Relationship Between Dual Time Point FDG PET/CT and Clinical Prognostic Indexes in Patients with High Grade Lymphoma: a Pilot Study

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Abstract

Purpose This study investigated the correlative relationship between metabolic parameters estimated from dual time point 2-deoxy-2-[¹⁸F] fluoro-D-glucose (¹⁸F-FDG) positron emission tomography/computerized tomography (PET/CT) and the clinical tools predicting the outcome of a lymphoma. We also measured metabolic and volumetric alterations between early and delayed ¹⁸F-FDG PET/CT in patients with high grade lymphoma (HGL).

Methods The samples were 122 lymph nodes and extralymphatic lesions from 26 patients diagnosed with HGL. All patients were applied to the International Prognostic Index (IPI), Ann Arbor stage, and revised IPI as clinical prognostic parameters. ¹⁸F-FDG dual time point PET/CT (DTPFP) consisted of an early scan 1 h after ¹⁸F-FDG injection and a delayed scan 2 h after the early scan. Based on an analysis of DTPFP, we estimated the standardized uptake value (SUV) of tumors from the early and delayed scans, retention index (RI) representing the percentage change between early and delayed SUV, and metabolic volume different index (MVDI) calculated using metabolic tumor volumes (MTV).

Results RI_{max} showed a multiple positive correlative relationship with stage and IPI in lesion-by-lesion analysis ($p < 0.01$). In the case of IPI, the high risk group exhibited higher RI_{max}

than the low risk group ($p = 0.004$). In the case of revised IPI, the RI_{max} of the low risk group were significantly lower than the intermediate and high risk groups, respectively ($p < 0.01$). The MVDIs of the best outcome group were decreased in comparison to the moderate outcome group ($p = 0.029$). There was a significant negative correlative relationship between RI_{max} and MVDI, and the inclinations for decreased MVDIs were slightly associated with increased RIs.

Conclusions RI_{max} extracted from DTPFP had a significant relationship to extranodal involvement, staging, IPI, and revised IPI. MVDI showed significant negative correlation with RI_{max}. Further large scale studies are warranted to support and extend these preliminary results.

Keywords Lymphoma · Fluorine 18-fluorodeoxyglucose (FDG) · Positron emission tomography/computed tomography (PET/CT) · International prognostic index · Metabolic tumor volume

Introduction

Malignant lymphoma (ML) is a malignant disease that originates from cells of the lymphatic system, and includes multiple inducing factors, diverse clinical manifestations, and immunohistochemical features [1]. The National Cancer Institute reported 69,740 new cases and 19,020 deaths from non-Hodgkin lymphoma (NHL) in the United States in 2013 [2]. In oriental countries, diffuse large B-cell lymphoma (DLBCL) in particular represents a considerable portion of the various types of NHLs [3]. Although there has been dramatic prognostic improvement with new treatment techniques, such as addition of rituximab (R) to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) in recent decades [4, 5], a little DLBCL patients seldom

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experience benefits from the R-CHOP regimen, with or without local radiation therapy. As such, it might be important to categorize patients with ML according to a prediction algorithm of prognosis before the start, or in the early stages of disease management.

In comparison to other malignancies, there are some more prognostic prediction systems such as the International Prognostic Index (IPI) and the International Working Group (IWG) response criteria with 2-deoxy-2- ^{18}F fluorodeoxyglucose (^{18}F -FDG) positron emission tomography/computed tomography (PET/CT) in lymphoma [6, 7]. Among them, the IPI-related criteria of revised IPI and age-adjusted IPI, are pretreatment prognostic indices, and revised IPI is reportedly a predictive marker in patients with DLBCL [8]. These could help hematological physicians to deal with individual specific management, and aid in predicting the long-term prognosis for each patient. Of course, although there are some limitations to distinguishing high risk groups with IPI in patients with R-CHOP [9], these prognostic standards have been accepted as initial risk stratification and basic prognosis models in ML management strategy.

Dual time point ^{18}F -FDG PET/CT (DTPFP) was introduced to differentiate benign disease from a malignant condition [10]. The basic mechanism of DTPFP is that with time cancer tissues increase ^{18}F -FDG uptake compared to the uptake of benign cells. In breast cancer, lung cancer, and head and neck cancers [11–13], DTPFP could have more accurate diagnostic accuracy and prognosis prediction. This potential is limited by the scarcity of reports concerning DTPFP in ML [14, 15]. To our knowledge, there are no publications evaluating the connection between quantitative parameters extracted from DTPFP, including volumetric measurement, and some specific prognostic factors particular to high grade lymphoma (HGL).

The purpose of this study was to investigate the correlative relationship between the quantitative and volumetric parameters estimated from DTPFP, and the clinical tools predicting lymphoma outcome, as well as to evaluate the measured metabolic and volumetric alterations between early and delayed ^{18}F -FDG PET/CT in patients with HGL.

Subjects and Methods

Subjects and Treatments

Between December 2009 and December 2014, 49 patients with newly diagnosed ML underwent DTPFP at the time of initial work up, prior to curative therapy. Among them, 23 patients were not enrolled in the current study. The causes of exclusion included low grade lymphoma or HL at final diagnosis ($n = 15$), other synchronous malignancy ($n = 2$), loss of delayed ^{18}F -FDG PET/CT ($n = 4$), and different target field

between early ^{18}F -FDG PET/CT and delayed ^{18}F -FDG PET/CT ($n = 2$). All patients with DLBCL and mantle cell lymphoma (MCL) received systemic chemotherapy with Rituximab (375 mg/m^2 on day 1), Cyclophosphamide (750 mg/m^2 on day 1), Doxorubicin (50 mg/m^2 on day 1), Vincristine (1.4 mg/m^2 , maximum 2 mg on day 1), and Prednisolone (100 mg/day on day 1–5), every 3 weeks (according to the standard R-CHOP regimen). The chemotherapy was delivered up to three cycles and involved field radiation therapy in stage I and II DLBCL, and a total of 6–8 cycles in stage III and IV DLBCL. The patients with peripheral T cell lymphoma (PTCL) and NK-T cell lymphoma (NKTL) received chemotherapy with standard CHOP regimen every 3 weeks up to three to six cycles, as with DLBCL, according to their stage. The one patient with NKTL received non-anthracycline based chemotherapy. She was treated with four cycles of the SMILE induction regimen (Dexamethasone, 40 mg/day on days 2–4; Methotrexate, 2 g/m^2 on day 1; Ifosfamide, 1.5 g/m^2 on days 2–4; L-asparaginase; 6000 U/m^2 on days 8, 10, 12, 14, 16, 18, and 20; and Etoposide, 100 mg/m^2 on days 2–4) prior to autologous hematopoietic stem cell transplantation. This retrospective research was approved by our Institutional Review Board (IRB No.2016-02-003).

Staging and Prognosis Prediction Models

All patients included in this study were classified by Ann Arbor stage, lactate dehydrogenase (LDH) level, and degree of extranodal involvement. As a pretreatment prognostic standard, IPI was applied to all patients and revised IPI was applied to all DLCL patients. IPI and revised IPI consist of five parameters (age, performance status, LDH, extranodal involvement, and stage) and were categorized into three different grades according to the number of each IPI factors (IPI: low (0), intermediate (1,2) and high risk (3–5) groups; revised IPI: best (0), moderate (1,2) and poorest outcome (3–5) groups) [3, 8, 9].

Imaging Protocol of DTPFP

All ^{18}F -FDG PET/CT studies were conducted with Gemini GXL 6 (Philips Healthcare, Hamburg, Germany) or Gemini TF 64 PET/CT systems (Philips Healthcare, Cleveland, Ohio, USA). All patients fasted for at least 6 h prior to ^{18}F -FDG injection, in order to sustain serum glucose concentrations $< 150 \text{ mg/dl}$. Patients were encouraged to receive adequate water intake or 500 ml of intravenous half-normal saline before testing. ^{18}F -FDG (about $3.7 \text{ MBq/body weight in kg}$) was injected into all patients 1 h prior to early ^{18}F -FDG PET/CT scanning. All patients received instruction of shallow breath and motion reduction during image acquisition. DTPFP was performed twice; the early scan ranged from mid-cranium to mid-thigh, and the delayed scan took place 120 min after the

early scan. For attenuation correction and anatomic information, a low-dose CT scan was obtained in the two PET/CT systems. The CT parameters were: 50 mA; 120 kV; 4 mm slice thickness; 4 mm increment; 0.83 pitch; 0.5 sec rotation time; and a matrix size of 512×512 . After CT scanning, emission data acquisition was performed caudocranially in the three-dimensional mode with a 144×144 matrix. The emission scan time at each position was 90 sec, which was the same in the early and delayed phases. The bed positions of the early and delayed scans were 7–12 and 3–11 beds, respectively. ^{18}F -FDG PET images were reconstructed with a three-dimensional row-action maximum likelihood algorithm (3D LOR-RAMLA) at Gemini GXL 6 PET/CT, and the standard Philips time-of-flight ordered-subsets expectation maximization reconstruction (33 subsets, three iterations) at GEMINI TF 64 PET/CT, respectively.

Image Analysis

All DTPFP images were reviewed and analyzed on Intellispace portal workstations (Philips Healthcare, Amsterdam, Netherlands). The significant positive standard was a conspicuous focus of FDG uptake within lymph node that was differentiated from adjacent surrounding tissue. All included lesions were interpreted by two experienced nuclear medicine physicians (JH Lee and SK Park, who are board-certified with 10 and 12 years of PET/CT description comprehension, respectively). Lesion axial diameters of all lymph nodes and extralymphatic lesions exceeded 1.5 cm. A region of interest (ROI) was estimated in each hypermetabolic lesion, including the hottest ^{18}F -FDG foci in early and delayed DTPFP scan, respectively. For semi-quantitative analysis of ^{18}F -FDG uptake, the standardized uptake value (SUV) was analyzed based on the patient's lean body mass (estimated decay-corrected ^{18}F -FDG concentration within ROI/administered dose/lean body mass). Maximum SUV (SUV_{max}) and mean SUV (SUV_{mean}) were calculated twice, in early and delayed scans, separately. The percentage change between early SUV and delayed SUV was estimated as a retention index (RI) as follows: $\text{RI} = (\text{Delayed SUV} - \text{Early SUV}) \times 100 / \text{Early SUV}$. The SUV_{max} was applied to this formula for estimation of RI_{max} , respectively. Metabolic tumor volumes (MTVs) were estimated with a fixed threshold set at 75% percentage of SUV_{max} in the lesion (VOI_{75}) (Fig. 1). In case adjacent VOI_{75} s overlapped with each other (30/122), each VOI_{75} was adjusted with a consensus drawn by two nuclear medicine physicians [16]. We calculated the percentage change between early VOI_{75} and delayed VOI_{75} as the metabolic volume difference index (MVDI), using the same method applied to evaluate RI. Reactive lymph nodes were excluded, and the definition of those was not differentiated from background ^{18}F -FDG activity regardless of size, and

showed no significant change of size or metabolism after treatment.

Statistical Analyses

The total estimated quantitative data are expressed as mean $\pm$ SD, and p values of less than 0.05 were considered statistically significant. Differences in SUV_{max} , SUV_{mean} , and MTV between early and delayed ^{18}F -FDG PET/CT were evaluated by a pair 2-tailed t-test at lesion-by-lesion analysis. The correlative relationship between metabolic or volumetric parameters and clinical factors was evaluated by Pearson's rank correlation at lesion-by-lesion analysis. The statistical differences of RI, MVDI, and SUVs according to IPIs and stage were determined using one-way analysis of variance (ANOVA) with Bonferroni post hoc test. Mann Whitney U test was used to investigate the difference according to LDH and extranodal involvement. All analyses were conducted using the SPSS software package (version 21.0, SPSS Inc., USA).

Results

Patient Characteristics

In this study, 26 patients (15 men and 11 women; mean age [$\pm$ SD], 57.5 ± 17.1 years) diagnosed with HGL were included, and other patient characteristics are summarized in Table 1. The clinical stages shown in this table were classified according to Ann Arbor Stage. Among them, 12 patients had elevated LDH (cutoff value; 300 mg/dl) and 16 patients had extranodal involvement. IPI was used to categorize patients into three groups: low risk ($n = 12$), intermediate risk ($n = 4$), and high risk ($n = 10$). Revised IPI classification was also applied to DLBCL patients: best outcome ($n = 7$), moderate outcome ($n = 4$), and poorest outcome ($n = 7$). Total estimated number of hypermetabolic lesions was 122 (extranodal lesions: 19). Lesion characteristics are summarized in Table 2. Of all lesions, only seven showed lowered SUVs of the delayed scan, with 83 lesions displaying decreased MTVs of the delayed scan, when compared to the early scan (Fig. 2).

Relationship Between Semi-quantitative Values of DTPFP and Volumetric Parameters

In the lesion-by-lesion analysis, significant correlative connections were found between the early SUV_{max} and delayed SUV_{max} , between early MTV and delayed MTV, and between early SUV_{mean} and delayed SUV_{mean} ($r = 0.970$, $r = 0.999$, and $r = 0.965$; $p < 0.001$, respectively). Significant negative correlative relationship was evident between MVDI and RI_{max} ($r = -0.272$, $p = 0.002$) (Fig. 3).

Fig. 1 FDG PET MIPs of stage I diffuse large B cell lymphoma. (a) Early FDG PET MIP shows a hypermetabolic lymph node (arrow) along right cervical level II. Metabolic and volumetric parameters were as follows: early SUV_{max} 11.5; early MTV 6528 mm³. (b) Delayed FDG

PET was performed 2 hours after early scan. Metabolic and volumetric parameters were as follows: delayed SUV_{max} 13.3; early MTV 6720 mm³. RI_{max} and MVDI were 15.72% and 4.81%, respectively

Relationship Between Metabolic Parameters Derived from DTPFP and Clinical Features

In lesion-by-lesion analysis, averages of delayed SUV_{max} and delayed SUV_{mean} were significantly higher than early SUV_{max} and early SUV_{mean} ($p < 0.001$, both), although the average of early MTV was higher than delayed MTV, as opposed to SUVs (Table 2). When evaluating the relationship between DTPFP parameters and IPI, revised IPI and stage, one way ANOVA with Bonferroni post hoc test was used. The high risk group exhibited higher RI_{max} than the low risk group ($p = 0.004$) (Fig. 4a). In the case of revised IPI, the RI_{max}

(Fig. 4b) of the best outcome group were significantly lower than the moderate and poor outcome groups, respectively ($p = 0.003$ and $p < 0.001$). According to Ann Arbor stage, RI_{max} was significantly increased stepwise ($p = 0.001$), with the exception of stage I (Fig. 4c). RI_{max} in patients with extranodal involvements were significantly higher than those without extranodal involvements (Fig. 4d) ($p < 0.001$). There was no significant relationship between MVDIs and IPI (Fig. 4e) ($p = 0.221$). However, the MVDIs of the best outcome group were decreased in comparison to the moderate outcome group ($p = 0.029$) in the case of revised IPI, although there is little difference between moderate and poor outcome groups (Fig. 4f). MVDI did not show significant difference according to stage and extranodal involvement (Fig. 4g and h) ($p = 0.608$ and $p = 0.456$).

Table 1 Patients characteristics

Characteristics	
Age (years)	
Mean ± SD, (range)	57.5 ± 17.1 (15 - 82)
Sex	
Male/female	15/11
Histologic type (%)	
DLBCL	18 (69)
PTCL	4 (15)
NKTL	3 (12)
MCL	1 (4)
Stage (lesions, %)	
I	5 (8, 6.6)
II	11 (37, 30.3)
III	5 (40, 32.8)
IV	5 (37, 30.3)

DLBCL diffuse large B cell lymphoma; PTCL peripheral T-cell lymphoma; NTCL natural killer/T-cell lymphoma; MCL mantle cell lymphoma

Table 2 Lesion characteristics

Characteristics	Mean ± SD, range
Early SUV _{max}	7.13 ± 4.16 (1.97 – 19.82) ^a
Early SUV _{mean}	5.35 ± 3.11 (1.55 – 16.28) ^a
Early MTV (mm ³)	25542.89 ± 176361.87 (640 – 1884416) ^b
Delayed SUV _{max}	9.39 ± 5.75 (2.40 – 27.51) ^a
Delayed SUV _{mean}	6.79 ± 5.75 (1.64 – 21.32) ^a
Delayed MTV (mm ³)	18540.81 ± 117561.56 (580 – 1246400) ^b
RI _{max}	29.62 ± 18.08 (-15.46 – 75.63)
MVDI	-9.08 ± 20.01 (-59.26 – 66.67)

MTV, metabolic tumor volume; RI, retention index; MVDI, metabolic volume different index

^a Delayed SUV_{max} and SUV_{mean} were significantly increased compared to early SUV_{max} and SUV_{mean} ($p < 0.001$, both).

^b Delayed MTV was significantly decreased compared to early MTV.

Fig. 2 A case of intestinal diffuse large B cell lymphoma (arrow). Early MIP (a) shows intense hypermetabolic lesion of small bowel (arrow) (SUV_{max} 15.2; SUV_{mean} 10.5; MTV 71744 mm³). In delayed MIP (b), the values of SUVs (SUV_{max} 18.7; SUV_{mean} 14) was increased but MTV (51200 mm³) was decreased, comparing early scans. This case shows positive RI_{max} (22.7%) but negative MVDI (-28.6%)

Discussion

This study demonstrates that there are variable significant relationships between the metabolic parameters, such as RI derived from DTPFP, and several well-known clinical diagnostic tools used to predict the prognosis of lymphoma patients. In addition, MVDI reflecting metabolic volumetric differences between early and delayed ¹⁸F-FDG PET/CT shows significant negative correlation with RI, and slight negative connection with revised IPI. To the best of our knowledge, only a few published reports have evaluated RI and MVDI, matching several clinical parameters, such as stage, LDH and IPI predicting overall prognosis of ML.

¹⁸F-FDG PET/CT has played an important role in treatment response evaluation since ¹⁸F-FDG PET/CT was applied

in earnest to lymphoma in 1990 [17]. As ¹⁸F-FDG PET/CT can demonstrate not only lesion size and attenuation change, but also specific intrinsic metabolism, it has resolved the insolubility problems of the IWG response criteria [6], such as residual mass possibly reflecting partial response (PR) or complete response unconfirmed (CRu) in 40% of patients with aggressive NHL and over 60% of patients with HL [18, 19]. However, as the interpretation of the positive or negative qualitative standards of ¹⁸F-FDG PET/CT might have varied with regards to each researcher, the range of the negative predictive value and positive predictive value of early ¹⁸F-FDG PET/CT were found to be 50–100% and 44–100% [20–22], respectively. In addition, although grades of ¹⁸F-FDG uptake after early ¹⁸F-FDG PET/CT could be defined according to separate studies, interobserver variability might inevitably be present. In order to overcome these demerits of qualitative assessment, quantitative analysis of ¹⁸F-FDG PET/CT has been applied to interim monitoring, as well as the evaluation of posttreatment responses in HGL. So, the principal purpose of our study was to investigate whether the metabolic and volumetric parameters derived from DTPFP could be utilized to evaluate the relationship between these factors and clinical prognostic guidelines such as IPI in especially HGL.

Although many clinicians have tried to evaluate the role of DTPFP by comparing single ¹⁸F-FDG PET/CT scan, there is little in the literature related to ML. In 2012, Nakayama et al. [14] reported that delayed SUV_{max} and the gap between early and delayed SUV_{max} showed significant potential to discriminate benign lymph nodes and ML lesions. However, RI did not show effective calibration potential, compared with other factors. Although there has continued to be a debate over DTPFP, a considerable number of published reports have mentioned the possibility of predicting diagnostic accuracy and prognosis of RI [12, 23, 24]. In many cancers, including

Fig. 3 Pearson's rank correlation analyses between RIs and volumetric parameter. In the case of MVDI, there are significant weak negative relationships associated with RI_{max} ($r = -0.272$, $p = 0.002$)

Fig. 4 The relationship between metabolic parameters and $RI_{\max}$ values (**a–d**). $RI_{\max}$ values show significant difference according to each grade of IPI (**a**) and revised IPI (**b**) ($p < 0.01$, both). According to Ann Arbor stage, $RI_{\max}$ (**c**) was significantly increased stepwise ($p = 0.001$), with the exception of stage I. $RI_{\max}$ in positive extranodal involvement group is higher than negative group (**d**) ($p < 0.001$). The relationship between metabolic parameters and MVDI (**e–h**). There was no significant relationship between MVDIs and IPI (**e**) ($p = 0.221$). The MVDIs of the best outcome group were decreased in comparison to the moderate outcome group (**f**) ($p = 0.029$). The MVDIs did not show significant difference according to stage (**g**) and extranodal involvement (**h**) ($p = 0.608$ and $p = 0.456$)

breast cancer [11, 25], colorectal cancer [26], lung cancer [21, 22], pancreatic cancer [27], cervical cancer [28], and pediatric tumors [29]. DTPFP has increased diagnostic sensitivity, allowed a high degree of coordination with immunohistochemical markers, distinguished between benign and malignant tumors, and increased the capacity to predict prognosis, compared to established one-time ^{18}F -FDG PET/CT. It does not seem that, in any specific cancer type, there is a significant potential of DTPFP to show a higher sensitivity or specificity, considering the many published reports regarding DTPFP. In addition, from the outset of this current study, it was hypothesized that with increased interval between early and delayed ^{18}F -FDG PET/CT, metabolic parameters extracted from DTPFP can reflect more unique cancerous features than from universally performed one time ^{18}F -FDG PET/CT about 60 min after ^{18}F -FDG injection. The time interval of our study between ^{18}F -FDG injection and delayed ^{18}F -FDG PET/CT took about 180 min; because of the sufficient delay time, RI can significantly differ according to stage and IPI grade. Most DTPFP applied to oncologic reports show less than about 90 min between early and delayed ^{18}F -FDG PET/CT.

Recently, intratumoral metabolic heterogeneity, estimated from ^{18}F -FDG PET/CT, has been utilized to evaluate the prognosis of cancer patients, and investigate the distinction between benign and malignant tumors [30, 31]. In our opinion, RI or MVDI extracted from DTPFP could reflect or support these unique cancerous heterogeneities. It is presumed that as aggressive cancer tissue has a greater chance of containing active metabolic components reflecting an aggressive prognosis, after a period, maximal tumoral ^{18}F -FDG uptake of this aggressive part could be more increased than uneven mixed tumor tissue even in HGL. So, RIs might be in agreement with the grade of IPI and revised IPI. Meanwhile, MVDI was shown to be inversely correlated with RI. Decreased trend of MVDI contrary to increased RI in HGL could represent the tumor heterogeneity in a different way. Kitao et al. [32] showed that when using a similar MTV measurement method as our tumor segmentation method, delayed MTV was significantly decreased compared to early MTV ($p < 0.01$), which agrees with our results. This was possibly related to the feature of relative threshold method applied to MTV. It is presumed

that delayed MTVs calculated with a relative threshold as 45% or 75% of SUV could be smaller than those calculated with a fixed threshold as $\text{SUV} = 2.5$ because most cancer tissues at delayed scan have more FDG uptake than early scan. The results obtained in recent studies suggest that there was no significant difference between the early and delayed MTV of lung cancer, in cases applying fixed threshold method or gradient-based method [32, 33]. In addition, MVDI might be one of the prognostic markers in DLBCL patients, based on a significant inverse relationship with the revised IPI grade.

This preliminary study has several limitations. First, the total number of patients was not sufficient to examine with statistical power. However, total lesions enrolled in this study were sufficient to allow a preliminary evaluation. Second, the enrolled patients did not divide effectively according to the Lugano response criteria, and showed insignificant results (not shown), because of a better prognosis of ML patients. Third, in comparison to other reports and practical purposes, our cut-off threshold of 75% SUV applied to MTV measurement might be higher than other cut-off values. This was why the application of high cut off threshold was better than other methods to effectively distinguish between neighboring lesions. To overcome these abovementioned drawbacks, further long-term studies involving a larger number of patients are required to validate the exact relationship between the multiple clinical parameters predicting prognosis and diverse metabolic parameters extracted from DTPFP in HGL.

Conclusion

$RI_{\max}$ differed significantly according to stage, IPI, and revised IPI which is regarded as a prognostic marker of ML. Also, MVDI showed a significant inverse relationship to RI indexes and weak negative connection with revised IPI. According to this preliminary study, the metabolic parameters of $RI_{\max}$ and MVDI could be useful imaging markers to predict patient prognosis in HGL before chemotherapy.

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Compliance with Ethical Standards

Conflict of Interest Jai Hyuen Lee and Do Hyoun Lim declare that they have no conflict of interest.

Ethical Statement All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Review Board of Dankook University Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

References

- Huh J. Epidemiologic overview of malignant lymphoma. *Korean J Hematol*. 2012;47:92–104.
- Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA: a cancer journal for clinicians*. *CA Cancer J Clin*. 2013;63:11–30.
- Wilder RB, Rodriguez MA, Medeiros LJ, Tucker SL, Ha CS, Romaguera JE, et al. International prognostic index-based outcomes for diffuse large B-cell lymphomas. *Cancer*. 2002;94:3083–88.
- 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;346:235–42.
- 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;123:837–42.
- Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol*. 1999;17:1244.
- Salles G, de Jong D, Xie W, Rosenwald A, Chhanabhai M, Gaulard P, et al. Prognostic significance of immunohistochemical biomarkers in diffuse large B-cell lymphoma: a study from the Lunenburg Lymphoma Biomarker Consortium. *Blood*. 2011;117:7070–78.
- 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;109:1857–61.
- Ziepert M, Hasenclever D, Kuhnt E, Glass B, Schmitz N, Pfreundschuh M, et al. Standard International prognostic index remains a valid predictor of outcome for patients with aggressive CD20+ B-cell lymphoma in the rituximab era. *J Clin Oncol*. 2010;28:2373–80.
- Matthies A, Hickeson M, Cuchiara A, Alavi A. Dual time point 18F-FDG PET for the evaluation of pulmonary nodules. *J Nucl Med*. 2002;43:871–5.
- Uesaka D, Demura Y, Ishizaki T, Ameshima S, Miyamori I, Sasaki M, et al. Evaluation of dual-time-point 18F-FDG PET for staging in patients with lung cancer. *J Nucl Med*. 2008;49:1606–12.
- Kumar R, Loving VA, Chauhan A, Zhuang H, Mitchell S, Alavi A. Potential of dual-time-point imaging to improve breast cancer diagnosis with (18)F-FDG PET. *J Nucl Med*. 2005;46:1819–24.
- Sanghera B, Wong WL, Lodge MA, Hain S, Stott D, Lowe J, et al. Potential novel application of dual time point SUV measurements as a predictor of survival in head and neck cancer. *Nucl Med Commun*. 2005;26:861–7.
- Nakayama M, Okizaki A, Ishitoya S, Sakaguchi M, Sato J, Aburano T. Dual-time-point F-18 FDG PET/CT imaging for differentiating the lymph nodes between malignant lymphoma and benign lesions. *Ann Nucl Med*. 2013;27:163–9.
- Shinya T, Fujii S, Asakura S, Taniguchi T, Yoshio K, Alafate A, et al. Dual-time-point F-18 FDG PET/CT for evaluation in patients with malignant lymphoma. *Ann Nucl Med*. 2012;26:616–21.
- Orlhac F, Soussan M, Maisonneuve JA, Garcia CA, Vanderlinden B, Buvat I. Tumor texture analysis in 18F-FDG PET: relationships between texture parameters, histogram indices, standardized uptake values, metabolic volumes, and total lesion glycolysis. *J Nucl Med*. 2014;55:414–22.
- Hoekstra OS, Ossenkuppe GJ, Golding R, Van Lingen A, Visser G, Teule G, et al. Early treatment response in malignant lymphoma determined by planar fluorine-18-fluorodeoxyglucose scintigraphy. *J Nucl Med*. 1993;34:1706.
- Surbone A, Longo DL, DeVita Jr VT, Ihde DC, Duffey PL, Jaffe ES, et al. Residual abdominal masses in aggressive non-Hodgkin's lymphoma after combination chemotherapy: significance and management. *J Clin Oncol*. 1988;6:1832–37.
- Bodet-Milin C, Eugène T, Gastinne T, Bailly C, Le Gouill S, Dupas B, et al. The role of FDG-PET scanning in assessing lymphoma in 2012. *Diag int Imaging*. 2013;94:158–68.
- Haioun C, Itti E, Rahmouni A, Brice P, Rain JD, Belhadj K, et al. [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. *Blood*. 2005;106:1376–81.
- Weber WA. 18F-FDG PET in non-Hodgkin's lymphoma: qualitative or quantitative? *J Nucl Med*. 2007;48:1580–82.
- Mikhael NG, Hutchings M, Fields PA, O'Doherty MJ, Timothy AR. FDG-PET after two to three cycles of chemotherapy predicts progression-free and overall survival in high-grade non-Hodgkin lymphoma. *Ann Oncol*. 2005;16:1514–23.
- Chan W, Ramsay SC, Szeto ER, Freund J, Pohlen JM, Tarlinton LC, et al. Dual-time-point 18F-FDG-PET/CT imaging in the assessment of suspected malignancy. *J Med Imaging Radiation Oncol*. 2011;55:379–90.
- Xiu Y, Bhutani C, Dhurairaj T, Yu JQ, Dadparvar S, Reddy S, et al. Dual-time point FDG PET imaging in the evaluation of pulmonary nodules with minimally increased metabolic activity. *Clin Nucl Med*. 2007;32:101–5.
- Zytoon A, Murakami K, El-Kholy M, El-Shorbagy E. Dual time point FDG-PET/CT imaging... Potential tool for diagnosis of breast cancer. *Clin Radiol*. 2008;63:1213–27.
- Fuster D, Lafuente S, Setoain X, Navales I, Perissinotti A, Pavia J, et al. Dual-time point images of the liver with 18 F-FDG PET/CT in suspected recurrence from colorectal cancer. *Revista Española de Medicina Nuclear e Imagen Molecular (English Edition)*. 2012;31:111–6.
- Higashi T, Saga T, Nakamoto Y, Ishimori T, Mamede MH, Wada M, et al. Relationship between retention index in dual-phase (18)F-FDG PET, and hexokinase-II and glucose transporter-1 expression in pancreatic cancer. *J Nucl Med*. 2002;43:173–80.
- Ma SY, See LC, Lai CH, Chou HH, Tsai CS, Ng KK, et al. Delayed (18)F-FDG PET for detection of paraortic lymph node metastases in cervical cancer patients. *J Nucl Med*. 2003;44:1775–83.
- Costantini DL, Vali R, Chan J, McQuattie S, Charron M. Dual-time-point FDG PET/CT for the evaluation of pediatric tumors. *Am J Roentgenol*. 2013;200:408–13.
- Kim DH, Jung JH, Son SH, Kim CY, Hong CM, Oh JR, et al. Prognostic significance of intratumoral metabolic heterogeneity on 18F-FDG PET/CT in pathological N0 non-small cell lung cancer. *Clin Nucl Med*. 2015;40:708–14.
- Tixier F, Le Rest CC, Hatt M, Albarghach N, Pradier O, Metges JP, et al. Intratumor heterogeneity characterized by textural features on baseline 18F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. *J Nucl Med*. 2011;52:369–78.
- Kitao T, Hirata K, Shima K, Tamaki N. Influence of uptake time on metabolic tumor volume (MTV) and total lesion glycolysis (TLG) on FDG PET in non-small cell lung cancer (NSCLC). *Soc Nuclear Med*. 2014;55 Suppl 1:1597.
- Liu H, Chen P, Wroblewski K, Hou P, Zhang CP, Jiang Y, et al. Consistency of metabolic tumor volume of non-small-cell lung cancer primary tumor measured using 18F-FDG PET/CT at two different tracer uptake times. *Nucl Med Commun*. 2016;37:50–6.