ORIGINAL ARTICLE

Prognostic role of ΔMTV and ΔTLG in Burkitt lymphoma

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Abstract

Objective Burkitt's lymphoma (BL) is an aggressive lymphoma sub-type with high 18F-FDG avidity, but no well established evidence of PET/CT's role in treatment evaluation or prognosis is currently available. The prognostic role of visual analysis and Deauville criteria for BL have already been demonstrated, while the potential usefulness of semi-quantitative PET/CT features remains unclear, especially the value of the rate of reduction in metabolic tumor volume (MTV) and total lesion glycolysis (TLG). The aim of this retrospective study was to investigate whether ΔMTV and ΔTLG can predict treatment response at the end of therapy and prognosis in BL.

Methods We retrospectively included 61 patients (mean age 61; 40 male, 21 female) who underwent baseline, interim and end-of-treatment 18F-FDG PET/CT. The PET/CT images were analyzed visually and semi-quantitatively by measuring total metabolic tumor volume (MTV) and total lesion glycolysis (TLG) for every scan. Then we calculated volume changes based on the percentage of MTV and TLG reduction between the baseline and interim PET (ΔMTVi and ΔTLGi) and between baseline and end-of-treatment PET/CT (ΔMTVeot and ΔTLGeot) and correlated them with clinical response and progression-free survival (PFS) and overall survival (OS). Survival curves were plotted according to the Kaplan–Meier method.

Results Forty patients had a complete response and 21 patients a partial response on interim 18F-FDG PET/CT. At end of treatment, 45 had a complete response, 11 partial response and 5 disease progression. At a median follow-up of 43 months, relapse/progression occurred in 18 patients and death in 11. ΔMTV and ΔTLG values were significantly higher in patients with complete response compared to no complete response. ΔMTVeot and ΔTLGeot were demonstrated to be independent prognostic factors for both PFS and OS, while ΔMTVi and ΔTLGi were not related to survival.

Conclusions Metabolic tumor features (ΔMTV and ΔTLG) were significantly correlated with response to treatment and long-term outcome in BL.

Keywords Burkitt lymphoma · 18F-FDG PET/CT · Prognosis · MTV · TLG

Introduction

Burkitt's lymphoma (BL) is a non-Hodgkin's lymphoma (NHL) sub-type with aggressive behavior and potentially involving both nodal and extra-nodal sites. BL is extremely chemosensitive and its survival ranges from 50% to over 80% related to the stage and age at diagnosis [1–6]. The effective role of fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) in the evaluation of BL patients is still under debate with

promising evidence accumulating with regard to staging and restaging [7–11], but no well established evidence regarding prognosis evaluation is yet available [12–14].

The prognostic role of Deauville criteria in evaluating the PET/CT results at the end of primary therapy in BL has already been demonstrated [13]. In addition to 18F-FDG PET/CT visual analysis and Deauville score scale, semi-quantitative PET/CT features may also have a prognostic impact. The standardized uptake value (SUV) is the most used metabolic index and represents a single-pixel value. This index ignores the extent of metabolic abnormality and the change in distribution of a tracer within a lesion. Moreover, SUV may potentially be affected by several variables, such as the timing between injection and imaging acquisition, risk of extravasation at the site of radiotracer injection, residual activity in the syringe, partial volume effects, decay

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of the injected dose and various technological parameters [15]. Thus, different variables which take into account the size as well as the metabolic activity of the lymphoma are needed. Metabolic tumor value (MTV) and total lesion glycolysis (TLG) are parameters which may meet this need because they reflect both the size of a lesion and its aggressiveness [15]. Their prognostic and predictive role with respect to the treatment response has only been partially investigated with promising evidence, but only a few studies about the rate of reduction in MTV and TLG (ΔMTV AND ΔTLG) after 2 cycles of chemotherapy (interim) and after 6 cycles of chemotherapy (end of therapy) are available in literature [16–19]. The aim of our retrospective study was to investigate whether these metabolic parameters (ΔMTV and ΔTLG) may predict the treatment response at end of treatment and prognosis in BL.

Materials and methods

Patients

We retrospectively screened about 35,000 patients studied with 18F-FDG PET/CT in our Nuclear Medicine center from January 2007 until January 2018 using our institutional Radiology Information System (RIS). Among them, 61 patients with histologically proven BL were retrospectively enrolled. We reviewed the medical reports of these patients: epidemiological data (age at diagnosis, gender, immune status), clinical data (stage, bulky disease, B-symptoms, IPI score, LDH level), metabolic features by 18F-FDG PET/CT, treatment modality and follow-up data were collected. International prognostic index (IPI) score and lactate dehydrogenase (LDH) level were dichotomized using a threshold value of 2 and 245 U/L respectively and tumor stage according to Ann Arbor classification in early (I and II) and advanced (III and IV) stage.

All patients were treated according to our institution's standard protocol with chemotherapy regimen. Fifty-four patients were treated according to the B-ALL/NHL 2002 protocol of the GMALL with six cycles of immuno-chemotherapy including methotrexate, cytosine arabinoside, cyclophosphamide, etoposide, ifosfamide, vincristine, adriamycin and rituximab–corticosteroids alternating every 3 or 4 weeks followed by 2 additional courses of rituximab afterward. The remaining 7 patients received short-term intensified chemo-immunotherapy (rituximab, vincristine, etoposide, doxorubicin, methotrexate, cytarabine, prednisone) according to CARMEN protocol.

All patients were performed baseline PET/CT, interim PET/CT after 2 cycles of chemotherapy and end-of-treatment PET/CT after the end of chemotherapy regimen (6 cycles).

18F-FDG PET/CT imaging and interpretation

18F-FDG PET/CT was performed after at least 6 h fasting at a glucose level lower than 150 mg/dl. An activity of 3.5–4.5 MBq/kg of 18F-FDG was administered intravenously and images were acquired 60 min after radiopharmaceutical injection from the skull base to mid-thigh on a Discovery ST PET/CT tomograph or a Discovery 690 tomograph (General Electric Company—GE®—Milwaukee, WI, USA) with standard parameters (CT: 80 mA, 120 kV without contrast; 2.5–4 min per bed-PET-step of 15 cm); the reconstruction was performed in a 128×128 matrix and 60 cm field of view. Patients were instructed to void before imaging acquisition, and no oral or intravenous contrast agents were administered or bowel preparation used for any patient. 18F-FDG PET/CT scans after therapy were interpreted visually by two nuclear medicine physicians with experience in lymphoma imaging (DA, GB) using the Deauville 5-point scale criteria. Considering the Deauville criteria, 18FDG PET was interpreted as follows: 1 = no uptake above background, 2 = uptake equal to or lower than mediastinum, 3 = uptake between mediastinum and liver uptake, 4 = uptake moderately increased compared to the liver and 5 = uptake markedly increased compared to the liver. With respect to the DC, 18F-FDG PET/CT scans were considered negative for scores 1–3 and positive for scores 4–5. Responses on PET/CT were determined according to the Lugano criteria [20]: complete response (CR), partial response (PR), stable disease (SD) and progression of disease (PD).

Interim PET/CT was performed within the week before the third cycle and end-of-treatment PET/CT at least 3 weeks after the completion of therapy.

Also a semi-quantitative analysis by measuring MTV and TLG was made. MTV was measured from attenuation-corrected 18F-FDG PET images using an SUV-based automated contouring program (Advantage Workstation 4.6, GE HealthCare) with an isocounter threshold method based on 41% of the SUVmax, as previously recommended by the European Association of Nuclear Medicine [21]. Total MTV was obtained by the sum of all nodal and extra-nodal lesions. TLG was calculated as the sum of the product of MTV of each lesion and its SUVmean.

We finally classified patients using quantitative analysis of metabolic volume changes based on the percentage of MTV and TLG reduction between the baseline and interim PET (ΔMTVi and ΔTLGi) and between baseline and end-of-treatment PET (ΔMTVeot and ΔTLGeot). ΔMTVi was calculated as follows:

$$\Delta MTVi(\%) = 100 \times [MTV(baseline) - MTV(interim)/MTV(baseline)].$$

ΔMTVeot was calculated as:

$$\Delta MTVeot(\%) = 100 \times [MTV(baseline)$$
$$- MTV(end\ of\ treatment)/MTV(baseline)].$$

$\Delta TLGi$ and $\Delta TLGeot$ were calculated with the same formula used for ΔMTV.

Table 1 Baseline characteristics of 61 patients

	Patients n (%)
Age average (range)	52 (18–80)
Sex	
Male	40 (66%)
Female	21 (34%)
Tumor stage at diagnosis (Ann Arbor)	
I	12 (19%)
II	5 (9%)
III	6 (10%)
IV	38 (62%)
B-symptoms	28 (46%)
Extra-nodal disease	33 (54%)
Immunocompetent	46 (75%)
Immunodeficiency	15 (25%)
Bulky disease	20 (33%)
LDH	
≤245	37 (61%)
> 245	24 (39%)
IPI score	
≤2	40 (65%)
> 2	21 (35%)
Baseline MTV average cm^3 (range)	394 (6.1–3000)
Baseline TLG g average (range)	4127 (18–22222)
Interim MTV cm^3 average (range)	18.2 (0–100)
Interim TLG g average (range)	171.8 (0–3723)
Eot MTV cm^3 average (range)	46 (0–555)
Eot TLG g average (range)	680 (0–10884)

LDH lactate dehydrogenase, *IPI* International Prognostic Score, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis, *eot* end of treatment

Statistical analysis

All statistical analysis was carried out using MedCalc Software version 17.1 for Windows (Ostend, Belgium). The descriptive analysis of categorical variables comprised the calculation of simple and relative frequencies. The numeric variables were described as mean, minimum and maximum (Table 1).

Mann–Whitney test was used to compare baseline metabolic PET/CT features (ΔMTV and ΔTLG values) of the complete response and no complete response groups after treatment completion.

For the entire population to evaluate the optimal cutoff values of MTV and TLG reduction rate for predicting PFS and OS, receiver operating characteristic (ROC) curve analysis was used (Table 2). OS was calculated from the date of baseline 18F-FDG PET/CT to the date of death from any cause or to the date of last follow-up. PFS was calculated from the date of baseline 18F-FDG PET/CT to the date of first disease progression, relapse, death or the date of last follow-up. Survival curves were plotted according to the Kaplan–Meier method and differences between groups were analyzed using a two-tailed log rank test. Cox regression was used to estimate the hazard ratio (HR) and its confidence interval (CI). A P value of < 0.05 was considered statistically significant.

Results

Tumor characteristics

Of the 61 patients with histologically proven BL, 40 (66%) were male and 21 (34%) female; average age was 53 with a range of 18–80 years. Patients were staged according to the Ann Arbor system as follow: stage I ($n = 12$), stage II ($n = 5$), stage III ($n = 6$) and stage IV ($n = 42$). Forty-six patients were immunocompetent and 15 were immunocompromised, namely 14 patients with HIV infection and one patient with post-transplant lymphoproliferative disease. B-symptoms were present in 28 (46%) patients, bulky disease in 20 cases (33%), and extra-nodal BL involvement was identified in

Table 2 metabolic PET/CT parameters cutoff calculated using receiver operating characteristic (ROC) curve analysis considering the entire population

Parameter	ROC curve				
	Cutoff (%)	AUC (95% CI)	p value	Sens (95% CI)	Spec (95% CI)
$\Delta MTVi$	94	0.574 (0.440–0.699)	0.359	52.9 (28.9–77)	70.5 (54.8–83.2)
$\Delta TLGi$	97	0.593 (0.459–0.716)	0.249	47.1 (23–72.1)	72.7 (57.2–85)
$\Delta MTVeot$	98	0.743 (0.615–0.846)	0.002	64.7 (38.4–85.7)	79.5 (64.7–90.2)
$\Delta TLGeot$	76	0.745 (0.617–0.848)	0.002	52.9 (27.9–77)	93.2 (81.3–98.5)

AUC area under curve, *CI* confidence interval, *sens* sensibility, *spec* specificity, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

42 patients (65%). LDH level was high in 24 patients and IPI score was superior or equal to 2 in 21 cases. Baseline features of the patients are summarized in Table 1. Average baseline MTV and TLG were 394 cm^3 (range 6.1–3000) and 4127 g (range 18–22,222), after two cycles of chemotherapy average interim MTV and TLG were 18.2 cm^3 (range 0–100) and 171.8 g (range 0–3723), after 6 cycles of chemotherapy end-of-treatment average MTV and TLG were 46 cm^3 (range 0–555) and 680 g (range 0–10884) respectively.

Evaluation of treatment response with 18F-FDG PET/CT

Based on the Lugano classification metabolic response categories [21], 40 patients had complete response and 21 patients had partial response at interim 18F-FDG PET/CT; while at end of treatment, 45 had complete response, 11 partial response and 4 progression of disease (Fig. 1). One patient died before finishing the chemotherapy regimen. Mean ΔMTVi and ΔTLGi were 89.7% (range 33–100%) and 89% (range 5–100%) respectively, while ΔMTVeot and ΔTLGeot were 82.1% (− 225–100%) and 71.6% (range − 400–100%) respectively. There was a statistically significant difference between ΔMTVi and ΔTLGi of complete response compared to no complete response groups both at interim (p 0.012 and 0.001, respectively) and at the end-of-treatment PET/CT ($p < 0.001$, respectively) (Table 3).

Role of 18F-FDG PET/CT in predicting survival

After a median follow-up of 43 months, relapse or progression of disease occurred in 18 patients with an average time of 18.7 months (range 4–82 months) from the baseline PET/CT and death occurred in 11 patients with an average time of 14.5 months (range 4–55). The median PFS was 50 months (range 4–154 months) and the median OS was 53 months (range 4–154 months). For evaluation of prognostic role of PET/CT features, ΔMTV and ΔTLG values were dichotomized using the ROC analysis used to identify optimal cutoff points (Table 2).

At univariate analysis, ΔMTVi and ΔTLGi were not related to outcome survival, for either PFS or OS (Fig. 2). Instead, ΔMTVeot and ΔTLGeot were significantly correlated with PFS and OS (Fig. 3). The other clinical and pathological variables (age, sex, tumor stage, IPI score, LDH level, bulky disease and immune system condition) were not significantly related to outcome survival. Also at multivariate analysis, ΔMTVeot and ΔTLGeot were confirmed to be independent prognostic factors for both PFS ($p = 0.010$ and $p < 0.001$) and OS ($p = 0.004$ and $p = 0.002$) (Table 4).
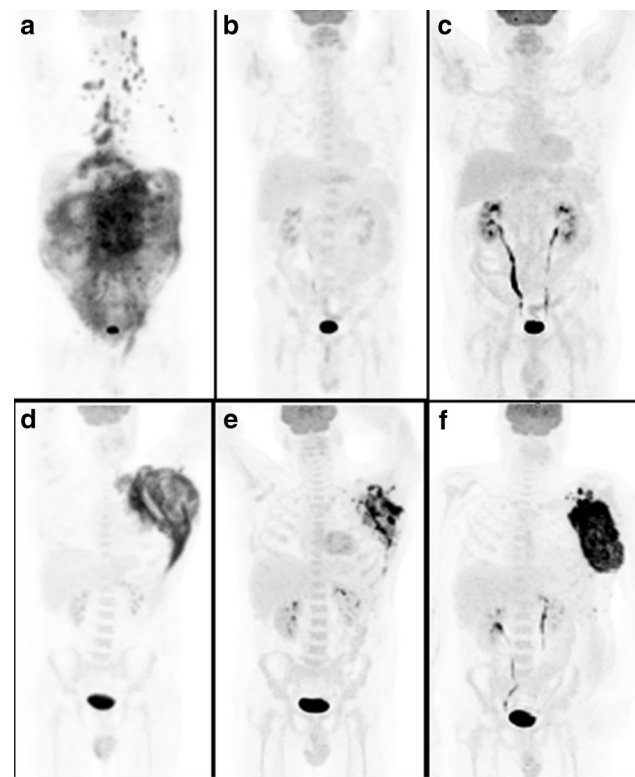
Fig. 1 A representative case of BL patient with diffuse disease at maximum intensity projection (MIP) at baseline PET/CT (**a**), with a complete response after two cycles of chemotherapy (**b**) and ΔMTVi and ΔTLGi of 100%, and a confirmed negative PET/CT scan after the end of chemotherapy (**c**) with a ΔMTVeot and ΔTLGeot of 100%. Another case of positive baseline PET/CT with bulky axillary disease (**d**), a partial response at interim PET/CT (**e**) with a ΔMTVi of 85% and ΔTLGi of 78% and a progression of disease at end-of-treatment PET/CT (**f**) with a ΔMTVeot of 10% and ΔTLGeot of − 35%

Table 3 Comparison of ΔMTV and ΔTLG between response groups at end-of-treatment

Parameter (mean)	End-of-treatment response		P value
	No complete response (%)	Complete response (%)	
ΔMTVi	81	92	0.012
ΔTLGi	75	95	0.001
ΔMTVeot	45	99	< 0.001
ΔTLGeot	10	99	< 0.001

MTV metabolic tumor volume, *TLG* total lesion glycolysis, *i* interim, *eot* end of treatment

Discussion

BL is an NHL sub-type with an aggressive nature derived from germinal or postgerminal center B cells and may affect both nodal and extra-nodal sites. Considering the
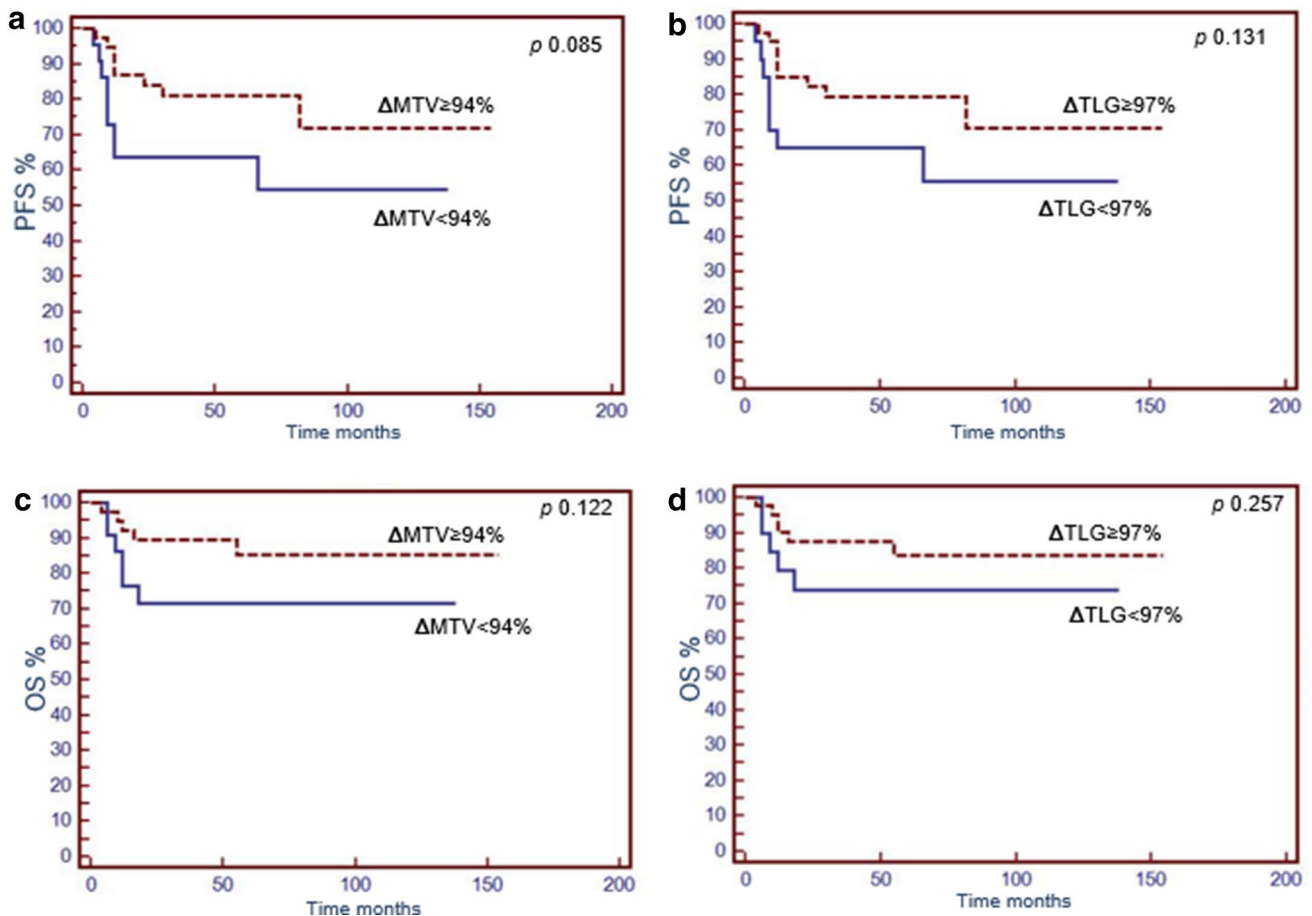
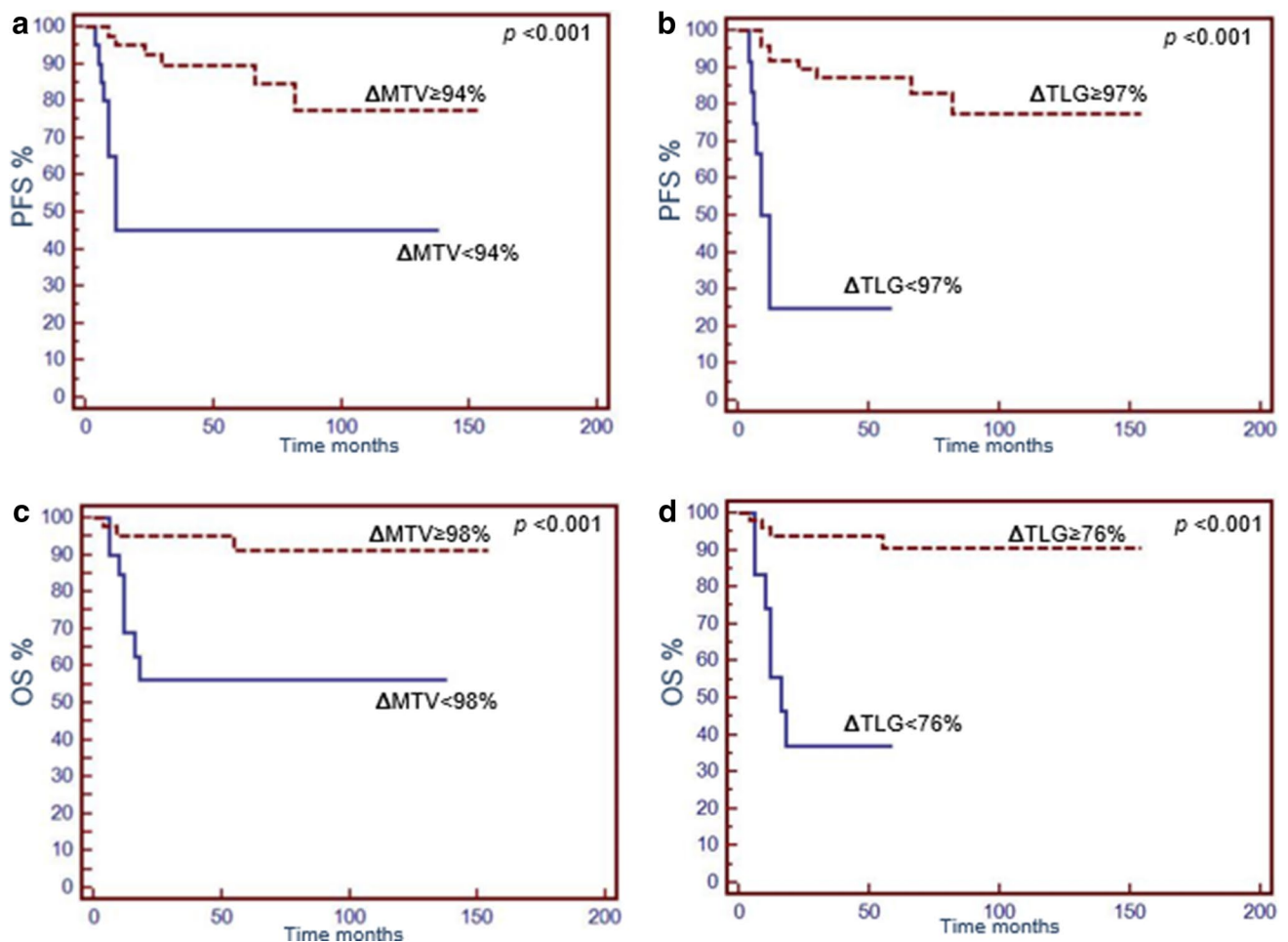Fig. 2 PFS and OS curves according to ΔTMVi (**a, c**) and ΔTLGi (**b, d**)

aggressiveness of this disease and the absence of validated and shared prognostic factors, there will be an increased need for baseline and post-therapy PET/CT scans for evaluation of treatment response and prognosis in BL. BL seems to be an 18F-FDG-avid lymphoma at presentation, as already described by several authors [7–9, 13], while the prognostic value of 18F-FDG PET/CT is still an open issue.

Albano et al. [13] showed that both International Harmonization Project and Deauville criteria results at the end of treatment significantly predicted outcome (OS and PFS) in BL while no significant correlation were demonstrated at interim PET scan. In another study, baseline MTV and TLG did not predict treatment response either at interim or the end of therapy [14]. Instead in our study, we found a significant difference between ΔMTV and ΔTLG at end-of-treatment response between the complete response and no complete response groups, but also at interim scan (Table 3). Thus ΔMTVeot and ΔTLGeot seem to be superior to absolute values of baseline MTV and TLG and also visual analysis (Deauville and IHP criteria). In fact ΔMTVeot and ΔTLGeot were significantly

higher in patients with complete response than no complete response after the end of chemotherapy.

Several authors have evaluated the prognostic role of 18F-FDG PET/CT in BL considering ΔSUVmax, a parameter which represents the reduction in the maximum standardizes uptake value between basal and after therapy scans. First, Carrillo-Cruz et al. [11] found ΔSUVmax < 66% to be the best cutoff for evaluation of therapy response with 100% positive predictive value and negative predictive value. On the other hand, Wei et al. [12] compared three different ΔSUVmax thresholds (25%, 50% and 75%) to predict outcome and found the best threshold a ΔSUVmax from the baseline PET/CT to post-therapy PET/CT of 50%. Also in a recent multicenter study, ΔSUV was demonstrated to be a prognostic parameter in aggressive non-Hodgkin lymphoma, including Burkitt lymphoma [22]. Until now, the possible role of ΔMTV and ΔTLG values in BL has not been evaluated.

MTV and TLG are parameters which consist of a combination of tumor volume and metabolism; these indices include both morphological and metabolic features and may be considered an expression of tumor aggressiveness

Fig. 3 PFS and OS curves according to ΔTMVeot (**a, c**) and ΔTLGeot (**b, d**)

together with tumor size. Several authors have demonstrated the significant prognostic value of MTV and TLG in other lymphoma sub-types [23–27] and also in BL our group previously documented the prognostic impact of baseline MTV and TLG on outcome survival [14]. ΔMTV and ΔTLG represent the reduction in the metabolic tumor volumes between basal and after therapy scans, and may reflect the metabolic behavior and response after treatment.

In this study, we demonstrated that ΔMTV and ΔTLG after the end of therapy were significantly correlated with outcome considering both PFS and OS. Change in metabolic PET/CT volumes may be a good index to represent tumor response after therapy. In contrast ΔMTV and ΔTLG after two cycles of chemotherapy (interim) did not show any prognostic significance.

The effective role of ΔMTV and ΔTLG in other lymphoma sub-types has been partially determined with promising results [16–19]; Jung et al. [19] using a cutoff of 98.7% confirmed the prognostic role of ΔMTV in 63 patients with

peripheral T-cell lymphoma; Yang et al. [16] with a cutoff of 99.3% showed similar results.

In a population of diffuse large B-cell lymphoma, Onate-Ocana et al. [17] demonstrated that a decrease of total MTV > 94% was associated with a complete response ratio in both univariate and multivariate analyses. In our analysis, we found a threshold of 98% for MTV and 76% for TLG, values similar to those noted in other work [16, 17, 19] although a direct comparison is not possible. Our preliminary study needs confirmation and validation in larger cohort studies. The limitations of our study are the retrospective nature of the study design and the relatively low number of patients analyzed, also due to the rarity of the disease.

Despite this, so far, the present study represents the first series of BL investigated with an analysis of 18F-FDG PET/CT semi-quantitative parameters (ΔMTV and ΔTLG values) and their prognostic role and predictive for therapy response.

In conclusion, in this study we demonstrated that ΔMTV and ΔTLG at end of treatment were significantly correlated with outcome survival, both for PFS and OS. Moreover,

Table 4 Univariate and multivariate analyses for PFS and OS

	Univariate analysis		Multivariate analysis	
	p value	HR (95% CI)	*p* value	HR (95% CI)
PFS				
Age	0.518	1.370 (0.529–3.549)		
Sex	0.214	0.546 (0.211–1.411)		
Tumor stage	0.255	1.968 (0.568–6.822)		
IPI score	0.734	0.836 (0.295–2.367)		
LDH level	0.867	1.086 (0.414–2.847)		
Bulky disease	0.102	2.264 (0.868–5.906)		
Immune system condition	0.210	1.943 (0.720–5.229)		
ΔMTVi*	0.101	0.448 (0.173–1.158)		
ΔTLGi*	0.153	0.498 (0.190–1.274)		
ΔMTVeot*	<0.001	0.182 (0.067–0.496)	0.010	0.213 (0.064–0.689)
ΔTLGeot*	<0.001	0.098 (0.034–0.277)	<0.001	0.044 (0.007–0.278)
OS				
Age	0.129	4.615 (0.987–21.572)		
Sex	0.274	0.497 (0.144–1.707)		
Tumor stage	0.196	3.222 (0.414–25.178)		
IPI score	0.688	1.298 (0.367–4.571)		
LDH level	0.499	0.635 (0.165–2.441)		
Bulky disease	0.242	2.113 (0.614–7.265)		
Immune system condition	0.676	1.342 (0.343–5.154)		
ΔMTVi*	0.093	0.342 (0.097–1.206)		
ΔTLGi*	0.204	0.442 (0.128–1.521)		
ΔMTVeot*	<0.001	0.101 (0.021–0.479)	0.004	0.175 (0.032–0.949)
ΔTLGeot*	<0.001	0.079 (0.020–0.306)	0.002	0.125 (0.012–0.749)

PFS progression-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

*Variables dichotomized using cutoff values after ROC analysis reported in Table 2

ΔMTV and ΔTLG (at interim and at end of treatment) were significantly higher in patients with a complete response compared to those with no complete response.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical 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. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participant included in the study.

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