT were included. Patients were sorted into two arms; DS 4–5 arm (n = 24) was matched at a 1:2 ratio with DS 1–3 arm (n = 48) using propensity score matching method. After a median follow-up time of 37.2 months, the recurrence-free survival rate (86.6% vs. 66.8%, $P = 0.041$) and overall survival rate (86.9% vs. 62.2%, $P = 0.009$) at 5 years were significantly different between the DS 1–3 and DS 4–5 arms. DS 4–5 arm showed higher 5-years locoregional recurrence-free survival (88.8% vs. 74.3%, $P = 0.155$) and distant failure-free survival (91.1% vs. 84.3%, $P = 0.333$) than DS 1–3 arm. In the multivariate analysis, DS was still a significant factor for recurrence-free survival [hazard ratio (HR), 3.840 and confidence interval (CI), 1.068–13.806; $P = 0.039$] and overall survival rates (HR 4.453 and CI 1.274–15.562; $P = 0.019$). This study showed and validated that Deauville score of 4–5 of PET-CT imaging taken after full-course of R-CHOP chemotherapy with or without RT could predict recurrence-free survival and overall survival in DLBCL patients.

Keywords Deauville score · Diffuse large B-cell lymphoma · Prognosis · Survival

Abbreviations

CI	Confidence interval
DLBCL	Diffuse large B-cell lymphoma
DS	Deauville score
ECOG	Eastern Cooperative Oncology Group
EOT	End-of-treatment
FDG	^{18}F-fluorodeoxyglucose
HR	Hazard ratio
IPI	International prognostic index
LRR	Locoregional recurrence

Electronic supplementary material The online version of this article (doi:https://doi.org/10.1007/s10585-019-09992-z) contains supplementary material, which is available to authorized users.

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PET/CT	Positron emission tomography-computed tomography
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone
RT	Radiotherapy
RFS	Recurrence-free survival
OS	Overall survival

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common form of aggressive non-Hodgkin lymphoma [1]. The addition of rituximab to the chemotherapy regimen consisting of cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (R-CHOP) has improved the survival of DLBCL patients in the recent time. The most common predictor for patients with DLBCL is the International Prognostic Index (IPI) [2]. However, the IPI has some limitations. It was established prior to the era of rituximab and could be affected by clinical characteristics before treatment, so there was substantial diversity in each patient [3, 4]. ^{18}F-fluoro-DeoxyGlucose Positron Emission Tomography-Computed Tomography (FDG-PET/CT) is regarded as an enhanced imaging modality for the diagnosis and response evaluation for DLBCL patients [5, 6]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that PET/CT scans should be interpreted by the 5-point Deauville score (DS) and Lugano response criteria, on the basis of visual assessment [7, 8].

Although treatment outcomes have improved since the inclusion of rituximab, 30 to 40% of patients with DLBCL still fail to cure completely with R-CHOP alone, leading to further therapeutic interventions [1, 6]. It is important to identify the poor responders to first-line R-CHOP chemotherapy in order to effectively manage the disease. We investigated patients with stage I-III DLBCL in the Korean Radiation Oncology Group (KROG) 17-02 trial. The aim of the current study was to evaluate the prognostic significance and cut-off of DS on the end-of-treatment (EOT) FDG-PET/CT imagings after full-course of R-CHOP ± RT.

Methods and materials

Patients and FDG-PET/CT imaging assessment

We retrospectively analyzed the data from DLBCL patients enrolled in the KROG 17-02 study. The study collected the data of 512 patients with stage I–III DLBCL (488 patients who had DS 1–3 and 24 patients who had DS 4–5 after R-CHOP) at five institutions from January 2010 to December 2015. The inclusion criteria for this analysis were: (1) histologically proven DLBCL with clinical stage I to III by the Ann Arbor staging system, (2) ECOG performance status 0–2, (3) initial treatment with six cycles of R-CHOP (rituximab, 375 mg/m^2; cyclophosphamide, 750 mg/m^2; doxorubicin, 50 mg/m^2; vincristine, 1.4 mg/m^2; and prednisolone, 100 mg), and (4) the presence of FDG-PET/CT imagings before and after completion of R-CHOP chemotherapy with or without radiotherapy. KROG 17-02 was approved by the institutional review board at each participating center and at KROG before enrolling patients. FDG-PET/CT was performed after R-CHOP and before RT, and the response to R-CHOP was evaluated according to the 5-point Deauville scale (DS) on FDG-PET/CT by institutional radiologists [7, 9]. According to previous reports [7, 9], the five-point DS determines FDG uptake in the involved site compared to the mediastinum and liver and yields results of (1) no uptake, (2) uptake ≤ mediastinum, (3) uptake > mediastinum but ≤ liver, (4) uptake moderately higher than the liver, and (5) uptake markedly higher than the liver and/or new lesion. Consolidative radiation therapy (RT) was executed at a median dose of 36 Gy (range, 30–45 Gy) at 1.8 to 2 Gy per fraction one to two months after R-CHOP treatment in 113 (22.1%) of 512 patients.

Propensity score matching and statistical analyses

To assess the associations between treatment outcomes and Deauville scores of the FDG-PET/CT, we divided the patients into two arms; DS 1–3 and DS 4–5. We conducted propensity-score matching for the enrolled patients. The propensity scores were calculated using a multivariate logistic-regression model based on the following variables; age (< 60 vs. ≥60), ECOG performance status (0–1 vs. 2), clinical stage (I–II vs. III), lesion size (< 5 vs. ≥5, cm), LDH level (< 230 vs. ≥230, IU/L), IPI score (0–1 vs. 2–4), and receipt of radiotherapy. A total of 488 patients in the DS 1–3 arm and 24 patients in the DS 4–5 arm were matched at a 1:2 ratio (n = 48 vs. 24, respectively). The matching model was well-calibrated (Hosmer-Lemeshow test, $P = 0.848$) with reasonable discrimination (c-index = 0.710).

After 1:2 matching, the patient characteristics were compared with the χ^2 test for categorical variables and the *t* test for continuous variables. The endpoints were recurrence-free survival (RFS) and overall survival (OS) between the two arms. RFS was defined as the interval from the date of last chemotherapy to any locoregional and/or distant failure and OS was defined as the interval from the date of last chemotherapy to death or last follow-up. The survival curves were extracted by Kaplan–Meier analysis and compared with the log-rank test. To evaluate the prognostic factors related to recurrence and survival, multivariate analysis was performed with the Cox proportional hazard method. Chi-squared or

Table 1 Patient characteristics

Characteristic—no. (%)	DS 1–3 (n = 48)	DS 4–5 (n = 24)	*P*-value
Age (years)			0.867
< 60	27 (67.5)	13 (32.5)	
≥ 60	21 (65.6)	11 (34.4)	
ECOG performance status			0.716
0–1	45 (66.2)	23 (33.8)	
2	3 (75.0)	1 (25.0)	
Clinical stage			1.000
I–II	38 (66.7)	19 (33.3)	
III	10 (66.7)	5 (33.3)	
Lesion size (cm)			1.000
< 5	24 (66.7)	12 (33.3)	
≥ 5	24 (66.7)	12 (33.3)	
Lactate dehydrogenase (IU/L)			0.450
< 230	7 (77.8)	2 (22.2)	
≥ 230	41 (65.1)	22 (34.9)	
IPI score			1.000
0–1 (low)	36 (66.7)	18 (33.3)	
2–4 (intermediate to high)	12 (66.7)	6 (33.3)	
Radiotherapy			0.063
No	38 (73.1)	14 (26.9)	
Yes	10 (50.0)	10 (50.0)	

DS Deauville score, *ECOG* Eastern Cooperative Oncology Group, *IPI* international prognostic index, *R-CHOP* Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone, *RT* radiotherapy

Fisher's exact test was used to evaluate the significance of any correlation between the categorical variables. A *P*-value of less than 0.05 was considered statistically significant. All analyses were conducted using SPSS Statistics version 12.0 (SPSS Inc., an IBM Company, Chicago, IL).

Results

A total of 72 patients (after 1:2 propensity score matching) were finally analyzed. The median age of the study participants was 57 years (range, 27–80 years). The median lesion size was 5 cm (range 1–12 cm). Among the analyzed patients, 52 received R-CHOP only and 20 received radiotherapy after R-CHOP. The patient characteristics are shown in Table 1. Patient age ($P = 0.867$), ECOG performance status ($P = 0.716$), clinical stage ($P = 1.000$), lesion size ($P = 1.000$), LDH level ($P = 0.450$), IPI score ($P = 1.000$), and RT ($P = 0.063$) were well-balanced between DS 1–3 arm and DS 4–5 arm after propensity score matching.

After a median follow-up time of 37.2 months (range, 6.0–137.8 months), disease failure including locoregional recurrence (LRR) and distant failure, occurred in 14 patients. Locoregional recurrence occurred in five (10.4%) of 48 patients in the DS 1–3 arm and five (20.8%) of 24 patients in the DS 4–5 arm. Distant failure occurred in four (8.3%) patients in the DS 1–3 arm four (16.7%) patients in the DS 4–5 arm and. Four patients failed at both locoregional and distant sites. The 5-years locoregional recurrence-free survival rates were 88.8% in the DS 1–3 arm and 74.3% in the DS 4–5 arm, respectively ($P = 0.155$, Fig. 1a). The 5-year distant failure-free survival rates were 91.1% in the DS 1–3 arm and 84.3% in the DS 4–5 arm, respectively ($P = 0.333$, Fig. 1b). The five-year RFS rates for the DS 1–3 arm and DS 4–5 arm were 86.6% and 66.8%, respectively (Fig. 2a). The five-year OS rates for the DS 1–3 arm and DS 4–5 arm were 86.9% and 62.2%, respectively (Fig. 2b). There were significant differences in RFS ($P = 0.041$) and OS ($P = 0.009$) between the two arms.

Table 2 shows the univariate and multivariate analyses of the prognostic factors for recurrence-free survival and overall survival. In the univariate analysis, age, clinical stage, lesion size, LDH level, IPI score, and RT were not significantly associated with RFS and OS. Good performance status (ECOG 0–1) showed improved OS in the univariate analysis ($P = 0.032$), but not in the multivariate analysis ($P = 0.466$). In the multivariate analysis, DS was a significant factor for the recurrence-free survival [hazard ratio (HR) 3.840 and confidence interval (CI) 1.068–13.806; $P = 0.039$] and overall survival (HR 4.453 and CI 1.274–15.562; $P = 0.019$).

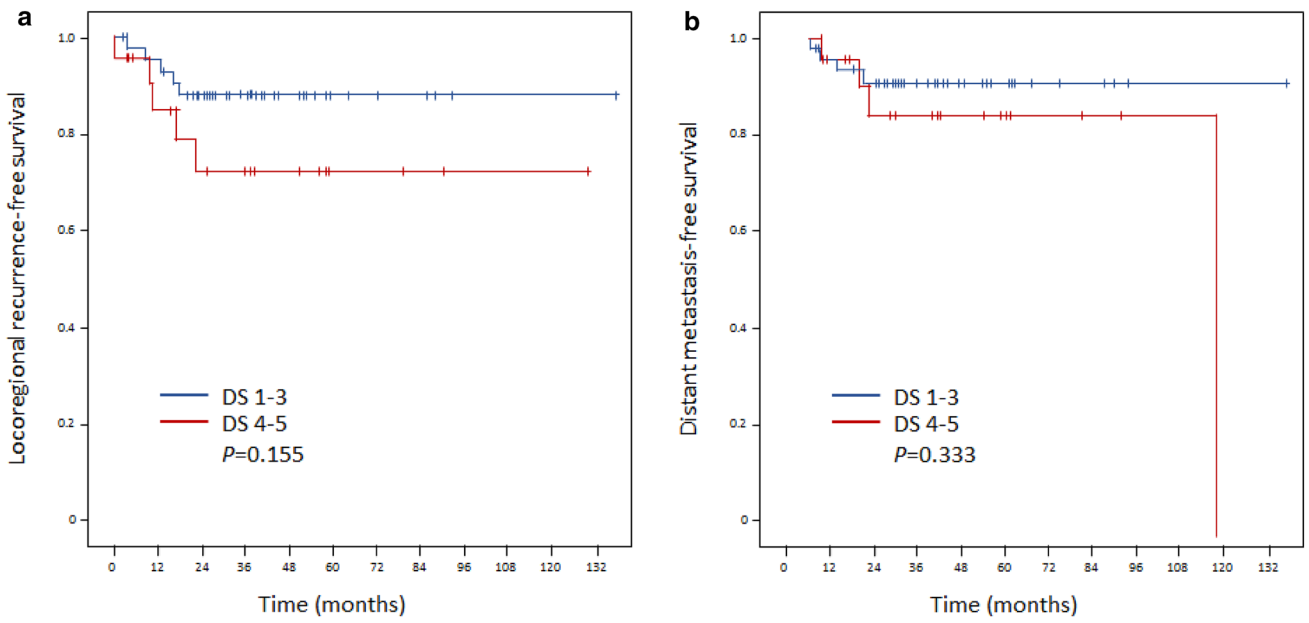

Fig. 1 Overall survival (OS) before propensity-score matching according to the Deauville score 1 to 5

Discussion

Our results showed that patients with Deauville scores of 4–5 from FDG-PET/CT imaging assessment after standard R-CHOP chemotherapy had significantly poorer recurrence-free survival and overall survival outcomes than patients with Deauville scores of 1–3. PET/CT in DLBCL possesses prognostic value for predicting response and treatment outcomes [3]. Interim PET/CT (iPET/CT), conducted after two to four cycles of chemotherapy has significant

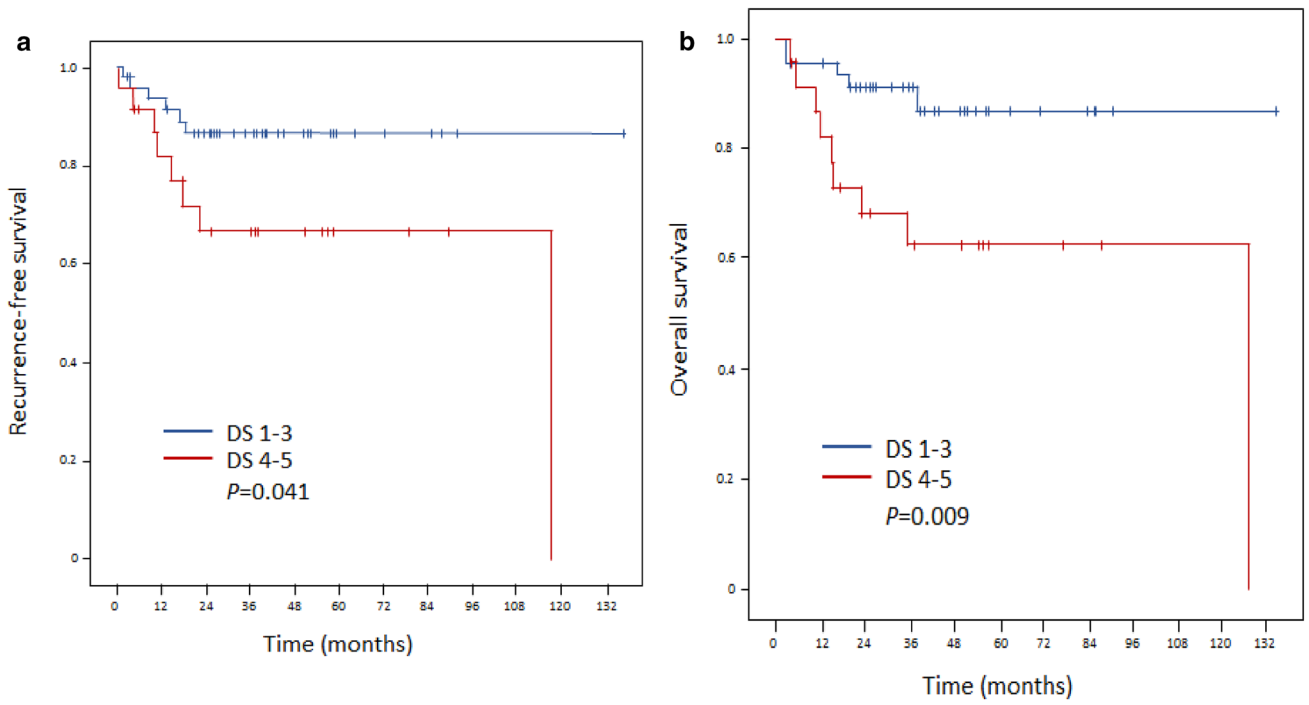

Fig. 2 **a** Locoregional recurrence-free survival and distant failure-free survival rates after propensity score matching (1:2) for the DS 1–3 and 4–5 arms. **b** Recurrence-free survival and overall survival rates after propensity score matching (1:2) for the DS 1–3 and 4–5 arms

Table 2 Univariate and multivariate analyses of prognostic factors for recurrence-free survival and overall survival

Factors	Recurrence-free survival				Overall survival			
	5-year rate (%)	Univariate (*P*)	Multivariate (*P*)	Hazard ratio (95% CI)	5-year rate (%)	Univariate (*P*)	Multivariate (*P*)	Hazard ratio (95% CI)
Age (years)		0.614	0.893			0.329	0.349	
< 60	81.6			Referent	82.3			Referent
≥ 60	78.5			0.927 (0.307–2.798)	74.3			0.561 (0.167–1.883)
ECOG performance status		0.507	0.888			0.032	0.466	
0–1	80.9			Referent	80.7			Referent
2	66.7			1.190 (0.106–13.397)	50.0			0.471 (0.062–3.563)
Clinical stage		0.090	0.952			0.083	0.952	
I–II	84.7				82.7			
III	62.8				65.2			
Lesion size (cm)		0.253	0.053			0.656	0.630	
< 5	75.3			Referent	76.4			Referent
≥ 5	85.1			4.353 (0.982–19.309)	80.6			1.403 (0.354–5.566)
Lactate dehydrogenase (IU/L)		0.168	0.060			0.671	0.890	
< 230	63.5			Referent	85.7			Referent
≥ 230	82.7			4.254 (0.939–19.268)	77.7			0.854 (0.092–7.901)
IPI score		0.254	0.962			0.216	0.956	
0–1 (low)	83.7				81.8			
2–4 (intermediate to high)	69.8				70.7			
Radiotherapy		0.214	0.393			0.229	0.371	
No	75.6				76.1			
Yes	82.5				80.3			
DS		0.041	0.039			0.009	0.019	
1–3	86.6			Referent	86.9			Referent
4–5	66.8			3.840 (1.068–13.806)	62.5			4.453 (1.274–15.562)

DS Deauville score, *ECOG* Eastern Cooperative Oncology Group, *IPI* international prognostic index, *R-CHOP* Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone, *RT* radiotherapy, *HR* hazard ratio, *CI* confidence interval

prognostic importance for RFS and OS in patients with DLBCL [3, 10, 11]. In the current study, EOT PET/CT was also performed after R-CHOP with six cycles similar to other studies [12, 13]. For EOT PET/CT, reports on the prognostic value have been controversial [11]. Jerusalem et al. [14] reported that EOT PET/CT was a very useful modality with a higher diagnostic and prognostic value which could distinguish tumors from fibrosis. According to Yoo et al. [15], iPET/CT might be unnecessary and omitted because their study found no difference in survival outcomes as a result of iPET/CTs. The prognostic efficacy of iPET/CT may be controversial but EOT PET/CT has a crucial prognostic value in lymphoma treatment [4].

Many studies on PET/CT in non-Hodgkin's lymphoma have used diverse assessment criteria [7, 16]. The studies suggested using visual assessment criteria, such as standardized uptake value, metabolic tumor volume, or DS, etc. [7, 16, 17]. The International Harmonization Project response criteria categorized complete response (CR), partial response (PR), stable disease (SD), and relapsed disease or progressive disease (PD) reflecting PET/CT and CT response [18]. Recent studies reported that DS predicted outcomes more effectively than IHP criteria when interpreting response in FDG-PET/CT imagings [19].

Different treatment outcomes can be indicated depending upon which score is used as a cutoff point in the DS [20–23]. While DS 1–2 are considered negative and DS 4–5 are positive and result in the escalation of therapy, DS 3 is considered negative in conservative readings and positive in sensitive readings [24]. However, sometimes, DS 3 may be considered an insufficient response, counted as positive, and result in de-escalation of therapy [8, 24, 25]. There is uncertainty in reading DS scores of 3. The International Conference on Malignant Lymphomas Imaging Working Group described DS 3 as "probably" representing a complete metabolic response, while DS 1 and 2 were clearly defined [26]. In the current study, patients who had achieved DS 1,2,3 after R-CHOP got together as a good prognostic group since there was no significant difference in the overall survival rate among them. In the whole collective data, ECOG performance status ($P=0.116$), clinical stage ($P=0.381$), lesion size ($P=0.545$), LDH level ($P=0.366$), IPI score ($P=0.460$), and RT ($P=0.551$) except for age ($P=0.045$) were not statistically different between DS 1–2 and DS 3 arms. When we categorized patients into the DS 1–3 and DS 4–5 arms, the RFS and OS between the two arms were significantly different (86.6% vs. 66.8%, $P=0.041$ and 86.9% vs. 62.2%, $P=0.009$, respectively). Thus, our results supported that DS 3 was a good prognostic group after chemotherapy for patients with DLBCL.

A complete response assessment is associated with better clinical outcomes compared to partial responses [12, 27, 28]. A residual mass with positive FDG-PET/CT finding after completion of therapy for DLBCL indicates the possibility of viable tumor and is associated with a high risk of disease progression or relapse, therefore, additional treatment should strongly be considered. Studies [12, 14, 28, 29] conducted before the introduction of Deauville scores described positive FDG-PET/CT scans as those with increased activity in a focal or diffuse area compared to normal anatomy. The current multi-institutional study verified that Deauville scores are important for evaluating the positivity of FDG-PET/CT imagings after treatment in the rituximab era and supports these previous reports.

In conclusion, DS 4–5 of FDG-PET/CT imagings after standard R-CHOP with or without radiation predicted poor recurrence-free survival and overall survival in DLBCL patients. This study also concluded that DS 3 could be included in the good prognosis group. For poor responders with DLBCL who had DS 4–5 after standard R-CHOP, further treatments, such as second-line chemotherapy or stem cell transplantation should be considered.

Acknowledgements The statistical analyses performed in this article were advised by Catholic Medical Center Clinical Research Coordinating Center.

Funding There is no funding relevant to this work to be declared.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no competing interests.

Ethical approval This study was approved by the Institutional Review Board (VC17RESI0046).

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