The Value of ^{18}F-FDG PET(/CT) in Patients with Post-Transplant Lymphproliferative Disorder (PTLD)

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Background

- **Post-transplant lymphoproliferative disorders (PTLD)** is a serious complication that can occur after solid organ transplantation or hematopoietic stem cell transplantation.
- Strong association with Epstein-Barr virus (EBV) is characteristic (60-80%).
  - EBV-positive: few genome mutation, early onset (≤ 1 year)
  - EBV-negative: common genome mutation, late onset (> 1 year, commonly 5-15 years)
- Known prognostic factors are age, performance status, allograft type, LDH, extranodal involvement, and multiple acute rejections.
- The clinical role of FDG-PET in the management of PTLD has been reported only in a few articles [1,2]. In addition, the prognostic value of metabolic parameters at initial PET/CT has not been fully investigated.

■ PTLD classification (WHO 2017)

Subtype	Clonality	Characteristics	EBV association
Nondestructive •plasmacytic hyperplasia •infectious mononucleosis-like •florid follicular hyperplasia	Polyclonal	Composed of plasma cells, small lymphocytes, immunoblasts	Almost 100%
Polymorphic	Mostly polyclonal	Mixture of B cells and T cells	> 90%
Monomorphic	Monoclonal	Fulfills specific WHO criteria for NHL	Both EBV +ve/-ve
Hodgkin`s lymphoma-like	Monoclonal	Fulfills specific WHO criteria for HL	> 90%

Objectives

- **To assess the diagnostic accuracy and clinical impact of FDG-PET(/CT) in patients with PTLD**
- **To identify prognostic factors for overall survival (OS) using PET/CT parameters**

Methods

Patients

- A total of **54 patients (M:F=28:26; median age 34 y; range 1-74 y)**, who had undergone FDG-PET(/CT) between 2006-2018 with a diagnosis of PTLD or clinical suspicion of PTLD* before treatment, were retrospectively analyzed.
- LDH, sIL-2R and EBV viral load at PET scanning and EBER expression from biopsy specimens were recorded.

*elevation of EBV viral load/sIL2-R; lymph node enlargement/mass lesion identified with CT/MRI

FDG-PET(/CT) scanning

- Scanners: Advance* (n=6), Discovery ST Elite† (n=31), Discovery IQ† (n=17)
- Fasting: at least 4 hr
- Injected Dose: 2-4 MBq/kg body weight
- Uptake phase: about 60 min

* dedicated PET scanner
† combined PET/CT scanner

PET/CT metabolic parameters

- Only FDG-avid lesions detected by combined PET/CT scanners were evaluated.
  - ➢ SUVmax: the highest SUVmax of the whole lesions
  - ➢ t-MTV: MTV of the total whole-body lesions
  - ➢ t-TLG: TLG of the total whole-body lesions

MTV = metabolic tumor volume
TLG = total lesion glycolysis

Analysis

- The diagnostic ability of FDG-PET(/CT) was evaluated both **visually** and **semiquantitatively**.
  - ➢ Visual analysis: Focally or diffusely increased FDG uptake above background, consistent with PTLD, was considered positive.
  - ➢ Semiquantitative analysis: The optimal cutoff value of SUVmax for predicting PTLD was determined using receiver operating characteristic (ROC) curve analysis so that its “sensitivity+specificity” would be maximal.
- PET/CT metabolic parameters were compared according to the presence of PTLD and subtypes, using Wilcoxon rank sum test.
- Prognostic value in predicting overall survival (OS) was assessed using univariate Cox regression analysis and Kaplan-Meier analysis.

Results

- **32**/54 (59%) patients were finally diagnosed with PTLD by biopsy or cytology.

■ Characteristics of 32 patients with PTLD

Characteristics	
Age (range)	48.5 y.o. (1-74)
Gender, Male / Female	18 / 14
Transplant type Kidney / Liver / Lung / Hematopoietic stem cell	 2 / 17 / 5 / 8
Time from transplantation to PET scan (range) < 1 year (early onset)	40.5 months (1.1-296) 9 (28%)
PTLD type Nondestructive Polymorphic Monomorphic (DLBCL / Burkitt / T-cell / Others) Hodgkin’s lymphoma-like Not determined (diagnosed by cytology)	 2 7 17 (10 / 3 / 1 / 3) 3 3
EBER positive	20 (71%)*
Extranodal disease	24 (75%)

* EBER was evaluable in 28 patients.

■ Diagnostic ability of FDG-PET(/CT) for PTLD

➢ Visual analysis

Abnormal FDG uptake	PTLD (+) (n=32)	PTLD (-) (n=22)	
Yes	28	7	PPV 80%
No	4	15	NPV 79%
	Sensitivity 88%	Specificity 68%	Accuracy 80%

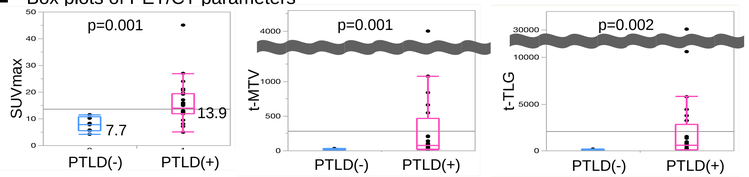
- False Positive (n=7): Pulmonary infection (3), Glioblastoma (1), Nodal marginal zone lymphoma* (1), Lymphadenitis/tonsillitis (2) (* not included in PTLD)
- False Negative (n=4): No abnormal FDG uptake (diagnosed by cytology) (3), Cecal lesion intermingled with multiple ALL lesions (1)

➢ Semiquantitative analysis

- Metabolic parameters were evaluable in **24 PTLD patients** and in **9 non-PTLD patients**
- Excluded PTLD patients (8): scanned by dedicated PET scanner (5), no abnormal FDG uptake (visually FN) (3)
- Included non-PTLD patients (9): visually FP (7), abnormal FDG uptake not considered as PTLD (2)
- The ROC curve analysis revealed that SUVmax of 11.8 best discriminated PTLD lesions from non-PTLD lesions (area under the curve [AUC] 0.89, p<0.001). For clinical convenience, the **SUVmax** cutoff value was set as **12**.

SUVmax ≥12	PTLD (+) (n=24)	PTLD (-) (n=9)	
Yes	17	0	PPV 100%
No	7	9	NPV 56%
	Sensitivity 71%	Specificity 100%	Accuracy 79%

■ Box plots of PET/CT parameters



- All PET/CT parameters were significantly higher in PTLD lesions than in non-PTLD lesions.
- Monomorphic (15.6) and HL-like (14.9) PTLD tended to show higher SUVmax than nondestructive (9.5) and polymorphic (8.7) PTLD (median SUVmax).

■ Survival analysis

- 9/32 patients died during follow-up period (median, 16.9 mo).
- Univariate Cox regression analysis revealed that **EBER positivity, high EBV viral load and high LDH** significantly associated with poor OS (p=0.010, 0.002 and 0.031, respectively), while no PET/CT parameters were significant predictors for OS.
- Kaplan-Meier analysis revealed that significant OS difference was observed between monomorphic PTLD and polymorphic PTLD (p=0.042).
- No EBER-negative patients died during follow-up, who were all monomorphic PTLD (7 DLBCL, 1 Burkitt lymphoma).

Discussion

- The sensitivity of FDG-PET(/CT) in diagnosing PTLD was comparable to previous results (88% vs. 88-89%), while the specificity was lower than previous results (68% vs. 89-91%) [1,2]. False-positive cases included pulmonary infections and other malignancies.
- The SUVmax was significantly higher in PTLD lesions (median 13.9, range 4.9-45) than in non-PTLD lesions (7.7, 4.1-11.5), as were t-MTV and t-TLG.
- Although considerable overlap of SUVmax existed between PTLD lesions and non-PTLD lesions, all non-PTLD lesions were SUVmax < 12.
- ✓ Although differentiating PTLD from other etiologies can be difficult, very intense FDG uptake (approximately SUVmax ≥ 12) is highly suggestive of PTLD under immunosuppressive condition after organ transplant.
- Monomorphic and Hodgkin’s lymphoma-type PTLD tended to show higher SUVmax than nondestructive and polymorphic PTLD, which was concordant with a previous study[4] .
- No PET/CT parameters were significant prognostic factors, while EBV positivity and high LDH were associated with poor OS.
- ✓ Generally, higher metabolic activity on FDG-PET/CT correlates with worse prognosis in many malignant tumors, including malignant lymphoma. This is the first study investigating the association between initial PET/CT metabolic parameters in PTLD patients and OS; further studies including larger cohorts with longer follow-up are needed for verification.
- ✓ EBV-negative PTLD was previously reported to have worse prognosis compared with EBV-positive PTLD; however, recent studies show some conflicting results[4]. Most of the EBV-negative cases are monomorphic PTLD, whose prognosis should have been affected by the progress of chemotherapy, particularly with the advent of Rituximab.

Conclusion

- **FDG-PET(/CT) is beneficial in diagnosing PTLD and in differentiating from other etiologies.**
- **No apparent correlations were observed between metabolic parameters in FDG-PET/CT and OS.**

References

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2) Dierickx D, et al. *Haematologica.* 2013;98:771-775.
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4) Luskin MR, et al. *Am J Transplant.* 2015;15:2665-2673.