의학석사 학위논문

An Additive Prognostic Value of Metabolic Tumor Volume on Baseline F-18 FDG-PET/CT to NCCN-IPI in Patients with Diffuse Large B-cell Lymphoma:

Further Stratification of the High-risk Group in NCCN-IPI

미만성 거대B세포 림프종 환자들의 치료전

F-18 FDG PET/CT에서 평가한 대사종양체적의

NCCN-IPI에 대한 부가적인 예후 가치: NCCN-IPI
고위험군의 추가적인 계층적 분류

2018년 12월

서울대학교 대학원

의학과 핵의학 전공

Qaid Ahmed Qaid Shagera

Abstract

An additive prognostic value of metabolic tumor volume on baseline F-18 FDG-PET/CT to NCCN-IPI in patients with diffuse large B-cell lymphoma: Further stratification of the high-risk group in NCCN-IPI

Qaid Ahmed Qaid Shagera

College of Medicine, Department of Nuclear Medicine

The Graduate School

Seoul National University

Aim: To evaluate the additional prognostic value of metabolic volumetric parameters as a quantitative index on pre-treatment F-18 FDG PET in patients with diffuse large B-cell lymphoma (DLBCL) to the National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI).

Methods: A total of 103 consecutive patients with DLBCL and baseline F-18 FDG-PET/CT were retrospectively enrolled. The total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG = MTV x SUVmean) were estimated using SUVmax of 2.5 as a threshold. Kaplan-Meier curve and Cox regression analyses were performed to test the relationship between

clinical factors and metabolic parameters and patient's progression-free-survival (PFS) and overall survival (OS). Those were evaluated in low- and high-risk groups by NCCN-IPI.

Results: Median follow-up was 32 months. The 3-yr PFS and OS were 60% and 73%, respectively. Patients with low-$TMTV_{2.5}$ (< 246 cm^3) had 83% 3-year PFS and 92% OS vs 41% 3-year PFS and 57% OS for those with high-$TMTV_{2.5}$ (≥ 246 cm^3, P < 0.0001). In univariate analyses, the high-$TMTV_{2.5}$ and NCCN-IPI ≥ 4 were significantly associated with inferior PFS and OS (P < 0.0001), as well as high-$TLG_{2.5}$ (P = 0.004 and P = 0.005, respectively). In multivariate analyses, $TMTV_{2.5}$ and NCCN-IPI were independent predictors of PFS (P = 0.007 and P = 0.009, respectively) and OS (P = 0.017 and P = 0.014 respectively). Moreover, $TMTV_{2.5}$ could separate the patients in the high-risk group (NCCN-IPI ≥ 4, n = 62) into two groups with significantly different outcomes; the group with low-$TMTV_{2.5}$ had 75% 3-year PFS and 88% OS while that with high-TMTV had 32% 3-year PFS and 47% OS (P = 0.003 and P = 0.004, respectively). However, $TMTV_{2.5}$ showed no further stratification of patients' prognosis in the low-risk group (NCCN-IPI = 0-3, n=41).

Conclusion: The pretreatment $TMTV_{2.5}$ had an independent prognostic value in patients with DLBC. We found for the first time in our knowledge that $TMTV_{2.5}$ had an additive predictive value for the prognosis in patients with high-risk by NCCN-IPI. Thus, combined information of a quantitative metabolic parameter, TMTV, with NCCN-IPI can improve the prognostication and may be helpful to guide the decision of aggressive treatment, especially in DLBCL patients with the high-risk by NCCN-IPI.

Keywords: FDG PET/CT, diffuse large B cell lymphoma, metabolic tumor volume, prognosis

Student number: 2017-24441

Contents

List of Tables

List of Figures

Introduction

Diffuse large B-cell lymphoma (DLBCL) accounts for approximately 30% of all newly-diagnosed non-Hodgkin lymphoma (NHL) and more than 80% of aggressive lymphomas. It is a heterogeneous group of lymphomas in terms of clinicopathological profiles and biological properties (1). The cure rate of the DLBCL has improved over the last two decades with the addition of rituximab to conventional cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisolone (CHOP) chemotherapy (R-CHOP) and improvements in dose intensity and supportive care (2, 3). However, approximately 30-40% of patients still experience relapse or refractory disease (4).

For the past 20 years, the international prognostic index (IPI) (5) has been the basis to determine the prognosis in the malignant NHL. Anyhow, its capacity has decreased after adding rituximab to CHOP therapy (6). Modified versions of IPI were elaborated such as the revised-IPI (7) and recently the National Comprehensive Cancer Network-IPI (NCCN-IPI) (8). These models have shown better risk stratification than IPI. Nonetheless, they still inaccurately predict the refractory disease. Therefore, there is an unmet need for finding a new biomarker or prognostic model to improve the prediction of refractory disease.

The use of fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (F-18 FDG PET/CT) has been increased in the last years. F-18 FDG-PET/CT in DLBCL has a function in the staging, restaging, aggressiveness evaluation, and response monitoring (9, 10). Since the improvement in PET/CT technology and image reconstruction, the quantitation of the metabolic parameters became an area of interest for researchers and clinicians.

The maximum standardized uptake value (SUVmax), total metabolic tumor volume (TMTV) and total lesion glycolysis (TLG) are the most commonly used in the clinical application and research studies. A few studies were published on the prognostic role of the metabolic PET parameters in DLBCL, however, with discordant results (11-15). There is no comprehensive evidence on which to use TMTV as a single marker or in combination with other parameters. The combination of the baseline TMTV and other prognostic factors such as the early response on PET (16) or gene expression (17, 18) in DLBCL have been reported with promising results. However, combining TMTV with the most recent clinical prognostic model (NCCN-IPI) has not been studied, yet.

Our purpose was to evaluate the added prognostic value of the metabolic volumetric parameters as quantitative indexes including TMTV on pre-treatment F-18 FDG PET/CT, to the NCCN-IPI in patients with diffuse large B-cell lymphoma (DLBCL).

Methods and Materials

Patients

We retrospectively analyzed 103 consecutive patients with newly diagnosed DLBCL and treated at Seoul National University Hospital between January 2010 and December 2015. The inclusion criteria were: (1) de novo DLBCL, (2) age ≥ 18 years at diagnosis, (3) immunocompetent, (4) FDG PET/CT before treatment, and (5) 1st line treatment with R-CHOP chemotherapy. Patients were excluded if they: (1) immunocompromised, (2) treated with non-R-CHOP (3) withdrawn from treatment, (4) have central nervous system lymphoma, (5) have a second tumor, and (6) pretreatment tumor excision Figure 1. Han's algorithm (19) was used to subtype DLBCL to germinal center B-cell (GCB) and non-GCB. The NCCN-IPI was estimated as following: categorized age 41–60 (1 point), 61–75 (2 points) and > 75 year (3 points), LDH > 1 (1 point) and > 3 times normal level (2 points), Ann Arbor stage III/IV disease (1 point), extra-nodal disease in major organs (1 point), and Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2 (1 point) (8). In addition, the low- (NCCN-IPI = 0-3) and high-risk (NCCN-IPI = 4-8) groups were classified. NCCN-IPI was used in our study as it was proposed to have better risk stratification than IPI and R-IPI (8). The study design and exemption of informed consent were approved by the Institutional Review Board of Seoul National University Hospital (IRB No. 1711-137-901).

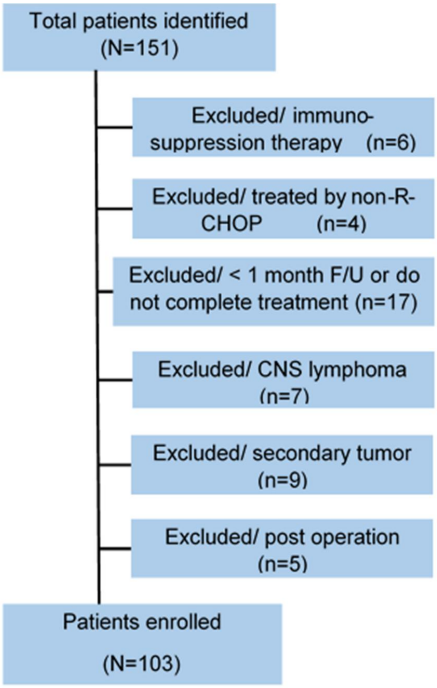


Figure 1. Flowchart of patient selection. Abbreviation: F/U; follow-up, CNS; central nervous system

FDG PET/CT Acquisition

F-18 FDG PET/CT without injection of iodine contrast agent was performed prior to treatment. The patients were asked to fast for at least 6 hours. All reported blood sugar levels were under 150 mg/dl. Images were acquired one hour after injection of F-18 FDG (5.18 MBq/kg) using dedicated PET/CT scanners (Biograph True-Point, Biograph mCT 40 and Biograph mCT 64; Siemens, Erlangen, Germany). PET images were acquired in a 3D acquisition mode (6-7 bed positions, 1-2 min/bed). The images were reconstructed using the ordered subset expectation maximization algorithm (OSEM) with 2 iterations and 21 subsets for the Biograph mCT 40 and 64 scanners and 4 iterations and 8 subsets for the Biograph True-Point scanner with CT-based attenuation correction.

FDG PET/CT Image Analysis

The images of FDG PET/CT in transverse, sagittal and coronal planes were reviewed. Abnormal lesions were determined by a consensus between two nuclear medicine physicians (4 and 15 years' experience) who were blinded to the clinical data, other imaging tests and outcome. Based on the visual assessment, spherical regions of interest (ROI) were drawn around pathological lesions (node or focal organ involvement), using a semiautomatic software program (Syngo.Via; Siemens Medical Solution, Knoxville, TN). The highest SUVmax, whole body MTV (the sum of all measured lesions' MTV) by setting the margin threshold at 2.5 ($TMTV_{2.5}$) and 40% ($TMTV_{40\%}$) were estimated. The circle was modified to include pathological lesions and to exclude physiological uptake sites (e.g., bladder, kidney, brain or myocardium) taking oval or round shape Figure 6. We used SUVmax of 2.5 threshold as it could outline the lesions properly, recommended by Freudenberg et al. (20), and easier to apply with less inter-observer

disagreement and good reproducibility (21). On the other hand, using a threshold setting of 40% of the SUVmax was recommended by the European guideline (22). Moreover, it was found to be reproducible and correlated with other parameters of tumor mass evaluation (23). However, the aforementioned methods of MTV quantitation are the most commonly used in literature and clinical application. Patients with CNS involvement were excluded because the limitation in quantitation of CNS lesions and immunocompromised patients as well because the presence of inflammatory lesions due to opportunistic infection made it difficult to differentiate them from lymphoma involvement. Spleen, liver, and bone marrow were only measured if there is focal uptake. The whole-body TLG was estimated as the summation of all lesions' (MTV x SUVmean).

Patients Survival Assessment

We retrospectively reviewed the patients' medical records and clinical investigations. The progression-free survival (PFS) was estimated from the documented date of diagnosis until the date of disease progression (new lesion or enlargement of the previous existing lesion), recurrence or death from the disease. The overall survival (OS) estimated from the date of diagnosis to the date of death from any cause. The disease response was evaluated after completing the treatment course by CT and/or FDG PET/CT, laboratory, and clinical evaluation.

Statistical Analysis

Pearson's correlation coefficient was used to check the correlation between the TMTV and clinical factors. Receiver-operating characteristic (ROC) curve analysis was used to estimate the optimal cut-off values of the quantitative metabolic metrics for PFS and OS. The association between clinical and metabolic variables and survival was assessed using the Kaplan-Meier method. The log-rank test was used to compare the differences between survival curves. Univariate and multivariate analyses were performed using Cox regression hazard model. The results were considered statistically significant if a two-tailed P-value < 0.05. Statistical analyses were performed using the Statistical Package for Social Sciences version 23.0 statistical software package (SPSS, Inc., Chicago, IL, USA).

서식 있음: 가운데, 줄 간격: 배수 3 줄

Results

Patient Characteristics

In total, the median age was 65 years (range 18-88 years) with 54 men and 49 women. Out of total, 101 patients have completed 6-8 cycles of R-CHOP or R-miniCHOP chemotherapy (additional radiotherapy (RT) for 9, salvage- and radiotherapy for 6 and autologous stem cell transplantation for 5 patients), one patient received 3 cycles followed by RT and one received 2 cycles followed by autologous stem cell therapy. The median follow-up period was 34 months (range 7-99 months). Forty-two patients (42%) had a disease progression at the median of 11.5 months and 33 patients (32%) have died at the median of 20 months duration. Bone marrow was positive in 15 (14.5%) patients (the biopsy performed for 92 patients). Thirteen patients had no response for the 1st line therapy; 12 of them had progression at a median of 7 months duration and 11 died at a median of 14 months. All clinical data were summarized in Table 1.

Table 1. Patient characteristics

Characteristics	*n* = 103 (%)
Gender Male / Female	54 (52.4%) / 49 (47.6)
Age	
≤ 40 year	8 (7.7)
41- ≤ 60 year	35 (34.0)
61- ≤ 75 year	36 (35.0)
>75 year	24 (23.3)
LDH	
Normal	41 (39.8)
> 1 to ≤ 3 times	48 (46.6)
> 3 times	14 (13.6)
Stage III/IV	68 (66)
ECOG ≥ 2	14(13.6)
ENI*	66 (64.1)
NCCN-IPI	
Low (0-1)	12 (11.7)
Low intermediate (2-3)	29 (28.2)
High intermediate (4-5)	44 (42.7%)
High-risk (6-8)	18 (17.5)
COO Non-GCB	65 (63.1)
Bulky disease (≥ 10 cm)	10 (9.7)
SUV_{max}	
Mean (SD)	22.9 (10.6)
Median (range)	20.0 (8-57)
TMTV2.5**	
Mean (SD)	616.2 (865)
Median (range)	273.0 (10-5156)
TLG2.5**	
Mean (SD)	4177.8 (5527)
Median (range)	1748.7 (40-33667)

LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group Performance Status; NCCN-IPI; National Comprehensive Cancer Network-International Prognostic Index; COO, cell of origin; GCB, germinal center B-cell like; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis; SD; standard deviation.

* ENI; extra nodal involvement (bone marrow, central nervous system, liver/gastrointestinal tract, or lung involvement) (8)

** TMTV was estimated using 2.5 SUVmax as a threshold.

Correlation between Metabolic Parameters and Clinical Factors

Pearson correlation analyses showed a strong correlation between the TMTV and LDH, and moderate correlation with both stage and NCCN-IPI (ρ = 0.67, ρ = 0.45 and ρ = 0.49, respectively, $P < 0.0001$). There were only weak or very weak correlation between the TMTV and the other clinical factors Table 2.

Table 2. Correlation analysis between metabolic volumetric parameters and clinical factors

Factor	$TMTV_{2.5}$	$TLG_{2.5}$
Age	0.123 (0.217)	0.049 (0.620)
LDH	0.670 (0.0001)	0.532 (0.0001)
Stage	0.454 (0.0001)	0.296 (0.002)
ECOG	0.136 (0.171)	0.149 (0.133)
ENI	0.248 (0.011)	0.094 (0.345)
NCCN-IPI	0.489 (0.0001)	0.311 (0.001)

Pearson's correlation coefficient (ρ) was classified as following: very weak (ρ = *0.0.19*), weak (ρ = *0.20-0.39), moderate* (ρ = *0.40-0.59), and strong* (ρ = *0.60-0.79), and very strong* (ρ = *0.80-1.00)*

PET Parameters and ROC Analysis for TMTV2.5 and TLG2.5

The median of SUVmax, TMTV and TLG were 20.0 g/ml, 273.0 cm^3 (1st to 3rd quartile; 102 to 842 cm^3) and 1748.7 cm^3, respectively Table 1. Using the ROC analysis, the optimal cut-off values of TMTV were 242.5 cm^3 for PFS and 248.5 cm^3 for OS (area under the curves (AUCs): 0.74 and 0.75, respectively, $P < 0.0001$). As there was no significant statistical difference, we selected 245.5 cm^3 (the average) as a cut-off value of TMTV (sensitivity 84% and specificity 62%). The optimal cut-off values of TLG were 1345 cm^3 for PFS and 1420 cm^3 for OS (AUCs: 0.68 and 0.69, respectively, $P = 0.001$). The average cut-off value of TLG was 1383 cm^3 (sensitivity, 80% and specificity, 52%). However, the AUCs of SUVmax were 0.51 for PFS and 0.54 for OS ($P = 0.809$ and $P = 0.520$, respectively) Figure 2.

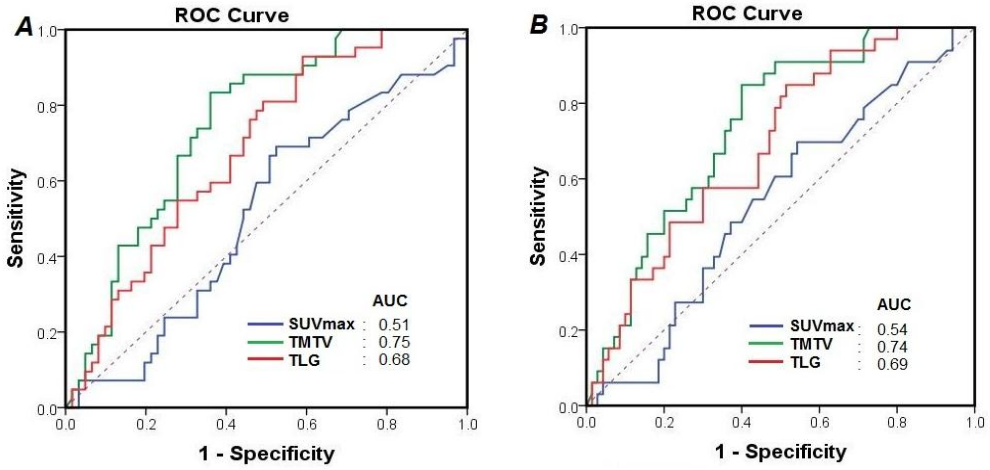
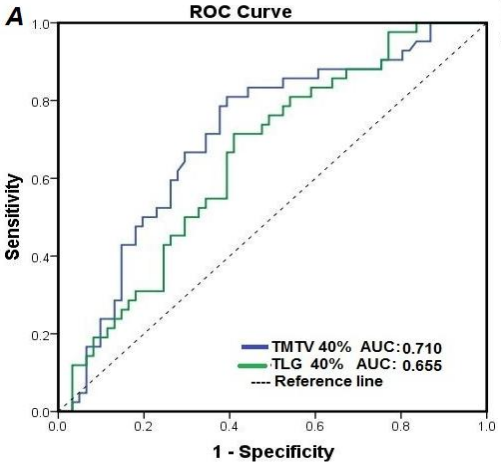
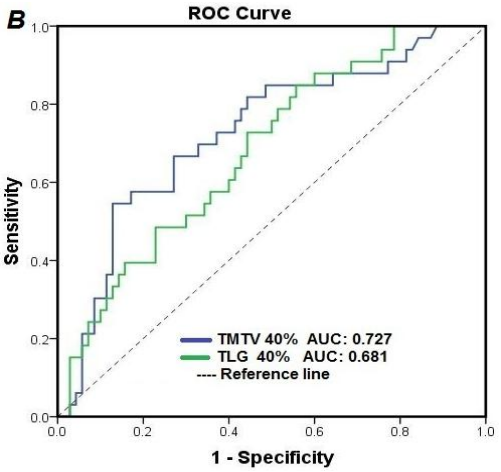


Figure 2. ROC analyses metabolic parameters for PFS (A) and overall survival (B). Abbreviations: AUC; area under the curve. The P values for PFS and OS were as follows: for $TMTV_{2.5}$, $P < 0.0001$ and $TLG_{2.5}$ $P = 0.001$ and SUVmax ($P = 0.809$ and $P = 0.520$, respectively).

PET Parameters and ROC Analysis for





TMTV40% and TLG40%

The median of TMTV and TLG were 124.45 cm^3 (1st to 3rd quartile; 37 to 235 cm^3) and 1247.11 cm^3, respectively. The optimal cut-off values of TMTV was 99.8 cm^3 for PFS and OS (area under the curves (AUCs): 0.71 and 0.73, respectively, $P < 0.0001$), with 78% sensitivity and 62% specificity. The optimal cut-off value of TLG was 996.6 cm^3 for PFS and OS (AUCs 0.65; $P = 0.008$ and 0.89; $P = 0.003$, respectively), with sensitivity 73% and specificity 56%. Figure 3.

Figure 3. ROC analyses metabolic parameters for PFS (A) and overall survival (B). Abbreviations: AUC, area under the curve. The P values for PFS and OS were as follows: for $TMTV_{40\%}$, $P < 0.0001$, and for $TLG_{40\%}$ $P = 0.008$ and $P = 0.003$, respectively).

Outcomes According to Metabolic Parameters ($TMTV_{40\%}$ and $TLG_{40\%}$)

Patients were stratified into two groups with different survival according to $TMTV_{40\%}$ and $TLG_{40\%}$. Patients with low-$TMTV_{40\%}$ (n = 47) had excellent survival (81% 3-year PFS and 89% OS) comparing to those with high-$TMTV_{40\%}$ (n = 56, 41% 3-year PFS and 59% OS, $P < 0.0001$) Figure 4. Similarly, patients with Low-$TLG_{40\%}$ (n = 48) had good outcomes (75% 3-year PFS and 87% OS) comparing to those with high-$TLG_{40\%}$ (n = 55, 45% 3-year PFS and 60% OS, $P = 0.002$ and $P = 0.005$, respectively). On multivariate analysis, Cox-regression analyses were performed using NCCN- as covariate Table 3. The $TMTV_{40\%}$ was independent in predicting PFS (HR=2.62, $P = 0.013$), but not independent in predicting the OS (HR= 2.12, $P = 0.087$). By the

way, $TLG_{40\%}$ could not retain independent of NCCN-IPI for predicting both PFS (HR= 1.72, P = 0.124) and OS (HR= 1.81, P = 0.141).

Table 3. Univariate and multivariate analyses of metabolic parameters and NCCN-IPI for progression-free survival (PFS) and overall survival (OS), using Cox-regression hazard model

	PFS		OS	
Parameter	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Univariate analyses				
$TMTV_{40\%}$	3.93 (1.87 – 8.22)	0.0001	3.54 (1.53 – 8.16)	0.003
$TLG_{40\%}$	2.67 (1.37 – 5.24)	0.004	2.94 (1.36 – 6.35)	0.006
Multivariate analysis*				
$TMTV_{40\%}$	2.62 (1.22 – 5.63)	0.013	2.11 (0.89 – 5.00)	0.087
NCCN-IPI	4.03 (1.64 – 6.87)	0.009	6.41 (1.88 – 21.79)	0.003

$TLG_{40\%}$*	1.72 (0.86 – 3.45)	0.124	1.81 (0.82 – 4.00)	0.141

*Multivariate analysis was performed by adjusting TLG to NCCN-IPI separately, due to the strong correlation between the TMTV and TLG (Pearson's ρ = 0.863)

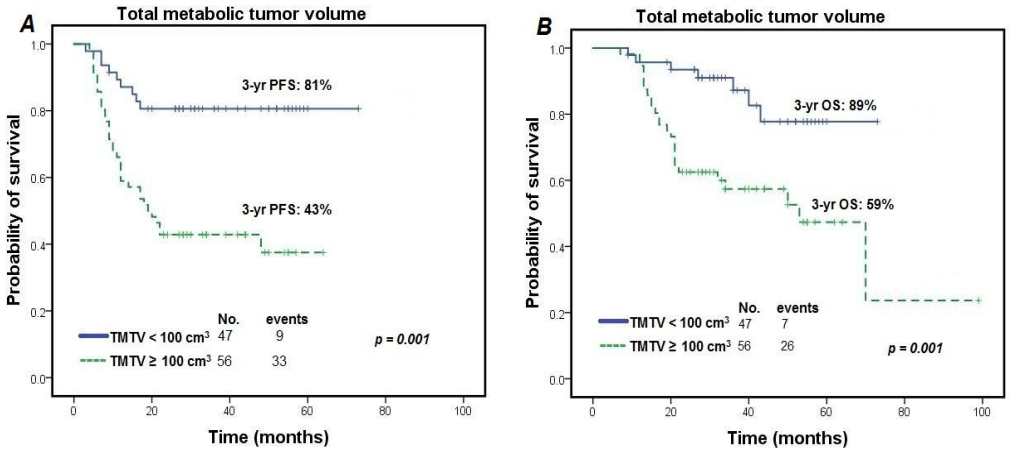


Figure 4. Outcomes of total patients according to $TMTV_{40\%}$. Kaplan–Meier plots compare PFS (A) and OS (B).

Outcome According to Metabolic Parameters ($TMTV_{2.5}$ and $TLG_{2.5}$) and NCCN-IPI

Kaplan-Meier curve analyses were performed using the optimal cut-off values of both $TMTV_{2.5}$ and $TLG_{2.5}$. Patients with high-$TMTV_{2.5} \geq 246$ cm^3 (n = 56) had 41% 3-year PFS and 57% OS while those with low-$TMTV_{2.5} < 246$ cm^3 (n = 47) had 83% 3-year PFS and 92% OS (P < 0.0001) Figure 4. Patients with high $TLG_{2.5} \geq 1383$ (n = 62) had 48% 3-year PFS and 61% OS, whereas those with low-$TLG_{2.5} < 1383$ (n = 41) had 78% 3-year PFS and 90% OS (P = 0.001 for PFS and P = 0.002 for OS). Patients with low-risk (NCCN-IPI = 0-3, n = 41) had 86% 3-year PFS and 95% OS while those with high-risk (NCCN-IPI = 4-8, n = 62) had 43% 3-year PFS and

58% OS (P < 0.0001) Figure 5. In univariate analyses, using Cox regression, $TMTV_{2.5}$, $TLG_{2.5}$ and components of NCCN-IPI were significantly associated with the patients' survival Table 4.

To investigate whether $TMTV_{2.5}$ adds a prognostic value beyond that obtained by clinical factors, a Cox model was fitted with components of NCCN-IPI as covariates. $TMTV_{2.5}$ was independent predictor of both PFS and OS (P = 0.002 and P = 0.012, respectively). Further analyses using the NCCN-IPI model as a covariate showed that $TMTV_{2.5}$ as well as NCCN-IPI were independent predictors for PFS (P = 0.007 and P = 0.009, respectively) and OS (P = 0.017 and P = 0.014, respectively) Table 5. The $TLG_{2.5}$ had a strong correlation with the $TMTV_{2.5}$ (Pearson's ρ = 0.92). Thus, a separate model was created of multivariate analysis; $TLG_{2.5}$ was adjusted to NCCN-IPI. However, $TLG_{2.5}$ was not independent from NCCN-IPI in predicting both PFS (P = 0.097) and OS (P = 0.188) Table 5.

	PFS		OS	
Parameter	**HR (95% CI)**	**P Value**	**HR (95% CI)**	**P Value**
Age	1.62 (1.14–2.28)	0.006	1.97 (1.31–2.99)	0.001
LDH	1.75 (1.16–2.64)	0.008	2.07 (1.28–3.37)	0.003
Stage	3.86(1.62–9.18)	0.002	4.41 (1.54–12.59)	0.006
ECOG	2.10 (1.01–4.40)	0.049	2.33 (1.04–5.20)	0.039
ENI*	3.06 (1.41–6.63)	0.004	2.93 (1.21–7.14)	0.018
Cell of Origin	1.37 (0.72–2.62)	0.329	1.71 (0.81–3.61)	0.160

NCCN-IPI	5.53 (2.32–13.16)	0.0001	8.38 (2.55–27.56)	0.0001
$TMTV_{2.5}$	4.98 (2.30–10.81)	0.0001	6.08 (2.34–15.81)	0.0001
$TLG_{2.5}$	2.96 (1.41–6.19)	0.004	3.62 (1.49–8.80)	0.005

	PFS		**OS**	

Table 4. Univariate analyses of the clinical factors, molecular biology, metabolic parameters and NCCN-IPI for progression-free survival (PFS) and overall survival (OS), using Cox-regression hazard model

LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group Performance Status; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index; COO, cell of origin; GCB, germinal center B-cell like; SUVmax, maximum standardized uptake value; TMTV, total metabolic tumor volume; TLG, total lesion glycolysis; SD, standard deviation.
*ENI; extra nodal involvement (bone marrow, central nervous system, liver/gastrointestinal tract, or lung involvement)

Table 5. Multivariate analyses using Cox regression of $TMTV_{2.5}$, NCCN-IPI and clinical factors for PFS and OS

Parameter	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
With individual NCCN-IPI factors				
Age	1.43 (0.97–2.10)	0.068	1.92 (1.22–3.04)	0.005
$TMTV_{2.5}$	4.07(1.65–10.07)	0.002	4.17 (1.37–12.67)	0.012
With NCCN-IPI				
$TMTV_{2.5}$	3.11 (1.37–7.07)	0.007	3.41 (1.24–9.38)	0.017
NCCN-IPI	3.42 (1.36–8.59)	0.009	5.06 (1.46–17.60)	0.014
$TLG_{2.5}$*	1.92 (0.88 – 4.16)	0.097	1.81 (0.75 – 4.37)	0.188

*Multivariate analysis was performed by adjusting TLG to NCCN-IPI only. TMTV was excluded due to the strong correlation between TLG and TMTV (Pearson's $\rho = 0.92$)

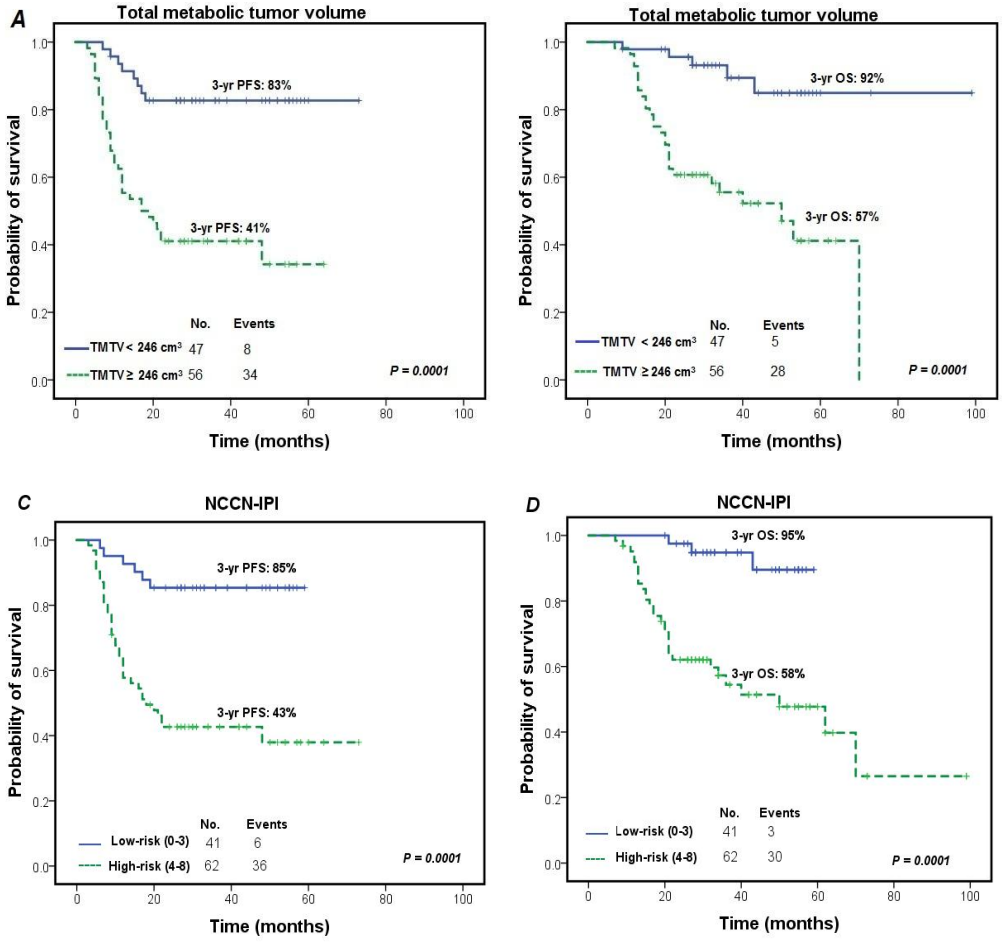


Figure 4. Outcomes of cases by $TMTV_{2.5}$ and NCCN-IPI. Kaplan–Meier plots compare PFS and OS of all patients. The top row is for TMTV, PFS (A) and OS (B). The bottom row is for NCCN-IPI; PFS (C) and OS (D).

Outcome According to $TMTV_{2.5}$ in the Subgroups of Low- and High-NCCN-IPI

Based on the NCCN-IPI, patients were classified into low- (NCCN-IPI = 0-3) and high-risk (NCCN-IPI = 4-8) groups. In the high-risk group, there were no significant differences in PFS (P = 0.354) and OS (P = 0.370) between NCCN-IPI scores of 4-5 and 6-8. On the other hand, there were significant differences in PFS (P = 0.003) and OS (P = 0.004) of patients with low- and high-$TMTV_{2.5}$. The $TMTV_{2.5}$ could significantly separate further the high-risk patients by NCCN-IPI into groups with much better (n = 16, 75% 3-year PFS and 88% OS) and poorer prognosis (n = 46, 32% 3-year PFS and 47% OS) Table 6, Figure 6 and 7. However, there were no significant differences in PFS (P = 0.585) and OS (P = 0.366) of patients with low- and high-$TMTV_{2.5}$ in the low-risk group by NCCN-IPI.

Table 6. Kaplan-Meier curve analyses of PFS and OS stratified by $TMTV_{2.5}$ in the low- and high-risk NCCN-IPI groups

Category	Parameter	Cases n=103	3-year PFS		3-year OS	
			Event(%)	X^2 (P value)	Event(%)	X^2 (P value)
Low-risk (NCCN-IPI < 4)	**Low-TMTV**	31	4 (87)	NS	3 (94%)	NS
	High-MTV	10	2 (80)		0 (100)	
High-risk (NCCN-IPI ≥ 4)	**Low-TMTV**	16	4 (75)	7.92 (0.005)	2 (88)	8.26 (0.004)
	High-MTV	46	32 (32)		28 (47)	

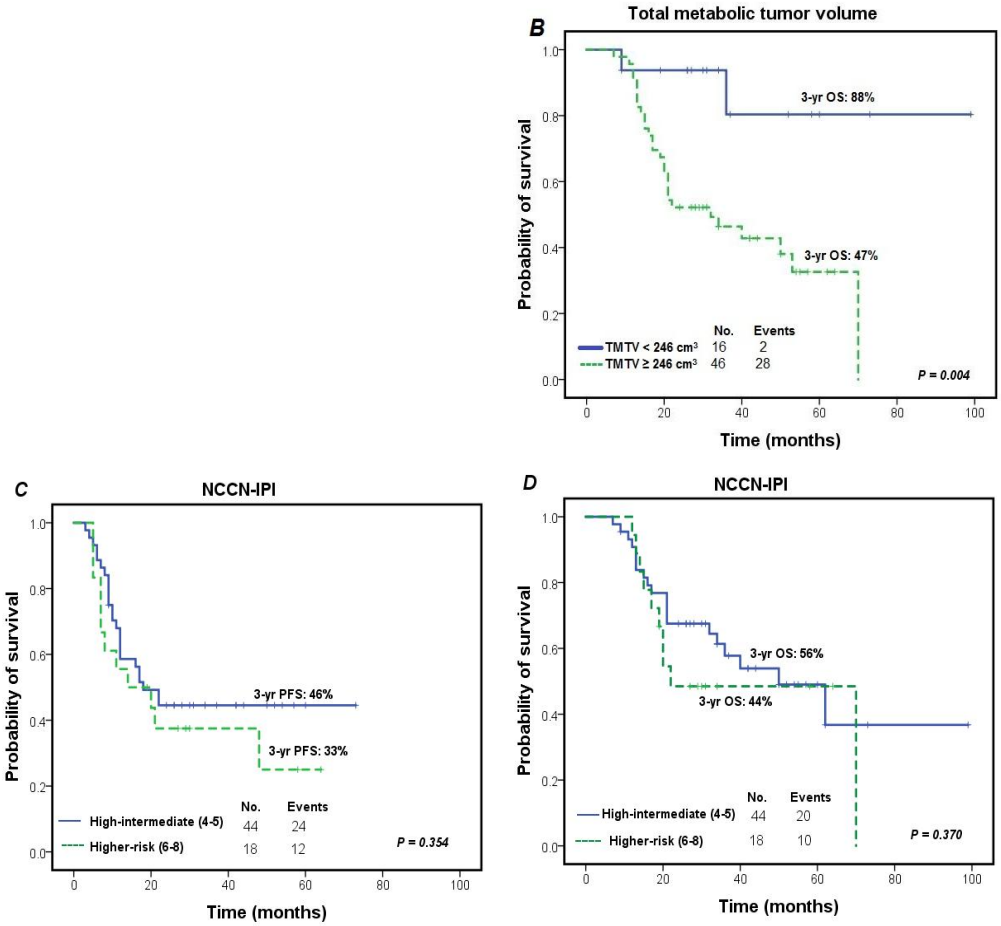

B
Total metabolic tumor volume
Probability of survival
3-yr OS: 88%
3-yr OS: 47%
No. Events
TMTV < 246 cm³ 16 2
TMTV ≥ 246 cm³ 46 28
P = 0.004
Time (months)
C
NCCN-IPI
Probability of survival
3-yr PFS: 46%
3-yr PFS: 33%
No. Events
High-intermediate (4-5) 44 24
Higher-risk (6-8) 18 12
P = 0.354
Time (months)
D
NCCN-IPI
Probability of survival
3-yr OS: 56%
3-yr OS: 44%
No. Events
High-intermediate (4-5) 44 20
Higher-risk (6-8) 18 10
P = 0.370
Time (months)

Figure 6. Kaplan-Meier plots of PFS and OS in the high-risk patients (NCCN-IPI ≥ 4). The top row shows low- vs high-$TMTV_{2.5}$ analyses for PFS (A) and OS (B). The bottom row shows NCCN-IPI high-intermediate score 4-5 vs higher-risk score 6-8, PFS (C) and OS (D).

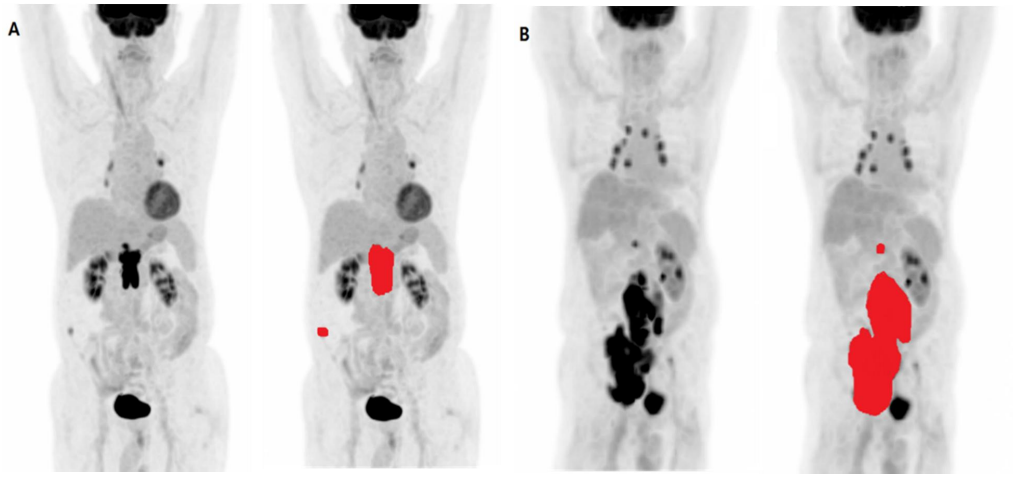


Figure 7. Examples of tumor segmentation for MTV estimation and risk re-classification by $TMTV_{2.5}$. (A) Patient with high-risk (NCCN-IPI = 6) had low-$TMTV_{2.5}$ (111 cm^3) and no progression/death during the follow-up duration of 27 months, (B) with high-$TMTV_{2.5}$ (842 cm^3) and NCCN-IPI = 7, this patient had progression after 7 months and died after 19 months of diagnosis. Note: the uptake in the hilar lymph nodes were considered benign, it is a common presentation in the old Korean population.

Discussion

In the current study, $TMTV_{2.5}$, a quantitative volumetric metabolic parameter, had an independent predictive value for both PFS and OS in addition to NCCN-IPI. There was a significant difference in outcomes between patients with low- and high-$TMTV_{2.5}$. Interestingly, $TMTV_{2.5}$ did further stratify patients with NCCN-IPI high-risk (4 to 8) into two groups with significantly different outcomes. Recently, NCCN-IPI was introduced in the NCCN-guideline 2016 as one of the prognostic models in DLBCL (24). Zhou et al. (8) have suggested that NCCN-IPI has a better risk stratification than IPI. Our results also confirmed the prognostic roles of NCCN-IPI in DLBCL. In this study, we further evaluated the prognostic roles of the TMTV in the high-risk group (NCCN-IPI = 4-8). According to our data, we found that $TMTV_{2.5}$ could re-stratify patients as followings: patients with low-$TMTV_{2.5}$ had a good survival and those with high-$TMTV_{2.5}$ had a poor survival which was statistically significant. Clinicians may have benefits in recognizing the higher-risk patients who need to treat more intensively and the others

with a good outcome to save them from over-exposures to chemotoxic therapy, by TMTV consideration in the high-risk group identified by NCCN-IPI.

As TMTV appears to represent the overall or gross metabolic activity of cancer cells, it can be a potential measure of biologically active tumor volume (25). In our data, TMTV had a significant correlation with the categorized LDH (strong, $\rho = 0.67$) and clinical stage (moderate, $\rho = 0.46$). This correlation may be caused by the facts that LDH and clinical stage reflects tumor turnover rates and disease extension (tumor burden) (5, 8). The staging system shows the extents of disease, rather than the exact tumor volume and LDH may change or remain within normal range due to the tumor status of necrotic or viable tissues. We believe that TMTV represents the tumor burden more precisely than Ann-Arbor staging and/or LDH as it measures the volume of viable tumors in 3D volumetric information. Therefore, TMTV can provide more precise additional quantitative data to the current prognostic models such as NCCN-IPI.

Previous studies have been published in DLBCL showing different optimal TMTV cut-off values (11-13, 16-18). This variation can be explained by the difference in quantitation method, tumor burden reflecting factors (LDH and stage) and the presence of bulky disease (≥ 10 cm). The relationship between bulky disease and high TMTV ($\rho = 0.557$) has been reported. (16) Studies on patients with low stages showed lower median and cut–off values than those with advanced stages and bulky disease. For example, Song et al. (12) reported cut-off as 220 cm^3 (median: 198) on stage II/III with 4% of bulky disease, while Mikhaeel et al. (16) reported cut-off as 400 cm^3 (median: 595) in all stages I-IV with 60% of stage IV and 40% of bulky disease. In our study, the optimal cut-off was 246 cm^3 (median: 273), which was lower than that reported by Mikhaeel et al. (16). This can be explained by the presence of only 10% of bulky disease in

our population. Another reason could be due to the difference in PET images acquisition time (60 minutes in our study vs 90 minutes in their study); obviously, the FDG uptake should be higher on late imaging causing overestimation of the SUVmax. Additionally, we excluded MTV from diffuse spleen, liver and bone marrow, which were not reported by Mikhaeel et al. Although our cut-off value was different, however, it could favorably identify the high-risk group, compared to the previous report (13). Unlike the TMTV cut-off value reported previously (16), the cut-off value in our study could predict both PFS and OS.

In contrast to our findings, Adams et al. (26) have reported that the SUVmax, TMTV, TLG were not independent prognostic factors to NCCN-IPI. This discordance might be due to the difference in population. In their study, approximately 85% of included patients had an advanced stage (III/IV) while only 65% had stage III/IV in our population. Furthermore, they have only 24% of patients with low risk comparing to 40% in our population. Adams et al.'s report was based on a lower number of patients and events than those in our study. Anyhow, our results implied that TMTV was highly associated with the stage, LDH and NCCN-IPI indicting its clinical meaning. Moreover, our findings were compatible with the report by Mixue Xie et al. (27) on 702 patients, that TMTV has a potential predictive value of both PFS and OS in DLBCL when compared to IPI. On the other hand, a retrospective study on 91 patients by Zhou et al. (15) reported that the TLG was the only independent predictive factor. In the current study, the TLG could also separate patients into different groups with a significant difference in outcomes, however, it was inferior to $TMTV_{2.5}$. Additionally, TLG had no additive prognostic value to NCCN-IPI; it couldn't retain independent in multivariate analysis (P = 0.090 for PFS and P = 0.093 for OS). The discrepancy could be explained by the difference in the population. In Zhou et al.'s study,

(15) most of the patients were younger than 60-year (58%) and low-risk (57%), whereas our population composed of 58% older than 60-yr and 60% were high-risk.

The SUVmax is the most widely-used metabolic parameter in daily clinical practice. Previous studies have reported that there is an association between SUVmax and tumor aggressiveness (28, 29). Dai Chihara et al. (14) suggested that high SUVmax > 30 is associated with poor PFS and OS. However, low- vs high-SUVmax showed limitations in predicting PFS (78% vs 51%, P = 0.06) and OS (86% vs 71%), compared with the old IPI. Additionally, they failed to estimate the TMTV and TLG. In the present study, SUVmax was not a significant predictor of patients' survival. Basically, SUV provides a semi-quantitative index of the FDG metabolic rate without accounting for the characteristics of total tumor volume. In our opinion, this drawback of SUVmax made it less reliable as a prognostic factor, especially in DLBCL.

The current study highlighted the benefits of integrative approaches including NCCN-IPI and $TMTV_{2.5}$ for patients with DLBCL at initial diagnosis. $TMTV_{2.5}$ could separate a significant subset of patients, especially in the NCCN-IPI high-risk group. It allows identifying patients with a favorable prognosis in a subpopulation which can no longer belong to the high-risk group. Patients with low risk by NCCN-IPI had excellent outcomes (86% 3-year PFS and 95% OS) by the current treatment, however, $TMTV_{2.5}$ showed limited risk stratification in this group. This might be due to the low number of population and/or events. In addition, patients in this group were presented with a low tumor burden. For clinical practice, we believe that the priority is to identify high-risk patients precisely, as low-risk patients are doing well with the current therapy. It has been reported that combined information of $TMTV_{2.5}$ with molecular markers might improve prognostication in DLBCL (17, 18). Cottereau et al. (18) have claimed that the

combination of TMTV and molecular data improved prognostication in 81 patients with DLBCL. In their study, the gene expression profiling was only confirmed in 57 patients and they compared TMTV with the older age adjusted-IPI which may be appropriate for patients with age ≤ 60 (24). In this current study, however, molecular data were existent for all included patients and classified to GCB and non-GCB based on Hans' algorithm (19) , which showed no prognostic implications among our population Table 3. Further studies with a larger population and a proper selection of molecular markers should be needed to the conclusion. On their reply to Adams HJ letter, Cottearreau et al. (30) suggested that TMTV could be combined with NCCN-IPI to predict the risk in DLBCL as well. Importantly, the NCCN-IPI was underestimated in their study that might be out to the small population. This makes it unsatisfactory to draw a concrete conclusion. In our study, we confirmed the independent predictive values of both NCCN-IPI and TMTV in multivariate on a larger population.

The limitations of this study arise from its retrospective nature in a single center. Determination of optimal cut-off value may be one of the other limitations because of the various kinds of methods for TMTV cut-off determination as well as quantitation, with the lack of standardization. However, with the improvement of PET/CT technology and metabolic quantification, the TMTV became easier to apply and promising prognostic marker. Multicenter study and research groups' cooperation are highly required to standardize the estimation method of TMTV, to validate these findings and to facilitate TMTV using in clinical trials.

서식 있음: 가운데

Conclusion

The pretreatment $TMTV_{2.5}$ had an independent potential prognostic value in patients with DLBCL. We found for the first time in our knowledge that $TMTV_{2.5}$ had an additive predictive value for the prognosis in patients with high-risk by NCCN-IPI. Thus, combined information of a quantitative metabolic parameter, $TMTV_{2.5}$ with NCCN-IPI can improve the prognostication and may be helpful to guide the decision of intensive treatments, especially in DLBCL patients with the high-risk by NCCN-IPI.

References

1. Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. *Hematology Am Soc Hematol Educ Program*. 2004:221-36.

2. Pfreundschuh M, Kuhnt E, Trumper L, Osterborg A, Trneny M, Shepherd L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. *Lancet Oncol.* 2011;12(11):1013-22.

3. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med.* 2002;346(4):235-42.

4. Friedberg JW. Relapsed/refractory diffuse large B-cell lymphoma. *Hematology Am Soc Hematol Educ Program*. 2011;2011:498-505.

5. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med.* 1993;329(14):987-94.

6. Bari A, Marcheselli L, Sacchi S, Marcheselli R, Pozzi S, Ferri P, et al. Prognostic models for diffuse large B-cell lymphoma in the rituximab era: a never-ending story. *Ann Oncol.* 2010;21(7):1486-91.

7. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood.* 2007;109(5):1857-61.

8. Zhou Z, Sehn LH, Rademaker AW, Gordon LI, Lacasce AS, Crosby-Thompson A, et al. An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era. *Blood*. 2014;123(6):837-42.

9. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25(5):579-86.

10. Barrington SF, Mikhaeel NG, Kostakoglu L, Meignan M, Hutchings M, Mueller SP, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. *J Clin Oncol.* 2014;32(27):3048-58.

11. Kim J, Hong J, Kim SG, Hwang KH, Kim M, Ahn HK, et al. Prognostic Value of Metabolic Tumor Volume Estimated by (18) F-FDG Positron Emission Tomography/Computed Tomography in Patients with Diffuse Large B-Cell Lymphoma of Stage II or III Disease. *Nucl Med Mol Imaging*. 2014;48(3):187-95.

12. Song M-K, Chung J-S, Shin H-J, Lee S-M, Lee S-E, Lee H-S, et al. Clinical significance of metabolic tumor volume by PET/CT in stages II and III of diffuse large B cell lymphoma without extranodal site involvement. *Ann Hematol*. 2012;91(5):697-703.

13. Sasanelli M, Meignan M, Haioun C, Berriolo-Riedinger A, Casasnovas RO, Biggi A, et al. Pretherapy metabolic tumour volume is an independent predictor of outcome in patients with diffuse large B-cell lymphoma. *Eur J Nucl Med Mol Imaging*. 2014;41(11):2017-22.

14. Chihara D, Oki Y, Onoda H, Taji H, Yamamoto K, Tamaki T, et al. High maximum standard uptake value (SUVmax) on PET scan is associated with shorter survival in patients with diffuse large B cell lymphoma. *Int J Hematol.* 2011;93(4):502-8.

15. Zhou M, Chen Y, Huang H, Zhou X, Liu J, Huang G. Prognostic value of total lesion glycolysis of baseline 18F-fluorodeoxyglucose positron emission tomography/computed tomography in diffuse large B-cell lymphoma. *Oncotarget.* 2016;7(50):83544-53.

16. Mikhaeel NG, Smith D, Dunn JT, Phillips M, Moller H, Fields PA, et al. Combination of baseline metabolic tumour volume and early response on PET/CT improves progression-free survival prediction in DLBCL. *Eur J Nucl Med Mol Imaging.* 2016;43(7):1209-19.

17. Toledano MN, Desbordes P, Banjar A, Gardin I, Vera P, Ruminy P, et al. Combination of baseline FDG PET/CT total metabolic tumour volume and gene expression profile have a robust predictive value in patients with diffuse large B-cell lymphoma. *Eur J Nucl Med Mol Imaging.* 2018;45(5):680-8.

18. Cottereau AS, Lanic H, Mareschal S, Meignan M, Vera P, Tilly H, et al. Molecular Profile and FDG-PET/CT Total Metabolic Tumor Volume Improve Risk Classification at Diagnosis for Patients with Diffuse Large B-Cell Lymphoma. *Clin Cancer Res.* 2016;22(15):3801-9.

19. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood.* 2004;103(1):275-82.

20. Freudenberg LS, Antoch G, Schutt P, Beyer T, Jentzen W, Muller SP, et al. FDG-PET/CT in re-staging of patients with lymphoma. *Eur J Nucl Med Mol Imaging.* 2004;31(3):325-9.

21. Ilyas H, Mikhaeel NG, Dunn JT, Rahman F, Moller H, Smith D, et al. Defining the optimal method for measuring baseline metabolic tumour volume in diffuse large B cell lymphoma. *Eur J Nucl Med Mol Imaging.* 2018;45(7):1142-54.

22. Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging*. 2015;42(2):328-54.

23. Meignan M, Sasanelli M, Casasnovas RO, Luminari S, Fioroni F, Coriani C, et al. Metabolic tumour volumes measured at staging in lymphoma: methodological evaluation on phantom experiments and patients. *Eur J Nucl Med Mol Imaging*. 2014;41(6):1113-22.

24. Horwitz SM, Zelenetz AD, Gordon LI, Wierda WG, Abramson JS, Advani RH, et al. NCCN Guidelines Insights: Non-Hodgkin's Lymphomas, Version 3.2016. *J Natl Compr Canc Netw*. 2016;14(9):1067-79.

25. Khalil MM. *Basic science of PET imaging*. Cairo, Egypt: Springer; 2017:312-313

26. Adams HJ, de Klerk JM, Fijnheer R, Heggelman BG, Dubois SV, Nievelstein RA, et al. Prognostic superiority of the National Comprehensive Cancer Network International Prognostic Index over pretreatment whole-body volumetric-metabolic FDG-PET/CT metrics in diffuse large B-cell lymphoma. *Eur J Haematol*. 2015;94(6):532-9.

27. Xie M, Wu K, Liu Y, Jiang Q, Xie Y. Predictive value of F-18 FDG PET/CT quantization parameters in diffuse large B cell lymphoma: a meta-analysis with 702 participants. *Med Oncol*. 2015;32(1):446.

28. Schoder H, Noy A, Gonen M, Weng L, Green D, Erdi YE, et al. Intensity of 18fluorodeoxyglucose uptake in positron emission tomography distinguishes between indolent and aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2005;23(21):4643-51.

29. Hutchings M, Loft A, Hansen M, Ralfkiaer E, Specht L. Different histopathological subtypes of Hodgkin lymphoma show significantly different levels of FDG uptake. *Hematol Oncol*. 2006;24(3):146-50.

30. Cottereau AS, Lanic H, Mareschal S, Meignan M, Vera P, Tilly H, et al. Molecular Profile and FDG-PET Metabolic Volume at Staging in DLBCL-Response. *Clin Cancer Res*. 2016;22(13):3414-5.

국문 초록

미만성 거대B세포 림프종 환자들의 치료전 F-18 FDG PET/CT에서 평가한 대사종양체적의 NCCN-IPI에 대한 부가적인 예후 가치: NCCN-IPI 고위험군의 추가적인 계층적 분류

Qaid Ahmed Qaid Shagera

서울대학교 대학원

의학과 핵의학 전공

목적: 미만성 거대 B 세포 림프종 (diffuse large B-cell lymphoma, DLBCL)에서 치료전 F-18 FDG PET 에서 정량적 지표로 평가한 대사종양체적의 National Comprehensive Cancer Network International Prognostic Index (NCCN-IPI)에 따른 추가적인 추가적인 예후 가치를 평가하고자 하였다.

대상과 방법: 치료전 FDG-PET / CT 를 시행 한 103 명의 DLBCL 환자를 후향적으로 등록하였다. 총대사성 종양부피 (total metabolic tumor volume, TMTV)와 총병변 당분해능(total lesion glycolysis, TLG = MTV × SUVmean)는 SUVmax 2.5 를 기준으로 추정되었다. 임상 인자와 대사 매개 변수, 무진행 생존(progression-

free survival, PFS) 및 전체생존 (overall survival, OS) 사이의 관계를 테스트하기 위해 Kaplan-Meier 곡선과 Cox 회귀분석을 수행하였고, NCCN-IPI 에 의해 저위험군과 고위험군으로 나누어 평가하였다.

결과: 추적 관찰기간의 중앙값은 32 개월이었다. 3 년 PFS 와 O 는 각각 60 %와 73 %였다. $TMTV_{2.5}$ 가 낮은 군(246 cm3 미만)은 83 %의 3 년 PFS 및 92 %의 OS 을 나타냈으며, $TMTV_{2.5}$ 가 높은 군(246 cm3 이상)은 각각 41 %의 3 년 PFS 및 57 %의 OS 를 나타냈다 $P < 0.0001$) 단변량 분석에서, 높은 $TMTV_{2.5}$ 와 4 점 이상의 NCCN-IPI 은 열등한 PFS 와 OS 과 연관성이 있었으며 (각각 $P < 0.0001$)와 높은 TLG 도 비슷한 결과를 나타냈다. ($P = 0.004$ 와 $P = 0.005$) 다변량 분석에서 $TMTV_{2.5}$ 와 NC CN-IPI 는 각각 PFS ($P = 0.007$, $P = 0.009$)와 OS ($P = 0.017$, $P = 0.014$)의 독립적인 예측 인자들이었다. 또한, TMTV 는 고위험군 (NCCN-IPI ≥ 4, $n = 62$)의 환자들을 크게 다른 예후를 보이는 두 그룹으로 분리 할 수 있었다. $TMTV_{2.5}$ 가 낮은군은 3 년 PFS 가 75 %이고 OS 가 88 % 인 반면 TMTV 가 높은 군은 3 년 PFS 가 32 %이고 OS 가 47 %이었다 ($P = 0.003$ 및 $P = 0.004$). 그러나 TMTV 는 저 위험군 (NCCN-IPI = 0-3, $n = 41$)에서 환자의 예후를 더 이상 층화하지는 않았다.

결론: DLBC 환자에서 치료전 시행한 F-18 FDG PET 상, $TMTV_{2.5}$ 는 독립적인 예후를 보였다. $TMTV_{2.5}$ 가 NCCN-IPI 고위험 환자의 예후에 대한 추가적 예후 예측 인자로서 가치를 있음을 처음으로 발견하였다. 따라서 정량적 대사 매개변수인 TMTV 와 NCCN-IPI 의 결합된 정보는 예후예측을 향상시킬 수 있으며, 특히

NCCN-IPI 에 의한 고위험군의 DLBCL 환자에서 적극적인 치료 방침 결정에 임상적 도움이 될 수 있을 것이다.

주요어: FDG PET / CT, 미만성 B 세포 림프종, 대사성 종양부피, 예후

학생 번호: *2017-24441*

Acknowledgments

I am so grateful and thankful to my parents and family who always are the driving and motivating force to my success and progress. I wish them all the best herein and thereafter. A very special thanks to my wife and children who sacrificed a lot of their time seeking for the completion of my thesis.

I am grateful to my supervisor professor Gi Jeong Cheon for his endless support, patience, guiding and enlightening during my research and thesis writing. I will never forget his advice and kind words. Without his support, this work could not come into existence.

I like to give thanks to all the professors at the Department of Nuclear Medicine; Chairman Keon Wook Kang, vice chairman Dong Soo Lee, June Key Chung, Jin Chul Paeng and Eushin Edmund Kim. I would like to express my deepest gratitude to my colleagues; residents, fellows, physicists, radiochemists, technologists and the department's secretary for being my family away from my home.

Special gratitude goes out to all down at Research Fund and the National Research Foundation of Korea for helping and providing the funding for the work.

And finally, last but not least, also to all the committee professors for their valuable and insightful comments.

Thanks for all your encouragement!

Qaid Ahmed Qaid Shagera

December, 2018