ORIGINAL ARTICLE

Predictive Value of Interim and End-of-Therapy 18F-FDG PET/CT in Patients with Follicular Lymphoma

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Abstract

Purpose ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is the standard imaging modality for response evaluation in FDG-avid lymphoma, but the prognostic value is not established in follicular lymphoma (FL). This study investigated the prognostic value of Deauville 5-point scale (D5PS) from paired interim PET/CT ($PET_{Interim}$) and end-of-induction therapy PET/CT (PET_{EOI}) in patients with FL.

Methods FL staging and response assessment PET/CT images from 2013 to 2015 were retrospectively reviewed. $PET_{Interim}$ was performed 3 or 4 cycles after chemotherapy and PET_{EOI} after 6 or 8 cycles. D5PS scores of 1, 2, and 3 were considered as negative (−), and scores 4 and 5 were considered as positive (+). Statistical analysis was done using Cox regression analysis, Kaplan–Meier survival analysis, and the log-rank test.

Results Thirty-three patients with set of baseline, interim, and end-of-induction therapy PET/CT studies were included. Ten patients (30.3%) had progression. The median progression-free survival (PFS) was 38.8 months (range 3.5–72.7 months). On $PET_{Interim}$, 23 patients were negative and 10 were positive. On PET_{EOI} scans, 29 patients were negative, and 4 were positive. On multivariate analysis, $PET_{EOI}(−)$ was associated with longer PFS. $PET_{Interim}(+)$ and $PET_{EOI}(+)$ patients had a significantly shorter PFS than $PET_{Interim}(−)$ patients (39.9 months, 95% confidence interval [CI] 23.0–56.9, versus 55.5 months, 95% CI 49.7–61.2, $p = 0.005$) and $PET_{EOI}(−)$ patients (14.2 months, 95% CI 8.5–19.8, versus 60.5 months, 95% CI 52.1–69.0, $p < 0.001$).

Conclusion For patients with FL, $PET_{Interim}$ and PET_{EOI} response is predictive of PFS, and $PET_{EOI}(+)$ is an independent prognostic factor for progression of FL.

Keywords Follicular lymphoma · ^{18}F-fluorodeoxyglucose · Positron emission tomography · Lugano classification · Progression-free survival

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Introduction

Follicular lymphoma (FL) is one of the most common subtypes of lymphoma, accounting for 12–15% of all non-Hodgkin lymphoma (NHL) in Western countries [1, 2]. FL is usually an indolent and slow-growing disease, and many patients have approximately 50% 10-year disease-free survival rate and 60–70% overall survival. Most FL patients show extensive disease at diagnosis [3], and for asymptomatic particularly elderly patients, watchful waiting is a valid clinical option [4]. However, FL patients can undergo histological transformation into a high-grade lymphoma (30–50%) which would go on to show poor prognosis [3].

In recent years, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has become the standard procedure for initial staging, restaging, and assessment of response in Hodgkin lymphoma (HL) and

most FDG-avid NHL subtypes [5]. In 2009, the First International Workshop on PET in Lymphoma proposed visual response criteria that defined simple and reproducible standards for PET reporting in FDG-avid lymphoma. The Deauville criteria using the 5-point scale (D5PS) has now been validated as the interpretation method for both interim and end-of-therapy PET scans in HL and NHL. FDG PET/CT is recommended for initial workup and response assessment, especially if radiotherapy is planned [5]. However, the prognostic value of D5PS in FL has not been verified. We examined the prognostic value of D5PS from interim PET/CT ($PET_{Interim}$) and end-of-induction therapy PET/CT (PET_{EOI}) studies in patients with FL.

Materials and Methods

Patient Population

We retrospectively reviewed 69 patients newly diagnosed with FL between 2013 and 2015. We excluded three patients under 18 years of age. We excluded 10 patients who had no baseline PET/CT scan, and 4 patients whose baseline PET/CT scans could not be analyzed. An additional 6 patients who were treated with tumor excision and 1 patient who showed lower FDG uptake in the tumor than liver at baseline PET/CT scan were excluded. We included patients treated with regimens of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), or R-CVP (rituximab, cyclophosphamide, vincristine and prednisone). We excluded 6 patients who did not have $PET_{Interim}$ ($n = 5$) or PET_{EOI} ($n = 1$) and 1 patient who changed chemotherapy regimen because of disease progression at $PET_{Interim}$ to ensure paired comparison of the interim and end-of-induction therapy images. Finally, 33 patients were analyzed in our study (Fig. 1). Treatment regimen was decided by the hemato-oncologist depending on the patient's condition, and response assessment PET/CT scans were performed after 3 or 4 cycles of chemotherapy. This study received IRB approval, and the need for written consent was waived for this retrospective cohort study.

Age, sex, pathologic grade, Ann Arbor stage, Eastern Cooperative Oncology Group (ECOG) performance score, Follicular Lymphoma International Prognostic Index (FLIPI), serum lactate dehydrogenase (LDH) level, and bone marrow (BM) involvement by bilateral BM biopsy were evaluated at initial admission, prior to treatment.

^{18}F-FDG PET/CT Imaging

At least 6 h of fasting was kept in all patients before the PET/CT scan. Blood glucose levels were checked to be < 200 m/dl at the time of FDG injection (intravenous 3.7–5.5 MBq/kg). After 60 min, images were acquired from combined PET/CT

system (Biograph TruePoint; Siemens Medical Solutions, USA). The non-contrast enhanced CT was obtained from the orbitomeatal line to the proximal thigh (120 kVp, 50 mAs, 5-mm slice thickness), PET scan over the same body region followed.
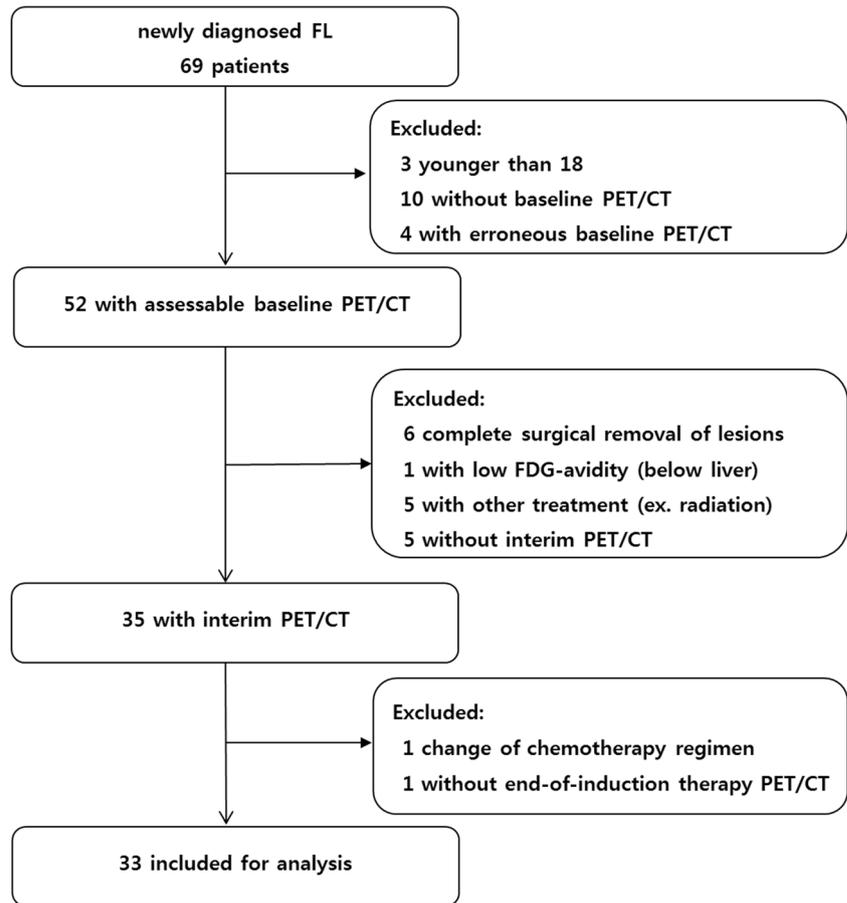
PET Scan Interpretation

All PET/CT images were assessed with Mirada XD3 software (Mirada Medical, Oxford, UK) by consensus of two experienced nuclear medicine physicians, who were aware of the patients' clinical information. $PET_{Interim}$ and PET_{EOI} scans were assessed using the Deauville criteria using the 5-point scale. 1 indicates no uptake, 2 indicates uptake less than or the equal to that of the mediastinum, 3 indicates uptake more than the mediastinum but less than the liver, 4 indicates uptake moderately more than the liver, and 5 indicates uptake markedly more than the liver or by new sites of disease [6]. Scores of 1, 2, and 3 were defined as PET negative (−), and scores 4 and 5 were defined as PET positive (+). All lesions showing discrete FDG uptake higher than the background were selected from the maximum intensity projection and reviewed on the axial images to determine where it could be follicular lymphoma involvement. Even for small nodes not meeting the size criteria, if the FDG uptake was discrete, it was considered to be lymphoma involvement. For Deauville scale, the suspected lesion was assessed on coronal view to include the liver or mediastinum blood pool for comparison of FDG activity. The standardized uptake value (SUV) was not routinely measured, but if the comparison with the reference organ was difficult, the reader chose to measure the SUVs to help make the decision between scores 2, 3, and 4. Clinical information was thoroughly considered to avoid calling a benign condition or physiologic activity as new lymphoma lesion.

Statistical Analysis

SPSS software (ver.24.0; IBM Corp., Armonk, NY, USA) was used to perform statistical analyses. The primary end point was progression-free survival (PFS), defined as the period from diagnosis to the disease progression or the last follow-up date. The patient was considered to have progression when sequential images over time such as CT or FDG PET/CT showed increased size of lymph nodes, increased FDG activity, or new lesions compared to previous images. When possible, the lesions were confirmed by biopsy. Progression was confirmed by biopsy in four patients. In six patients, the lesions were in sites difficult to approach for biopsy, and progression was assumed as both the FDG uptake on PET/CT and the lesion size were increased on enhanced CT at follow-up. The prognostic association of variables was evaluated with the Cox proportional hazards regression model. The variables with $p < 0.05$ in univariate analysis were included for

Fig. 1 Patient selection process. *FL* follicular lymphoma; *ex* example

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                    │   newly diagnosed FL    │
                    │      69 patients        │
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                              │        │ Excluded:                        │
                              │───────▶│  3 younger than 18               │
                              │        │ 10 without baseline PET/CT       │
                              │        │  4 with erroneous baseline PET/CT│
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                    │ 52 with assessable      │
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                              │        │ Excluded:                            │
                              │        │  6 complete surgical removal of      │
                              │───────▶│    lesions                           │
                              │        │  1 with low FDG-avidity (below liver)│
                              │        │  5 with other treatment (ex. radiation)│
                              │        │  5 without interim PET/CT            │
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                    │ 35 with interim PET/CT  │
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                              │───────▶│  1 change of chemotherapy regimen    │
                              │        │  1 without end-of-induction therapy  │
                              ▼        │    PET/CT                            │
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                    │ 33 included for analysis│
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multivariate analysis. Survival curves were obtained by Kaplan–Meier method and compared by log-rank test.

Results

Baseline Patient Characteristics

Patient characteristics are summarized in Table 1. There were 17 males and 16 females with histologically proven FL. The median age at diagnosis was 50 years (range, 29–84 years). Twelve received R-CVP and 21 received R-CHOP as first-line therapy and 27 patients completed maintenance rituximab treatment. Median follow-up time of all patients was 41.6 months (mean ± standard deviation [SD] 43.8 ± 11.1 months).

Two patients died during the follow up period, and the data was insufficient to compute the overall survival (OS).

Risk Factors for Progression-Free Survival Analysis

Ten of 33 patients (30.3%) had progression and a median PFS of 38.8 months (range 3.5–72.7 months) of observed. On univariate analysis, rituximab maintenance therapy, $PET_{Inerim}(-)$

and $PET_{EOI}(-)$ were significantly associated with a superior prognosis for PFS (Table 2). On multivariate analysis, only PET_{EOI} result was found to be significantly associated with PFS (Table 3).

ECOG and Ann Arbor stage could not be analyzed, because there were no progression cases for ECOG 2 or higher or Ann Arbor stage I/II.

Predictive Value of $PET_{Interim}$ Response Assessment

On $PET_{Interim}$ scan, 23 patients were PET(−) and 10 patients were PET(+) (Table 4). Of the 10 PET(+) patients, 6 became PET(−) and 4 patients remained PET(+) at end-of-induction therapy. All 23 $PET_{Interim}(-)$ patients remained PET(−) at end-of-induction therapy.

The PET(−) group showed a significant longer PFS of 55.5 months (95% CI 49.7–61.2), compared to the PET(+) group's mean PFS of 39.9 months (95% CI 23.0–57.0), $p = 0.005$ (Fig. 2a).

Predictive Value of PET_{EOI} Response Assessment

On PET_{EOI} scan, 29 patients were PET(−) and 4 patients were PET(+) (Table 4). The PET(−) group had a significant longer

Table 1 Characteristics of all follicular lymphoma patients ($N = 33$)

Characteristics	Number of patients (%)
Gender	
Male	17 (51.5)
Female	16 (48.5)
Age	
< 60	25 (75.8)
≥ 60	8 (24.2)
ECOG	
0–1	32 (97.0)
≥ 2	1 (3.0)
LDH	
Normal	18 (54.5)
≥ Normal	15 (45.5)
Ann Arbor stage	
I/II	2 (6.1)
III/IV	31 (93.9)
BM involvement	
Absent	20 (60.6)
Present	13 (39.4)
Grade	
Low (grade 1 and 2)	23 (69.7)
High (grade 3A and 3B)	8 (24.2)
Not evaluated	2 (6.1)
FLIPI score	
Low (0–1)	6 (18.2)
Intermediate (2)	11 (33.3)
High (≥ 3)	16 (48.5)
Treatment	
R-CHOP	21 (63.6)
R-CVP	12 (36.4)
Maintenance rituximab	
Yes	27 (81.8)
No	6 (18.2)
$PET_{Interim}$	
Negative	23 (69.7)
Positive	10 (30.3)
PET_{EOI}	
Negative	29 (87.9)
Positive	4 (12.1)

ECOG Eastern Cooperative Oncology Group, *LDH* lactate dehydrogenase, *BM* bone marrow, *FLIPI* Follicular Lymphoma International Prognostic Index, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, *R-CVP* rituximab, cyclophosphamide, vincristine, prednisone, *EOI* end-of-induction therapy

PFS of 60.5 months (95% CI 52.1–69.0), compared to the PET(+)'s 14.2 months (95% CI 8.5–19.8), $p < 0.001$ (Fig. 2b).

All four patients with PET(+) at end-of-induction therapy had progression, and two of them expired.

Table 2 Univariate analyses for PFS in analyzed patients

Parameters	HR	95% CI	*p* value
Female (vs. male)	0.5	0.1–2.2	0.378
Age ≥ 60 (vs. < 60)	1.1	0.3–4.3	0.871
Elevated LDH	1.8	0.5–6.8	0.367
BM involvement	2.4	0.7–8.6	0.173
High grade (vs. low grade)	1.0	0.2–4.8	0.974
FLIPI score			
Low vs. indeterminate	1.3	0.1–15.4	0.812
Low vs. high	3.6	0.4–30.9	0.239
R-CHOP (vs. R-CVP)	2.7	0.6–13.1	0.219
Maintenance therapy	0.3	0.1–1.0	0.043
$PET_{Interim}$	5.1	1.4–18.2	0.043
PET_{EOI}	66.9	7.1–629.5	0.0002

LDH serum lactate dehydrogenase, *BM* bone marrow, *FLIPI* Follicular Lymphoma International Prognostic Index, *R-CHOP* rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, *R-CVP* rituximab, cyclophosphamide, vincristine, prednisone, *EOI* end-of-induction therapy, *HR* hazard radio, *CI* confidence interval

Discussion

In this study, we retrospectively reviewed 33 FL patients who had all three sets of initial staging, interim, and end-of-induction therapy FDG PET/CT scans from 2013 to 2015 to evaluate the predictive value of D5PS. Our results confirmed that patients with score of 4 or 5 at $PET_{Interim}$ and PET_{EOI} show shorter PFS compared to score 1, 2, or 3 patients. And PET_{EOI} was an independent factor of progression of FL. On univariate analysis, 27 patients who received rituximab maintenance therapy showed longer PFS as would be expected clinically.

Multiple studies have demonstrated the efficacy of FDG PET/CT in management of FDG-avid lymphoma subtypes. A few studies of patients with FL have shown that FDG PET/CT is a sensitive staging modality [7–10], and the end-of-induction therapy FDG PET/CT could predict the PFS and OS [7, 8, 11–18]. However, there were only a few studies on whether the $PET_{Interim}$ has prognostic value, and the results were inconclusive [11, 12, 14]. Two studies reported no significant difference in PFS between positive and negative PET scans [11, 14], whereas one study showed interim PET-

Table 3 Multivariate analyses for PFS in analyzed patients

Parameters	HR	95% CI	*p* value
Maintenance therapy	3.0	0.6–15.7	0.190
$PET_{Interim}$	2.8	0.4–17.5	0.278
PET_{EOI}	27.5	1.9–389.0	0.014

EOI end-of-induction therapy, *PFS* progression-free survival, *HR* hazard radio, *CI* confidence interval

Table 4 Results and analysis of $PET_{Interim}$ and PET_{EOI} scans

	No. of patients	No. of patients progression (%)	PFS (months) (95% CI)	p value
$PET_{Interim}$				
Negative	23	4 (17.4)	55.5 (49.7–61.2),	
Positive	10	6 (60.0)	39.9 (23.0–57.0)	0.005
PET_{EOI}				
Negative	29	6 (20.7)	60.5 (52.1–69.0)	
Positive	4	4 (100.0)	14.2 (8.5–19.8)	< 0.001

EOI end-of-induction therapy, *PFS* progression-free survival

positive patients to have a significantly shorter PFS than PET-negative patients [12]. Our results were similar to those by Dupuis et al. [12], and $PET_{Interim}$ and PET_{EOI} results correlated with PFS. However, there were some differences in our study. Dupis et al. included patients with FL grade 1, 2, and 3A and high tumor burden (on lesion > 7 cm), whereas our study included all grades of FL regardless of tumor burden and most patients received rituximab maintenance. Furthermore, we identified that PET_{EOI} is a better prognostic factor for progression compared to the clinical factors.

Rituximab maintenance therapy after first-line treatment significantly improved PFS [19], and European Society of Medical Oncology guideline recommends the use of rituximab maintenance in follicular lymphoma patients [20]. In this study, 27 (81.8%) of 33 patients received maintenance treatment with rituximab, which was associated with a significant improvement in PFS on univariate analysis. However, the follow-up period of our study was short and with two deaths, we could not confirm the impact on survival.

The World Health Organization (WHO) classified FL into three grades. Grades 1 and 2 FL are thought to be indolent low-grade lymphoma, while grade 3 is thought to be high-grade lymphoma, and thus more active treatment is recommended. Grade 3 can be divided into 3A and 3B, and 3B is considered aggressive lymphoma and treatment regimen is the same as DLBCL [21]. However, some studies have shown that there is no difference in outcome between grade 3A and 3B of FL [22], or grade 3B can be cured by aggressive therapy [23]. However, pathologic grade alone cannot predict the clinical outcome. There were four patients identified in our study as 3B, none of whom showed progression but we had deaths in low-grade patients from progression (Fig. 3). In our study, the FLIPI and pathologic grade which are clinically used for prognosis were not statistically significant. Instead, the results of response assessment by PET/CT showed better predictive ability. Although we did not quantitatively analyze the baseline, a study showed inferior 5-year PFS and an increased risk of death in patients with high tumor burden on PET/CT [24].

We performed only visual analysis using liver activity as the reference. Another response PET criterion developed by the Response Assessment Subcommittee of the International Harmonization Project (IHP) evaluates the remaining FDG uptake in the end-of-therapy PET using mediastinal blood
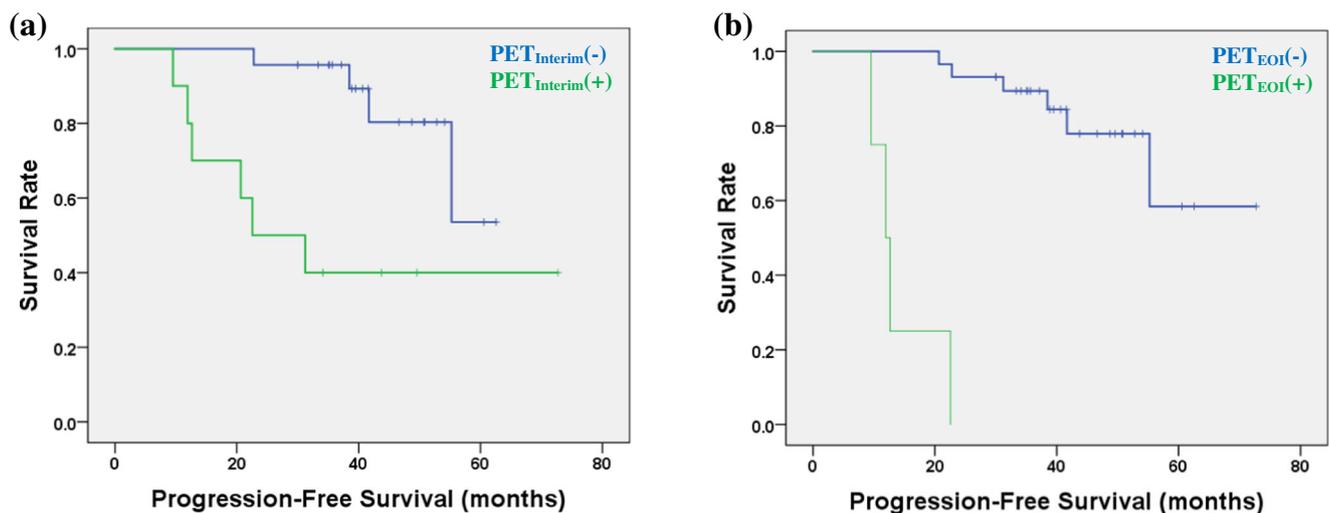

Fig. 2 Kaplan–Meier graphs of correlation between PET and clinical outcomes. **a** For follicular lymphoma patients, progression-free survival (PFS) is significantly longer with PET(−) at interim. **b** PET(−) is also associated with significantly longer PFS at end-of-induction therapy. (−) negative; (+) positive
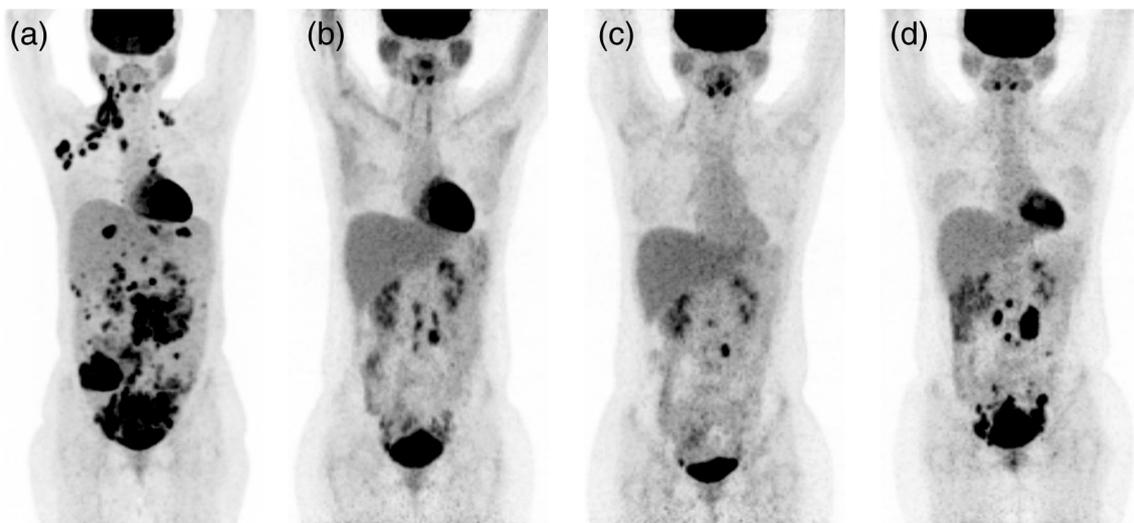
Fig. 3 Serial PET images of 29-year-old woman with stage IV follicular lymphoma, grade 2. **a** shows baseline with multiple lymph nodes and mesentery involvement. **b** obtained after 3 cycles of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) shows lymph nodes with residual FDG uptake, interpreted as PET positive (+).

c obtained after 6 cycles of R-CHOP shows abdominal lymph nodes with focal residual FDG uptake, interpreted as PET(+). The patient eventually showed progression (**d**) and even with additional immunochemotherapy, the patient expired 12 months later

pool activity as reference [25]. Meter et al. [26] evaluated IHP and D5PS in assessing residual masses at end-of-therapy for lymphoma patients and showed D5PS has higher sensitivity and accuracy than IHP. There are limited studies with quantitative analyses [27, 28]. The quantitative assessment may have a lower inter-reader variability, but it may be inconvenient to measure PET parameters for multiple lesions, and there may be a concern about which lesions should be measured when near-complete metabolic regression is observed. On the other hand, visual analysis is simple, the inter-reader agreement is good for scores of 4 or 5, and the results can be reviewed in clinical settings [12, 29, 30].

Our study has several limitations. First, this study is retrospective in design. Second, a small number of patients were included in our study as our inclusion criteria were relatively strict to ensure paired interim and end-of-therapy comparison. Third, because the follow-up period was short, we could not assess the independent prognostic values of $PET_{Interim}$ and PET_{EOI} for overall survival. Our patients received two treatment regimens for first-line therapy, but there was no statistically significant difference between the R-CHOP and R-CVP groups. Further studies should be designed to assess prognosis with larger sample sizes and longer follow-up with homogeneous treatment regimen.

We suggest that patients with $PET_{Interim}(+)$ and $PET_{EOI}(+)$ should be considered for additional treatment to achieve better outcomes. As in randomized prospective study of $PET_{Interim}$-adapted therapy in advanced Hodgkin's lymphoma [31], further studies are required to identify how changing treatment strategy in $PET_{Interim}$ or $PET_{EOI}(+)$ patients could improve the outcome in FL.

Conclusion

Our study validates the predictive value of $PET_{Interim}$ and PET_{EOI} applying the D5PS in patients with FL receiving rituximab containing chemotherapy for first-line treatment. In patients with $PET_{EOI}(+)$, clinicians may consider additional treatment or more vigilant follow up.

Compliance with Ethical Standards

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