Original Article

The value of FDG-PET/CT metabolic parameters and treatment metabolic response in predicting long-term survival of patients with diffuse large B-cell lymphoma

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Received: 09 June, 2024; Accepted: 03 November, 2024

DOI: 10.22037/nbm.v13i1.45530

Abstract

Background: Few trials have been conducted regarding using PET/CT metabolic parameters as a predictor for the long-term survival of patients with lymphoma. The present study aimed to determine the prognostic value of quantitative metabolic parameters based on FDG-PET/CT in predicting 2-year mortality and disease recurrence in patients with diffuse large B-cell lymphoma (DLBCL).

Materials and Methods: This cross-sectional study was performed on patients who suffered DLBCL and assessed by FDG-PET/CT. All patients have been scheduled for first-line therapy, including the R-CHOP regimen (Rituximab, Cyclophosphamide, Hydroxydaunomycin, Oncovin, and Prednisone). The records of patients eligible for the study were extracted from the hospital archive. All subjects were followed up for 2 years to assess progression-free survival (PFS) and overall survival (OS).

Results: Complete response to treatment was revealed in 80.0%, while the disease was progressive in 5.7% and stable in 2.9%. At the end of 2 years of follow-up, in all groups, five people (14.2%) experienced disease relapse, and one person (2.9%) died. Comparing metabolic parameters of PET/CT between survived and non-survived groups showed no difference between the two groups. Similarly, the median value of pointed metabolic parameters was insignificant between groups with and without disease relapse. The comparison of the treatment metabolic response state between non-survived and survived subgroups showed no difference. However, regarding the metabolic response status according to the presence or lack of recurrence, those with disease recurrence experienced a higher rate of progressive metabolic disease condition. Treatment metabolic non-response status and higher Deauville 5-point score (D5PS) score could effectively differentiate the groups with and without disease recurrence.

Conclusion: FDG-PET/CT complete metabolic response can predict longer PFS in patients with DLBCL, but its related metabolic parameters may not predict disease outcome.

Keywords: Diffuse large B-cell lymphoma, MTV, TLG, FDG PET/CT, Prognosis

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Please cite this article as: Yousefikoma A, Mohamad Mahdi Karimy Taha. The value of FDG-PET/CT metabolic parameters and treatment metabolic response in predicting long-term survival of patients with diffuse large B-cell lymphoma. Novel Biomed. 2025;13(1):1-9.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is now identified as a curable malignancy by employing therapies including the anti-CD20 antibody (rituximab) combined with other chemotherapies such as doxorubicin, cyclophosphamide, and vincristine[1,2]. Despite using these standard-of-care treatments, the patients may experience high relapse rates following first-line therapy as well as poorer post-therapeutic outcomes[3]. Therefore, to improve the treatment outcomes in these patients, it is necessary to develop new treatment methods to improve the overall survival of the patients and, at the same time, lead to their relapse-free survival. Along with improving treatment methods and achieving optimal drug effectiveness, early diagnosis of drug effectiveness is also very vital in these patients. In this regard, some imaging techniques have significantly helped in the early diagnosis of the disease, predicting the disease's recurrence, and evaluating the treatment's effectiveness. In this regard, positron emission tomography (PET) imaging with fluoro-2-deoxy-D-glucose (FDG), particularly when integrated with PET/computed tomography (CT), has proven a valuable tool for the assessment of treatment response[4,5]. It has been shown that using this technique differentiates DLBCL from benign pathologies such as fibrotic lesions[6].

Moreover, some cohort studies have shown a close link between PET/CT findings and patients' outcomes[7,8]. However, few trials could help guide oncology practice using end-induction PET/CT as a surrogate for patients' survival and a potential surrogate marker for treatment-related outcomes. The present study aimed to determine the prognostic value of quantitative metabolic parameters based on FDG-PET/CT metabolic parameters in predicting 2-year death and disease recurrence in patients suffering DLBCL.

Methods

Study population: This cross-sectional study was performed on patients who suffered DLBCL referred to Masih Daneshvari Hospital between 2014 and 2021 and assessed by FDG-PET/CT. The primary diagnosis of the disease was confirmed using the pathological assessment and immunohistochemistry assay. All patients underwent 18F FDG PET/CT scans before and at the end of treatment and were treated with an R-CHOP regimen (rituximab, doxorubicin, cyclophosphamide, vincristine, and prednisolone) for 6 to 8 cycles. The patients with a history of other malignancies, a history of hepatitis or HIV infections, with evidence of primary lymphoma of the central nervous system, or a history of radiation or chemotherapy before FDG-PET/CT were all excluded from the study.

Study assessments: The records of patients eligible for the study were extracted from the hospital archive, and the following items were extracted for a more accurate interpretation of the images: sex, age, Lugano staging, previous imaging and laboratory records, and history of surgery, chemotherapy, or radiotherapy. Baseline and end-of-treatment scans were performed on the same scanner. End-of-treatment PET-CT was performed 2 weeks after the last chemoimmunotherapy.

The need for radiotherapy was assessed using criteria defined by staging data. PET-CT scans were performed before RT treatment was started in all included cases. Patients were fasting for 4 to 6 hours according to the PET/CT imaging protocol. Blood sugar was assessed before 18F-FDG injection, which should be below 200 mg/dL. Patients received 18F-FDG (0.8 mCi/10 kg or 4.6 MBq/kg, intravenously) seated and were asked to drink water and rest for one hour before scanning. Images were taken 55 to 60 minutes after the injection while the patients were lying on their backs with slow breathing with a Discovery 690 VCT scanner (GE Healthcare, Milwaukee, USA) from the top of the skull to the middle part of the thigh. CT was then performed (28 to 40 mAs, 120 Kv, 2.5 mm thickness), and PET scanning was planned. All PET/CT images were interpreted using Advantage Workstation v4.5 software and by two independent experts blinded to clinical information. 3D-FDG-PET images were analyzed for lesions with increased focal uptake. Then quantitative parameters including maximum standard uptake value (SUVmax), mean standard uptake value (SUVmean), maximum metabolic tumor volume (MTVmax), total metabolic tumor volume (MTVsum), total lesion

glycolysis maximum (TLGmax), and total lesion glycolysis sum (TLGsum) were measured. Tumor metabolic volume was calculated for lesions with SUV>2.5. The total metabolic tumor volume (TMTV) was also determined. Total TLG (TTLG) was calculated as the product of MTV times the average SUV across all lesions. Response to R-CHOP chemotherapy was classified according to Lugano criteria as complete remission (CR), partial remission (PR), stable disease (SD), progressive metabolic disease (PD), complete metabolic response (CR), and incomplete metabolic response (Non-CR). Lugano classification for metabolic response assessment of PET/CT incorporating the Deauville 5-point score (D5PS) is as follows: score 1, no FDG uptake above background; score 2, FDG uptake≤mediastinum; score 3, FDG uptake>mediastinum but≤liver; score 4, FDG uptake moderately>liver; and score 5, FDG uptake markedly higher than liver and/or new lesions. Finally, after the treatment period, the patients were followed up for two years through telephone interviews or hospital records, and disease survival and recurrence were evaluated. In this regard, progression-free survival (PFS) was defined as the time from the initial diagnosis to the first occurrence of disease recurrence, progression, disease-related death, or at the end of the follow-up period. Overall survival (OS) was also defined as the time from initial diagnosis to death from disease or the end of the follow-up period.

The ethics committee of Shahid Beheshti University of Medical Sciences approved the study. The principles of the Declaration of Helsinki were fully respected. The objectives of the research and its importance were explained to the research units. The research units were given the right to choose to participate in the research. The research units were assured that all the obtained information would remain confidential. If desired, the research results were provided to them.

Statistical analysis: The results were analyzed using SPSS software (version 23). The information was reported in two descriptive and analytical sections. In the descriptive part, mean and standard deviation were used for quantitative variables, and number and percentage were used for qualitative variables. In the analytical part, the scaling scores between the two groups were compared using the independent T-test or the Mann-Whitney U-test if required. The comparison of qualitative parameters was done using the Chi-Square test. In all tests, the significance level was $P<0.05$.

Ethical considerations: The study proposal has received approval from the Ethics Committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.NRITLD.REC.1400.067.).

Results

Baseline characteristics are shown in Table 1. The average age of patients was 48.9 ± 15.8 years, and 51.4% were male. The ECOG/WHO performance status is a prognostic factor categorized on a scale of 0 to 4. In this context, all patients demonstrated either full activity or were fully ambulatory and capable of carrying out light work (ECOG=0-1). Concerning response to treatment, complete response was revealed in 80.0%, while the disease was progressive in 5.7% and stable in 2.9%. Based on the D5PS classification, in 8.6%, the FDG uptake was moderately higher than in the liver, and in 11.4%, it was markedly higher than in the liver and/or new lesions. In this regard, the high Lugano stage was found in 62.9%. Also, PET/CT indicated higher than one extra-nodal site involvement in 37.1% of patients. Regarding tumor stage, stages III and IV were revealed in 11.4% and 51.4%, respectively.

At the end of 2 years of follow-up, in all groups, five people (14.2%) experienced disease relapse, and one person (2.9%) died. The 2-year progression-free and 2-year overall survival rates in all groups were 31 (85.7) and 34 (97.1%), respectively (Figure 1). There was one death in patients classified as non-complete metabolic responders. Also, all five relapses occurred in patients classified in the treatment metabolic non-response group. Regarding the outcome state, according to the response assessment of PET/CT incorporation, one patient who died had a D5PS score of five. Disease recurrence was also revealed in 1 patient with a D5PS score of 4 and 4 patients with a D5PS score of 5. According to the Log Rank test, no difference was found in the death rate across the different D5PS score groups (P=0.101). In contrast, a significant difference was shown in the likelihood of recurrence between the

Table 1. Baseline characteristics of the study population**.**

Gender, n (%)		Female	17 (48.6 %)
		Male	18 (51.4 %)
Mean age (year)			48.9 ± 15.8
Performance Status, %		ECOG 0	54.3%
		ECOG 1	45.7%
Treatment Response, n (%)		Complete Response	28 (80.0 %)
		Non-Complete Response	7 (20.0 %)
		Complete Response	28 (80.0 %)
		Progressive Disease	2 (5.7 %)
		Partial Response	4 (11.4 %)
		Stable Disease	1 (2.9 %)
Deauville 5-point score (D5PS state), n (%)		D5PS1	23 (65.7 %)
		D5PS2	2 (5.7 %)
		D5PS3	3 (8.6 %)
		D5PS4	3 (8.6 %)
		D5PS5	4 (11.4 %)
PET/CT metabolic parameters	Total TLG	1279.03 (77.06, 4417.23) *	
	TLG MAX	498.89 (66.08, 2185.78) *	
	Total MTV	192.34 (17.95, 565.31) *	
	MTV MAX	56.62 (14.79, 201.43) *	
	SUV MAX	13.71 (9.56, 26.37) *	
Lugano Stage, n (%)		Low (I + II)	13 (37.1 %)
		High (III +IV)	22 (62.9 %)
Lugano Stage, n (%)		I	3 (8.6 %)
		II	9 (25.7 %)
		III	5 (14.3 %)
		IV	18 (51.4 %)
Extra-nodal Site, n (%)		Negative (0)	6 (17.14 %)
		Site= 1	16 (45.71 %)
		Site >1	13 (37.15 %)
Tumor stage, n (%)		I	1 (2.86 %)
		IE	2 (5.71 %)
		II	7 (20.00 %)
		IIE	3 (8.57 %)
		III	4 (11.43 %)
		IV	18 (51.43 %)

different D5PS groups (P<0.001).

As shown in Table 2, comparing metabolic parameters of PET/CT between survived and non-survived groups showed no difference between the two groups. Similarly, the median value of pointed metabolic parameters was insignificant between groups with and without disease relapse (Table 2).

The treatment metabolic response state comparison between non-survived and survived subgroups (Table 3) showed no difference (P=0.365). However, regarding the metabolic response status according to the presence or lack of recurrence, those with disease recurrence experienced a higher rate of progressive disease condition (P<0.001).

The condition of the D5PS score according to patients' survival and disease recurrence was also summarized in Table 4. In this context, there was no association between the D5PS score and patients' survival (p =

Table 2. Comparing metabolic parameters between survived and none-survived groups**.**

FDG-PET Parameter	Survived	Deceased	P-value
Total TLG	1180.9 (74.43, 4030.29)	9803.23	0.286
TLG Max	481.21 (62.61, 1901.59)	4141.56	0.400
Total MTV	176.62 (17.77, 526.60)	1684.77	0.171
MTV Max	56.05 (14.38, 161.59)	885.30	0.229
SUV MAX	15.745 (9.29, 26.57)	11.67	0.743
FDG-PET Parameter	**Without Recurrence**	**With Recurrence**	**P-value**
Total TLG	1082 (52.325, 3768.36)	2863 (444.8225, 10059.85)	0.292
TLG Max	463.53 (39.22, 1996.32)	698.525 (351.84, 4380.0825)	0.428
Total MTV	160.9 (15.65, 445.045)	409.46 (108.17, 1754.315)	0.187
MTV Max	55.48 (11.455, 164.21)	134.43 (40.6975, 936.995)	0.172
SUV MAX	13.71 (8.385, 23.7)	19.02 (10.6175, 33.3475)	0.482

Data are presented as median (1^{st}, 3^{rd} percentiles)

Table 3. The response status according to the presence or lack of death or recurrence**.**

Response state	Survived	Deceased	P-value
Complete Response	28 (84.8%)	0 (0.0%)	0.182
Progressive Disease	1 (2.9%)	1 (100%)	
Partial Response	4 (11.7%)	0 (0.0%)	
Stable Disease	1 (2.9%)	0 (0.0%)	
Response state	**Without Recurrence**	**With Recurrence**	**P-value**
Complete Response	28 (90.3%)	0 (0.0%)	<0.001
Progressive Disease	0 (0.0%)	2 (40.0%)	
Partial Response	1 (3.2%)	3 (60.0%)	
Stable Disease	1 (3.2%)	0 (0.0%)	

Table 4. The D5PS score classification according to the presence or lack of death or recurrence**.**

D5PS score	Survived	Deceased	P-value
D5PS1	23 (67.8%)	0 (0.0%)	0.254
D5PS2	2 (5.8%)	0 (0.0%)	
D5PS3	3 (8.8%)	0 (0.0%)	
D5PS4	3 (8.8%)	0 (0.0%)	
D5PS5	3 (8.8%)	1 (100%)	
D5PS score	**Without Recurrence**	**With Recurrence**	**P-value**
D5PS1	23 (76.7%)	0 (0.0%)	<0.001
D5PS2	2 (6.7%)	0 (0.0%)	
D5PS3	3 (10.0%)	0 (0.0%)	
D5PS4	2 (6.7%)	1 (20.0%)	
D5PS5	0 (0.0%)	4 (80.0%)	

0.254).

However, a higher D5PS score was found in those patients with disease recurrence (P<0.001).

According to the ROC curve analysis (Table 5), the PET/CT-based metabolic parameters could not effectively predict 2-year death in patients suffering DLBCL (Figure 2). Similarly, the treatment metabolic response state and D5PS score were unacceptable in

Table 5. The ROC curve analysis in determining the value of metabolic parameters and response rate status to predict 2-year disease outcome**.**

Variable	2-year death		2-year recurrence	
	AUC (95% CI)	P-value	AUC (95% CI)	P-value
Total TLG	0.71 (0.45, 0.98)	0.320	0.64 (0.42, 0.87)	0.274
TLG Max	0.64 (0.35, 0.92)	0.522	0.61 (0.40, 0.82)	0.406
Total MTV	0.73 (0.41, 1.00)	0.286	0.68 (0.43, 0.92)	0.175
MTV Max	0.65 (0.27, 1.00)	0.477	0.68 (0.46, 0.91)	0.161
SUV MAX	0.68 (0.23, 1.00)	0.394	0.60 (0.34, 0.85)	0.457
Treatment Response (CR, PR, SD, PD)	0.78 (0.41, 1.00)	0.189	0.91 (0.74, 1.00)	0.002
Treatment Response (D5PS)	0.77 (0.43, 1.00)	0.214	0.93 (0.78, 1.00)	0.001

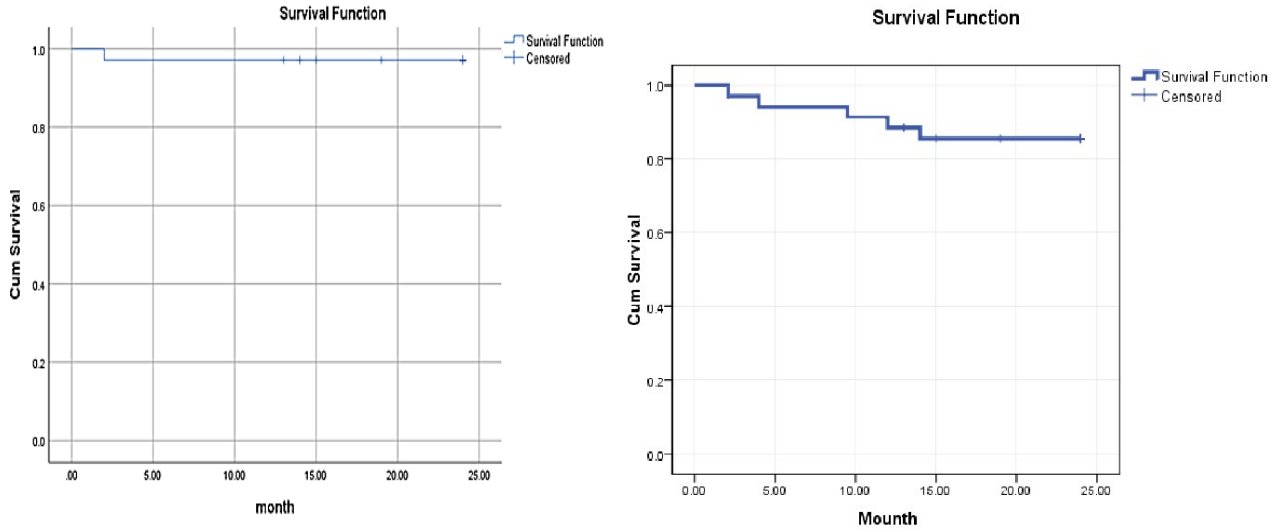

Figure 1. Two-year overall survival (A) and recurrence-free survival (B).

predicting 2-year death (Table 5 and Figure 2). Similarly, metabolic parameters could not predict 2-year disease recurrence (Figure 2), but treatment metabolic non-response status and higher D5PS score could effectively differentiate the groups with and without disease recurrence (Table 5 and Figure 2).

Discussion

Many investigations focus on prognostic factors associated with DLBCL patients undergoing R-CHOP chemotherapy. It is important to identify patients who are at high risk of relapse and choose appropriate treatment strategies for them. The International Prognostic Index (IPI), Revised IPI, and NCCN-IPI are internationally recognized prognostic indices widely used in pre-treatment risk classification. However, adding rituximab to this regimen somewhat challenges their prognostic value. Compared to IPI, many studies have shown that PET/CT parameters can quantify the degree of invasion and tumor burden in individuals, which can be more helpful in predicting prognosis and guiding personalized treatment plans.

In this study, after 2 years of follow-up, 14.3% of patients experienced disease relapse, and 2.9% died. The rates of 2-year progression-free survival and 2-year overall survival in all groups were 85.7% and 97.1%, respectively. The response rate in FDG-PET at the end of treatment could moderately predict the recurrence and progression of the disease within 2 years, but it could not predict the death caused by the disease within this follow-up time. In this regard, response to treatment by different scores in the Deauville 5-point scale score was the most predictive for disease recurrence. Additionally, the average 2-year progression-free survival of the disease showed a significant difference

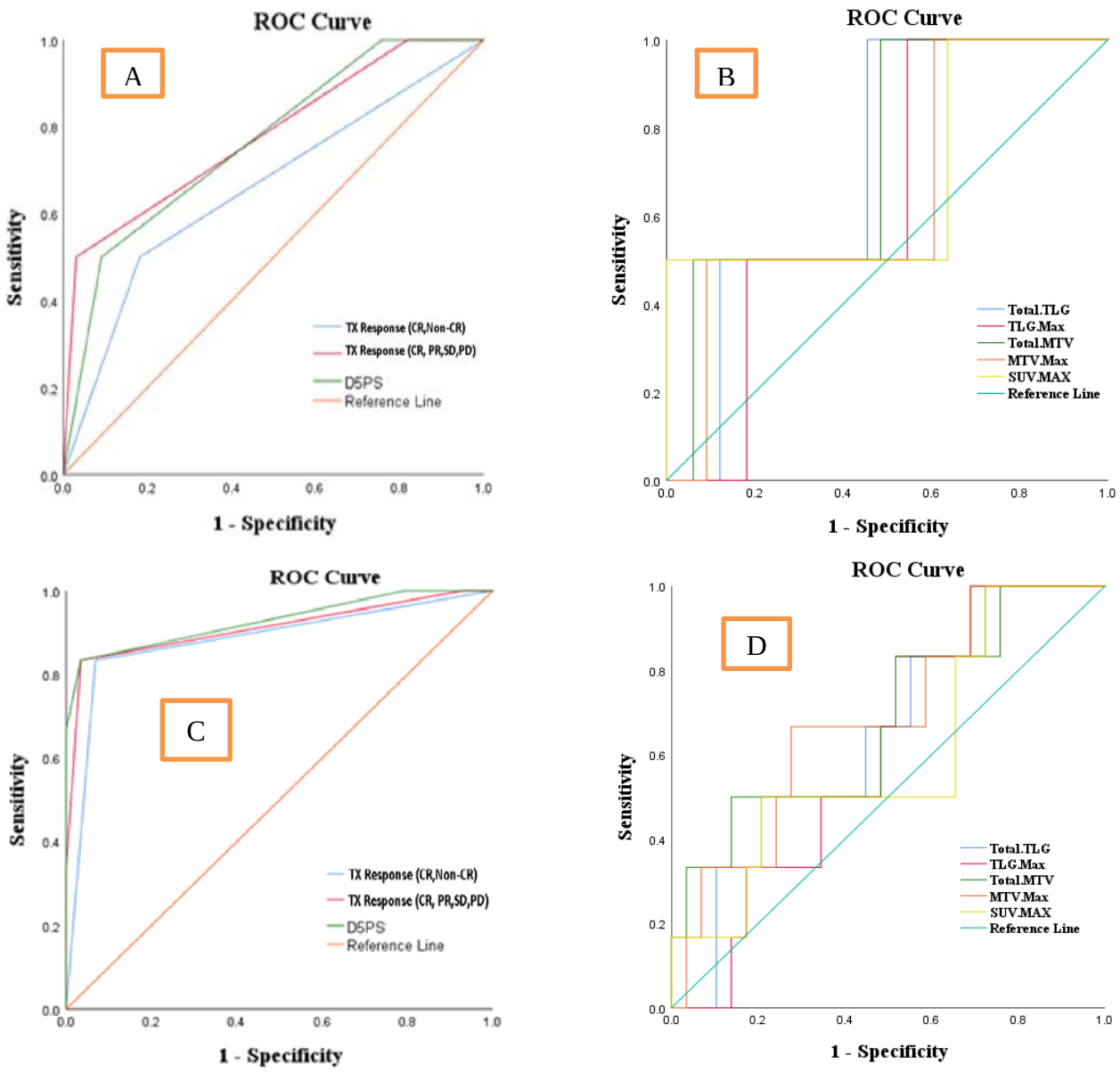

Figure 2. The ROC curve analysis to determine the value of metabolic parameters, response status, and D5PS in predicting 2-year death (A and B) and disease recurrence (C and D).

between different modes of response to treatment in this regard; patients with complete response PET compared to non-complete response PET after R-CHOP treatment had a higher 2-year progression-free survival rate. However, due to the small number of samples leading to death, it was not possible to evaluate the role of metabolic indicators as well as the rate of response to treatment to predict the mortality of patients with high accuracy and sensitivity.

Similar studies have been conducted regarding the value of PET/CT indicators in predicting the outcome of DLBCL patients, and different results have been published from these studies. In a study by Kostakoglu et al. 2021(9), end-of-treatment PET complete response was an independent predictor of progression-free and overall survival. Thus, it was introduced as a promising prognostic marker for DLBCL outcomes. Results from this large prospective cohort confirmed previously published data with smaller sample sizes. Tokola et al. 2021 (10) showed that when evaluating treatment response in PET-CT, a Deauville score ≥4

was considered positive regarding treatment failure. In their study, the rate of 2-year failure-free survival was significantly higher in patients with a negative PET response rate. However, they judged that the value of PET-CT as an assessment tool suffers from a high false positive rate and is insufficient to justify treatment decisions alone. In this context, biopsy results can provide more reliable prognostic information to assess treatment response and outcome and should be used to evaluate patients with a positive PET-CT scan. Zhu et al.[11] showed that the risk of relapse, progression, and death within 2 years in patients with a non-complete response on Interim PET/CT was significantly higher than in patients with a complete response and Interim treatment response as an independent predictor 2-year progressive-free survival and overall survival. Adams et al.[12] determined that patients who could not respond to chemotherapy in the mid-term had a poor prognosis, but there was no clear evidence that the prognostic value was better than IPI. They acknowledged that at the clinic, even patients with a good Interim response to therapy and a negative Interim PET might still have the potential to relapse or progress to a later stage. Therefore, it is not sufficient to judge the prognosis based solely on the response of the tumor to chemotherapy.

The present study also showed that the quantitative parameters obtained from PET/CT, such as TTLG, TLGmax, TMTV, MTVmax, and SUVmax, were not recognized as predictive factors for 2-year death and recurrence. Zhu et al.[11] showed that although MTV and TLG were not independent predictors of 2-year PFS and OS, they found that they were significantly associated with 2-year PFS and OS. On the other hand, they did not show any significant relationship between SUVmax, SUVmean, and PFS, OS, which is consistent with the results of Manohar et al.'s study[13]. Based on this, they suggested that the level of tumor metabolism alone is not the main influencing factor in prognosis, but high MTV and TLG, even if the IPI score is low, may have poor survival prospects. Kim et al.[14] suggested that the TLG parameter is better than IPI as a prognostic indicator in DLBCL patients. Parvez et al.[15] found that MTV with an SUV threshold of 3 or 6 was associated with overall survival in patients with aggressive DLBCL. Also, Song et al.[16] proposed the MTV parameter as a prognostic factor for DLBCL.

Conclusion

This study demonstrated that the treatment response rate in FDG-PET at the end of treatment can predict 2-year recurrence but not 2-year mortality in DLBCL patients following R-CHOP treatment. Patients who achieve a complete metabolic response show higher rates of two-year progression-free survival and overall survival than those with a non-complete metabolic response. However, this study could not demonstrate the predictive role of quantitative metabolic parameters in FDG-PET before treatment (for example, Total MTV) in 2-year mortality and disease recurrence. Further studies with a larger sample size are recommended.

Acknowledgment

None.

Conflict of interest

The authors further declare that they have no conflict of interest.

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