

Diagnostic Value of ^{18}F -PET/CT in Patients with Primary Lymphoma and the Prognostic Value of Maximum Standardized Uptake Value (SUV_{\max}) in Diffuse Large B-Cell Lymphoma (DLBCL)

Lin Zhu

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Kai Nie

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Yinan Chen

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

Jing Liu

Shanghai Zhabei District Central Hospital

Yongxing Xiao

Shanghai Changzheng Hospital

Hong Yu (✉ yuhongphd@163.com)

Shanghai Chest Hospital: Shanghai Jiao Tong University Affiliated Chest Hospital

<https://orcid.org/0000-0002-1094-4334>

Research Article

Keywords: ^{18}F -PET/CT, SUV_{\max} , lymphoma, diffuse large B-cell lymphoma, Ki-67 index

Posted Date: May 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-511261/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background

The diagnostic accuracy of ^{18}F -PET/CT was assessed in patients with primary lymphoma and the clinical application value of SUV_{\max} was determined.

Results

The diagnostic accuracy of a total of 97 patients with initial ^{18}F -PET/CT scans between January 2015 and February 2020 were assessed, and the SUV_{\max} was compared according to the different pathological subtypes. The relationship between SUV_{\max} and immunophenotype, clinical characteristics, and genetic types were estimated. According to the pathological results, 10 cases were misdiagnosed by PET/CT, and the accuracy was about 90%. Statistical analysis did not reveal a significant difference between Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL) ($p = 0.9071$). Among NHL, the average SUV_{\max} was statistically different between diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) ($p = 0.0004$), FL and natural killer/T-cell lymphoma ($p = 0.0078$), FL and peripheral T-cell lymphoma (PTCL) ($p = 0.0117$), DLBCL and mantle cell lymphoma (MCL) ($p = 0.0294$). In patients with DLBCL, SUV_{\max} was correlated with the expression level of proliferation index Ki-67 ($r = 0.33, p = 0.018$), while average SUV_{\max} shows no difference between various immunophenotype expression levels, ages, gender, skeletal invasion situations, clinical grade stages, international prognostic index (IPI) score, and different gene types (germinal center B cell-like (GCB) and non-GCB).

Conclusions

Although ^{18}F -PET/CT had a marked diagnostic value in patients with primary lymphoma, some misdiagnosis was probable. The SUV_{\max} is valuable in the differential diagnosis of different pathological types of NHL. Simultaneously, the SUV_{\max} of patients with DLBCL correlated with Ki-67 might reflect the tumor invasiveness, thereby revealing a prognostic value.

Background

A lymphoma is a group of malignant tumors originating from lymph nodes or extranodal lymphoid tissues with high heterogeneity and classification complexity. ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) has high clinical value in staging and re-staging, evaluation of curative effect, follow-up after treatment, and prognosis in lymphoma [1, 2]. ^{18}F -FDG PET/CT can effectively identify areas that are missed or lymphoma lesions that are misclassified by CT alone. Although many researches have studied the application of ^{18}F -FDG in lymphoma, most of them focus on the application in grade or prognosis evaluation in one specific lymphoma subtype [3–5].

However, the use of ^{18}F -FDG PET/CT imaging for the analysis of the metabolic activity (uptake of FDG) difference among various lymphoma subtypes have not yet been addressed adequately. The uptake of FDG may be different in lymphomas of different pathological subtypes, as well as the same pathological subtypes with different immunophenotypes. Although some previous studies considered that the level of ^{18}F -FDG uptake in lymphoma lesions is related to the grade and expression level of some immunophenotypic molecules of the tumor, the phenomenon is yet controversial and deserves further research [5–8]. For example, ki67 was confirmed to be related to SUV_{\max} in some studies, but in some studies it was proved to be unrelated [4, 9, 10]. In order to reveal the performances for the variable ^{18}F -FDG uptake in different types of lymphoma lesions and the value of uptake in judging the prognosis of lymphoma, we compared and analyzed the ^{18}F -FDG uptake in lymphoma lesions among 97 patients with newly diagnosed lymphoma and evaluated the accuracy of PET-CT diagnosis. Consecutively, the difference in uptake among different pathological subtypes was assessed. In addition, we explored the correlation between uptake value and clinical features, prognosis index [international prognostic index (IPI) factors], gene expression and different immunophenotypes of patients with diffuse large B-cell lymphoma (DLBCL).

Methods

1. Patients

We collected data on lymphoma patients, who underwent ^{18}F -FDG PET-CT imaging at the Shanghai Chest Hospital, Shanghai Changzheng Hospital and Dongfang Hospital from January 2015 to February 2020. According to the criteria for inclusion and exclusion, 97 patients with NHL were enrolled in this study, including 50 males and 47 females, aged 18–85 (54.3 ± 16.9) years. A total of 5 cases were Hodgkin's lymphoma (HL), and the remaining were non-Hodgkin's lymphoma (NHL). Among non-Hodgkin's lymphoma, 57 cases were diffused large B-cell lymphoma (DLBCL), 8 were follicular lymphomas (FL), 7 were natural killer (NK)/T-cell lymphomas, 8 were peripheral T-cell lymphomas (PTCL), 4 were mucosa-associated lymphoid tissue (MALT), 4 were mantle cell lymphomas (MCL), and the remaining 4 were diagnosed as NHLs but the specific pathological type not clarified. According to the result of pathology, all the patients were enrolled according to the following criteria: (1) diagnosed by pathology, and detailed immunohistochemical results were included in the diagnosis; (2) untreated; (3) PET- CT imaging and pathological examination did not exceed 4 weeks as assessed by the same method; (4) the highest FDG uptake area in the lesion was coherent to that in the biopsy or operation area. Patients, who had undergone surgery or received chemotherapy, were excluded. Table 1 summarizes the characteristics of all included patients.

2. ^{18}F -FDG PET/CT imaging and interpretation

2.1 Imaging method

All patients underwent staging ^{18}F -FDG PET/CT before any treatment (local surgery or chemotherapy). In both hospitals, Philips GXL 16 PET-CT (Philips Medical Systems, Inc., Cleveland, OH, USA) was used as the imaging device. The imaging agent ^{18}F -FDG was provided by Shanghai Atomic Kexing Pharmaceutical Co., Ltd. with radiochemical purity >95%. ^{18}F -FDG was injected after at least 6 h fasting and the glucose level <10 mmol/L. The dose of ^{18}F -FDG was 3.70–5.18 MBq/kg, and the images were acquired at 60±10 min after the injection. Written consent was obtained from all hospitals before the study.

2.2 Detection of metabolism activity of lymphoma

The SUV_{max} of lymphoma was obtained by the average of 4–8 consecutive layers of lesions on PET images. For every layer, a manual region of interest (ROI) over the area of maximum activity was drawn, and SUV_{max} was estimated as the highest SUV of the pixels within the ROI. In the case of single lesions, the SUV_{max} was measured directly, while for multiple lesions, the highest SUV_{max} value in the whole body was considered as the SUV_{max} value of the patient, and if the intake was negative value, the SUV_{max} value of the largest lesion in the whole body was considered as the SUV_{max} value of the patient.

2.3 Immunophenotype, clinical information, and gene information

Immunohistochemistry was used for detecting the samples. The specimens were fixed in 10% neutral buffer formaldehyde solution, embedded in paraffin, and sliced into 4-μm-thick sections. The staining was performed for molecules Bcl-6, Bcl-2, CD10, CD23, Mum-1, Pax-5, Ki67, CD2, CD3, CD5, EMA, CD138, CD30, and ALK, and the results were determined based on the number of positively stained cells recorded. The results were recorded as follows: negative (-): <10%; weakly positive (+): 10–30%; moderately positive (++) 30–75%; strongly positive (+++): >75%; an expression of ≥10% is considered positive. The clinical characteristics of the patients, including age (according to the age division regulation of WHO, the patients were divided into youth group with age <44 years, middle-age group with age 45–59 years, and elderly group with age >60 years), gender (male and female), tumor clinical grade stage (stage I/II was divided into low-grade group and stage III/IV was classified into the high-grade group), presence of bone metastasis, and IPI score (low-risk, IPI 0–2 or aaipi 0-1 and high-risk, IPI 3–5 or aaipi≥2) were assimilated. Consecutively, the genotype of the patients was assessed (GCB or non-GCB).

2.4 Statistical analysis

All statistical analyses were conducted using SAS 9.2 software (SAS Institute, Carey, NC). The statistical significance of SUV_{max} between pathological subtype groups, different levels of molecule expression groups and different gene expression groups was analyzed by Fisher's exact test or Student's t-test and Wilcoxon two-sample test. The correlation between SUV_{max} and Ki-67 was evaluated by Pearson's correlation test. p<0.05 was considered statistically significant.

Results

3.1 Accuracy of PET-CT diagnosis

A total of 10 diagnostic errors were detected among all the enrolled patients, of which, 2 were misdiagnosed with the negative uptake of PET-CT; the pathological subtypes were MALT and DLBCL (Fig. 1), and SUV_{max} values were 0.8 and 2.1, respectively. The remaining 8 cases were misdiagnosed as high uptake of PET-CT. The pathological subtypes included 5 cases with DLBCLN, 1 with FL, 1 with classic HL, and 1 with NHL, whose specific subtype could not be determined. All cases of missed diagnosis occurred in the gastrointestinal tract and the detail information are showed in Table 2.

3.2 Analysis of the metabolic activity of different lymphoma subtypes

Different lymphoma subtypes have significantly different metabolic activities. Among all included patients, the highest lesion was measured in the abdominal lymph nodes of a patient with DLBCL with SUV_{max} value of 51. (Fig. 2). Based on the pathological type of grouping, the average SUV_{max} value was calculated for each pathological type. The average SUV_{max} of HL was 16.8 ± 5.3 , and that of NHL was 17.0 ± 5.1 ; among these, the value for DLBCL was 18.9 ± 4.9 , FL was 7.8 ± 1.4 ; PTCL was 16.4 ± 4.9 ; NK/T-cell lymphoma was 18.7 ± 2.6 ; MALT was 13.7 ± 4.6 , and MCL was 9.2 ± 3.4 . The detail information was listed in Table 3. Statistical analysis did not reveal any significant difference between HL and NHL ($p = 0.9071$). Among NHL, the mean SUV_{max} differed significantly between DLBCL and FL ($p = 0.0004$), FL and NK/T-cell lymphoma ($p = 0.0078$), FL and PTCL ($p = 0.0117$), and DLBCL and MCL ($p = 0.0294$) (Fig. 3A).

3.3 Relationship between major clinical indications, immunophenotype molecular expression, and gene expression in DLBCL and SUV_{max}

As DLBCL has the highest incidence in China, the largest proportion of cases would allow further exploration of the correlation between SUV_{max} and the expression of various immune markers in DLBCL. The metabolic activity and the main immunophenotype of 57 cases of DLBCL subtype are summarized in Table 4. The statistical analysis of the average SUV_{max} showed no difference in different gender ($p = 0.907$), different ages [young (< 44-year-old, 14.6 ± 3.9), middle-aged (45–59-year-old, 18.6 ± 8.1), elderly (> 60-year-old, 20.9 ± 10.5), $p = 0.226$], skeletal invasion ($p = 0.749$), different IPI groups ($p = 0.1264$), different clinical stages ($p = 0.0996$) and gene expression (GCB and non-GCB groups, $p = 0.3819$). The comparison of SUV_{max} value between positive and negative groups based on the immunohistochemical index of Bcl-6, BCL-2, CD10, CD23, Mum-1, Pax-5, EMA, CD138, CD30, and ALK were made and these results did not show any significant difference ($p > 0.05$); However, the SUV_{max} value exhibited a fair correlation with the expression rate of proliferation marker Ki-67 in patients with DLBCL ($r = 0.33$, $p = 0.018$) (Fig. 3B).

Discussion

PET-CT is critical for the detection of lymphoma, several previous studies have proved that the application of PET-CT plays a major role in the diagnosis, assessment of treatment outcome, and

prognosis of lymphoma [11–13]. Juweid et al. carried out the Imaging Subcommittee of International Harmonization Project, which suggested PET-CT as a routine monitoring method in the treatment of lymphoma in the future. Although the utility of PET/CT in lymphoma has been continually studied, few studies have focused on its misdiagnosis rate and missed diagnosis, as well as the analysis of the characteristics of these cases. Therefore, among nearly 100 cases of lymphoma, we were concerned about the rate of misdiagnosis of PET-CT. In the current study, a final confirmation by pathology retrieved 10/97 lymphoma cases that were either misdiagnosed or missed in the initial PET-CT scan. Our multicenter study showed that the misdiagnosis rate of PET/CT was approximately 10.3%; 2/10 patients were missed diagnosis and negative on PET-CT with no uptake. Both cases were lymphomas of gastrointestinal system that were proved to be MALT by pathology, which agrees the findings of Hoffmann et al. and the inert biological behavior of MALT. [14, 15] Hoffmann et al. firstly described that gastric MALT lymphoma was not ¹⁸F-FDG avid tumor and concluded that FDG-PET is not useful for staging and follow-up of MALT-type lymphoma; However, other authors investigated the ¹⁸F-FDG PET/CT performance in the evaluation of MALT lymphoma and the results were flexible and achieved a wide range of conclusions [16–19]. This phenomenon prompted the present study and based on our results, it seems that ¹⁸F-FDG PET/CT was not recommended in these patients who are suspected of having gastric MALT lymphoma. In future studies, we will collect additional cases to verify the PET-CT findings of the gastrointestinal MALT. The other 8 cases were misdiagnosed, half of these were localized in the gastrointestinal tract, putatively due to the specific FDG uptake pattern of lymphoma in the gastrointestinal tract and this phenomenon is consistent with many previous studies that primary gastrointestinal lymphoma is a specific type of digestive system tumor and its FDG uptake pattern is more likely to have low intake due to physiologic FDG activity in the gastrointestinal tract although variability in the degree of uptake occurred in various histologic subtypes of primary gastrointestinal lymphoma [17, 20, 21]. Hwang et al. also confirmed that SUV_{max} can be used as a prognostic marker for gastrointestinal lymphoma as it differed markedly from other gastrointestinal cancers and is one of the reliable differential diagnostic criteria [22, 23]. However, the disease is insidious in onset and still easy to be misdiagnosed and missed in the examination; In this study, two of the misdiagnosed cases were misdiagnosed as inflammation, while the remaining were misdiagnosed as other tumors. Thus, although the application of PET-CT has greatly improved the diagnosis rate of lymphoma, it is still necessary to focus on the characteristic manifestations of lymphoma and differentiate it from other benign lesions or other tumors.

The definite diagnosis of different lymphoma subtypes plays a key role in the subsequent treatment and prognosis of the patient and several previous studies have focused on SUV_{max}, but the value of PET-CT in the differential diagnosis of lymphoma subtypes remains controversial [24–26]. In this study, the main subtypes of NHL and HL were assessed, and the SUV_{max} of each pathological subtype was estimated. The current study showed that although no significant difference was observed in HL and NHL, the SUV_{max} value of FL was significantly lower than other subtypes, and varied significantly from DLBCL, PTCL, and NK/T cell lymphoma. Moreover, a significant difference was detected between DLBCL and MCL ($p = 0.0294$), indicating that PET-CT is not only useful in detecting and finding the lesions but also

provides information in the differential diagnosis of lymphoma. Thus, help determine the pathological subtypes of lymphoma and develop an appropriate treatment plan, which is considered significant.

The incidence of DLBCL in China is > 40% with respect to NHL, which is similar to our collected cases. We aspire to further analyze the correlation between the clinical indicators and prognostic indicators with SUV_{max} in DLBCL as the immunophenotype is critical for determining follow-up treatment plan for different patients; The results showed that SUV_{max} was positively correlated with the expression of Ki-67 in B cells. Although there have been several studies on Ki-67 in lymphoma, whether SUV_{max} is related to Ki-67 is yet controversial. For example, studies of Storto et al. and Novelli et al. showed that the Ki-67 expression did not relate to SUV_{max} in T-cell NHL and MALT [5, 8], while the current study was similar to that of Watanabe et al. [27], which proved that SUV_{max} on ^{18}F -FDG-PET was associated with Ki-67 expression level and reflected the tumor aggressiveness in NHL. Ki-67 is a proliferative cell-associated nuclear antigen [28], and its function is closely related to mitosis. It is a popular biological indicator used in the investigation of many malignant tumors which can reflect the proliferation of malignant tumor cells. Therefore, our data showed that SUV_{max} may judge the malignant degree and prognosis of B-cell NHL.

In the current study, no significant difference was found in the SUV_{max} values with respect to other grouping indicators, including age, sex, bone metastasis, IPI score, clinical grade, genotype, and other immunohistochemical indexes. Of these, the significant correlation between SUV_{max} and IPI is yet controversial worldwide. Our findings were consistent with those of Ding et al. and Adams et al. [29, 30] that no significant correlation was established between SUV_{max} and IPI. However, some other studies found that SUV_{max} was associated with revised-IPI and the progression-free survival (PFS), and predicted the survival outcome in lymphoma patients [31, 32]. The possible reasons for the discrepancy between the results of this study and some previous studies is that the subtypes of lymphoma are different. We only focused on DLBCL and the expression of immune molecules of different subtypes is quite different, as well as the SUV_{max} value. Furthermore, the number of temporarily included cases may not be enough to reflect these relationships. Thus, we will increase the number of cases in future studies to further verify the significance of SUV_{max} in DLBCL.

Conclusion

Although ^{18}F -PET/CT has significant diagnostic value in patients with primary lymphoma, some misdiagnosis occurs; hence, it is recommended to combine the clinical features and pathology when diagnose especially when diagnosing primary gastric lymphoma. Besides, SUV_{max} is valuable in the differential diagnosis of different pathological types of NHL. More importantly, the SUV_{max} of patients with DLBCL correlated with Ki-67 reflect that it may be a promising prognostic and efficacy indicator for invasiveness in patients with DLBCL.

Abbreviations

¹⁸F-FDG PET/CT

18-fluorodeoxyglucose positron emission tomography/computed tomography; SUV_{max}:maximum standardized uptake value; HL:Hodgkin's lymphoma; NHL:non-Hodgkin's lymphoma; DLBCL:different between diffuse large B-cell lymphoma; NK:natural killer; FL:follicular lymphoma; PTCL:peripheral T-cell lymphoma; MALT:mucosa-associated lymphoid tissue; MCL:mantle cell lymphoma; IPI:international prognostic index; GCB:germinal center B cell-like; ROI:region of interest.

Declarations

Ethics approval and consent to participate

All procedures followed were in accordance with the ethical standards of the institutional and national research committee and with the Helsinki Declaration of 1975 as revised in 2008. Informed consent was obtained from all patients for being included in the study and written informed consent of legal representative of the patients under 18 years old was also obtained.

Consent for publication

All patients signed written informed consent for the use of their data in this Article.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

Fundings:

This work was supported by the National Nature Science Foundation of China under Grant number 81671679; and National Nature Science Foundation of China under Grant number 81871353.

Authors' contributions

Conception and design: LZ, KN, HY; Acquisition, analysis and interpretation of data: LZ, KN, YNC, YXX; Writing the manuscript or revising it critically for important intellectual content: LZ, HY, JL.

Acknowledgements

Not applicable.

References

1. Juweid ME, Stroobants S, Hoekstra OS, et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2007 Feb 10;25(5):571-8.
2. Suh KJ, Kim KH, Kim R, et al. Costs and clinical outcomes of patients with diffuse large B-cell lymphoma in first remission: role of PET/CT surveillance. *The Korean journal of internal medicine.* 2019 Jul;34(4):894-901.
3. Zhang Y, Fan Y, Ying Z, et al. Can the SUV(max-liver)-based interpretation improve prognostic accuracy of interim and posttreatment (18)F-FDG PET/CT in patients with diffuse large B-cell lymphoma? *Leukemia & lymphoma.* 2018 Mar;59(3):660-669.
4. Winter A, Rybicki L, Shah SN, et al. Prognostic value of pre-transplant PET/CT in patients with diffuse large B-cell lymphoma undergoing autologous stem cell transplantation. *Leukemia & lymphoma.* 2018 May;59(5):1195-1201.
5. Novelli S, Briones J, Flotats A, et al. PET/CT Assessment of Follicular Lymphoma and High Grade B Cell Lymphoma - Good Correlation with Clinical and Histological Features at Diagnosis. *Advances in clinical and experimental medicine : official organ Wroclaw Medical University.* 2015 Mar-Apr;24(2):325-30.
6. Broyde A, Boycov O, Strenov Y, et al. Role and prognostic significance of the Ki-67 index in non-Hodgkin's lymphoma. *American journal of hematology.* 2009 Jun;84(6):338-43.
7. Hofman MS, Hicks RJ. Using positron emission tomography to assess tumor proliferation in non-Hodgkin lymphoma. *Leukemia & lymphoma.* 2010 Feb;51(2):183-5.
8. Storto G, Di Giorgio E, De Renzo A, et al. Assessment of metabolic activity by PET-CT with F-18-FDG in patients with T-cell lymphoma. *British journal of haematology.* 2010 Oct;151(2):195-7.
9. Meyer HJ, Wienke A, Surov A. Correlations Between Imaging Biomarkers and Proliferation Index Ki-67 in Lymphomas: A Systematic Review and Meta-Analysis. *Clinical lymphoma, myeloma & leukemia.* 2019 Jun;19(6):e266-e272.
10. Albano D, Bosio G, Giubbini R, et al. 18F-FDG PET/CT and extragastric MALT lymphoma: role of Ki-67 score and plasmacytic differentiation. *Leukemia & lymphoma.* 2017 Oct;58(10):2328-2334.
11. Angelopoulou MK, Mosa E, Pangalis GA, et al. The Significance of PET/CT in the Initial Staging of Hodgkin Lymphoma: Experience Outside Clinical Trials. *Anticancer research.* 2017 Oct;37(10):5727-5736.
12. Isik EG, Kuyumcu S, Kebudi R, et al. Prediction of outcome in pediatric Hodgkin lymphoma based on interpretation of (18)FDG-PET/CT according to Δ SUV(max), Deauville 5-point scale and IHP criteria. *Annals of nuclear medicine.* 2017 Nov;31(9):660-668.
13. Wang K, Zhao X, Chen Q, et al. A new diagnostic marker for differentiating multicentric gliomas from multiple intracranial diffuse large B-cell lymphomas on 18F-FDG PET images. *Medicine.* 2017

Aug;96(32):e7756.

14. Hoffmann M, Kletter K, Diemling M, et al. Positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose (F18-FDG) does not visualize extranodal B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)-type. *Annals of oncology : official journal of the European Society for Medical Oncology*. 1999 Oct;10(10):1185-9.
15. Hoffmann M, Kletter K, Becherer A, et al. 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) for staging and follow-up of marginal zone B-cell lymphoma. *Oncology*. 2003;64(4):336-40.
16. Ambrosini V, Rubello D, Castellucci P, et al. Diagnostic role of 18F-FDG PET in gastric MALT lymphoma. *Nuclear medicine review Central & Eastern Europe*. 2006;9(1):37-40.
17. Radan L, Fischer D, Bar-Shalom R, et al. FDG avidity and PET/CT patterns in primary gastric lymphoma. *European journal of nuclear medicine and molecular imaging*. 2008 Aug;35(8):1424-30.
18. Fu L, Li H, Wang H, et al. SUVmax/THKmax as a biomarker for distinguishing advanced gastric carcinoma from primary gastric lymphoma. *PloS one*. 2012;7(12):e50914.
19. Perry C, Herishanu Y, Metzer U, et al. Diagnostic accuracy of PET/CT in patients with extranodal marginal zone MALT lymphoma. *European journal of haematology*. 2007 Sep;79(3):205-9.
20. Yi JH, Kim SJ, Choi JY, et al. 18F-FDG uptake and its clinical relevance in primary gastric lymphoma. *Hematological oncology*. 2010 Jun;28(2):57-61.
21. Sharma P, Suman SK, Singh H, et al. Primary gastric lymphoma: utility of 18F-fluorodeoxyglucose positron emission tomography-computed tomography for detecting relapse after treatment. *Leukemia & lymphoma*. 2013 May;54(5):951-8.
22. Hwang JP, Lim I, Byun BH, et al. Prognostic value of SUVmax measured by pretreatment 18F-FDG PET/CT in patients with primary gastric lymphoma. *Nuclear medicine communications*. 2016 Dec;37(12):1267-1272.
23. Li XF, Fu Q, Dong YW, et al. (18)F-fluorodeoxyglucose positron emission tomography/computed tomography comparison of gastric lymphoma and gastric carcinoma. *World journal of gastroenterology*. 2016 Sep 14;22(34):7787-96.
24. Bennett MH, MacLennan KA, Vaughan Hudson G, et al. Non-Hodgkin's lymphoma arising in patients treated for Hodgkin's disease in the BNLI: a 20-year experience. *British National Lymphoma Investigation. Annals of oncology : official journal of the European Society for Medical Oncology*. 1991 Feb;2 Suppl 2:83-92.
25. Skarin AT, Canellos GP. Chemotherapy of advanced non-Hodgkin's lymphoma. *Clinics in haematology*. 1979 Oct;8(3):667-84.
26. Brown DC, Heryet A, Gatter KC, et al. The prognostic significance of immunophenotype in high-grade non-Hodgkin's lymphoma. *Histopathology*. 1989 Jun;14(6):621-7.
27. Watanabe R, Tomita N, Takeuchi K, et al. SUVmax in FDG-PET at the biopsy site correlates with the proliferation potential of tumor cells in non-Hodgkin lymphoma. *Leukemia & lymphoma*. 2010 Feb;51(2):279-83.

28. Gerdes J, Pileri S, Bartels H, et al. [Proliferation marker Ki-67: correlation with histological diagnosis, neoplasm grading and clinical course]. Verhandlungen der Deutschen Gesellschaft fur Pathologie. 1986;70:152-8.
29. Ding CY, Liu HY, Guo Z, et al. [Value of Pretherapeutic (18)F-FDG PET/CT in the Diagnosis, Staging and Prognosis Evaluation of Adult Burkitt's Lymphoma]. Zhongguo shi yan xue ye xue za zhi. 2017 Apr;25(2):438-443.
30. Adams HJ, de Klerk JM, Fijnheer R, 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. European journal of haematology. 2015 Jun;94(6):532-9.
31. Liang JH, Sun J, Wang L, et al. Prognostic significance of bone marrow infiltration detected by PET-CT in newly diagnosed diffuse large B cell lymphoma. Oncotarget. 2016 Apr 5;7(14):19072-80.
32. Huang H, Xiao F, Han X, et al. Correlation of pretreatment 18F-FDG uptake with clinicopathological factors and prognosis in patients with newly diagnosed diffuse large B-cell lymphoma. Nuclear medicine communications. 2016 Jul;37(7):689-98.

Tables

Table 1. Baseline characteristics of included patients

	HL	NHL					
		DLBCL	FL	PTCL-U	NK/T	MALT	MCL
Number	5	57	8	8	7	4	4
Percentage	5.1%	58.7%	8.2%	8.2%	7.2%	4.1%	4.1%
Male	3	22	6	5	5	4	3
Female	2	35	2	3	2	0	1
Average age (years)	30.8	57.2	58.5	54.9	39	60.5	54

Four cases of included patients with pathological diagnosis as non-Hodgkin's lymphoma without specific pathologic subtype. HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; DLBCL, diffused large B-cell lymphoma; FL, follicular lymphomas; NK/T, natural killer (NK)/T-cell lymphomas; PTCL, peripheral T-cell lymphoma; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma.

Table 2
Details of error diagnosis

	Missed diagnosis	Misdiagnosis
Number	2	8
Sex	male	Male:female 1:1
Age (years)	44 and 84	≤ 44 (2); 45–59 (5); ≥ 60 (1)
Pathological type	MALT	DLBCL (5); others (3)
Disease site	Gastrointestinal tract (100%)	Gastrointestinal tract (4; 50%) Others (4)
SUV_{max}	Negative	2.6 ~ 20.3(12.5 ± 6.9)
PET-CT diagnosis	Normal	Gastric carcinoma (4) Inflammation (2) Thymoma (1) Metastasis (1)

MALT, mucosa-associated lymphoid tissue; DLBCL, diffused large B-cell lymphoma.

Table 3
Mean SUV_{max} of different subtypes of lymphoma

Pathological Type	Number	SUV _{max} ($X \pm S$)
HL	5	16.8 ± 5.3
NHL	95	17.0 ± 5.1
DLBCL	60	18.9 ± 4.9
FL	8	7.8 ± 1.4
PTCL	8	16.4 ± 4.9
NK/T	7	18.7 ± 2.6
MALT	4	13.7 ± 4.6
MCL	4	9.2 ± 3.4

HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; DLBCL, diffused large B-cell lymphoma; FL, follicular lymphomas; PTCL, peripheral T-cell lymphoma; NK/T, natural killer (NK)/T-cell lymphomas; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma.

Table 4
Subgroup analysis of patients with DLBCL

	Number (%)	SUV _{max}	P-value
Gender			0.9069
Male	22 (38.6%)	18.9 ± 9.1	
Female	35 (61.4%)	19.2 ± 9.2	
Age (years)			0.2269
< 44	9 (15.8%)	18.9 ± 9.1	
44–59	20 (35.1%)	19.2 ± 9.2	
> 60	28 (49.1%)	14.6 ± 3.9	
Skeletal invasion			0.7491
(+)	16 (32.7%)	20.4 ± 9.2	
(−)	33 (67.3%)	19.6 ± 8.7	
IPI (aaIPI)			0.1264
Low risk	18 (41.9%)	15.6 ± 8.1	
High risk	25 (58.1%)	21 ± 10.9	
Grade			0.0996
Ⅲ–Ⅳ	22 (42.3%)	18.6 ± 10.3	
Ⅰ–Ⅱ	30 (57.7%)	22.1 ± 6.5	
Gene expression			0.3819
GCB	22 (46.8%)	16.9 ± 7.8	
non-GCB	25 (53.2%)	19.8 ± 9.4	
IHC marker			
Bcl-6(+)	43 (81.1%)	19.3 ± 9.6	0.4261
Bcl-6(−)	10 (18.9%)	16.6 ± 7.1	
Bcl-2(+)	40 (88.9%)	18.3 ± 7.8	0.1146
Bcl-2(−)	5 (11.1%)	24.5 ± 10.9	

Partial immunohistochemical results of the patient could not be obtained. IPI: International Prognostic Index; aaIPI: low age-adjusted International Prognostic Index. GCB, germinal center B cell-like.

	Number (%)	SUV _{max}	P-value
CD10(+)	18 (36.3%)	18.1 ± 8.1	0.9339
CD10(-)	31 (63.3%)	20.0 ± 10.1	
CD23(+)	18 (45%)	17.6 ± 7.4	0.3755
CD23(-)	22 (55%)	19.8 ± 8.1	
MUM-1(+)	30 (71.4%)	17.8 ± 6.8	0.1394
MUM-1(-)	12 (28.6%)	14.3 ± 7.2	
Pax-5(+)	30 (93.8%)	19.9 ± 8.9	0.4362
Pax-5(-)	2 (6.3%)	16.8 ± 1.1	
EMA(+)	9 (25.7%)	20.3 ± 13.8	0.7315
EMA(-)	26 (74.3%)	18.9 ± 8.4	
CD138(+)	8 (40%)	16.2 ± 7.4	0.9190
CD138(-)	12 (60%)	15.8 ± 7.9	
CD30(+)	5 (20.8%)	20.0 ± 7.0	0.3778
CD30(-)	19 (79.2%)	16.2 ± 8.6	
ALK(+)	1 (6.7%)	20.86	NA
ALK(+)	14 (93.3%)	21.6 ± 12.5	

Partial immunohistochemical results of the patient could not be obtained. IPI: International Prognostic Index; aalPI: low age-adjusted International Prognostic Index. GCB, germinal center B cell-like.

Figures

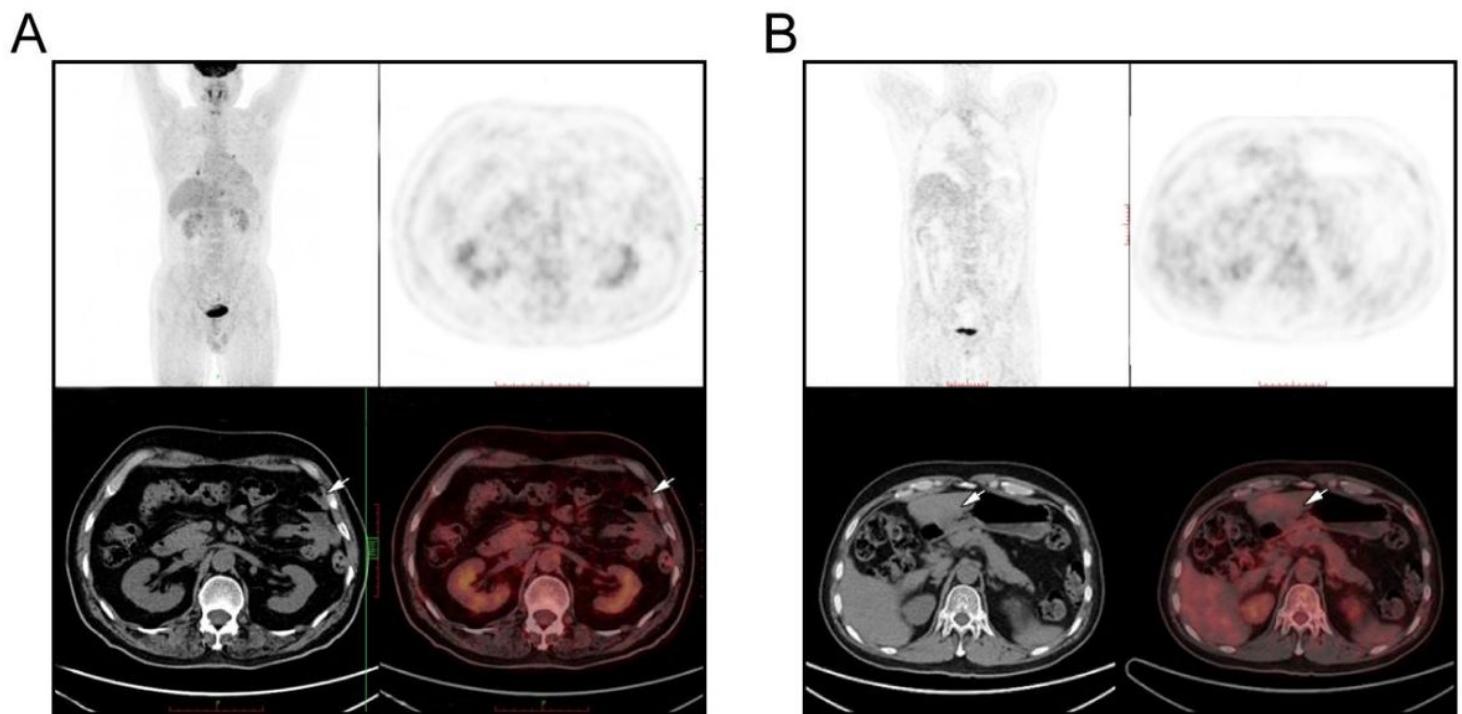


Figure 1

Two misdiagnosed cases with the negative uptake of PET-CT. (A) case 1, men, 64 years old, the left side of the patient's colon wall is slightly thicker (white arrow), but there is no significant uptake of standardized uptake value (SUV). (B) Case 2, female, 68 years old, gastric wall of gastric antrum thickens significantly (white arrow) but no significant uptake of SUV.

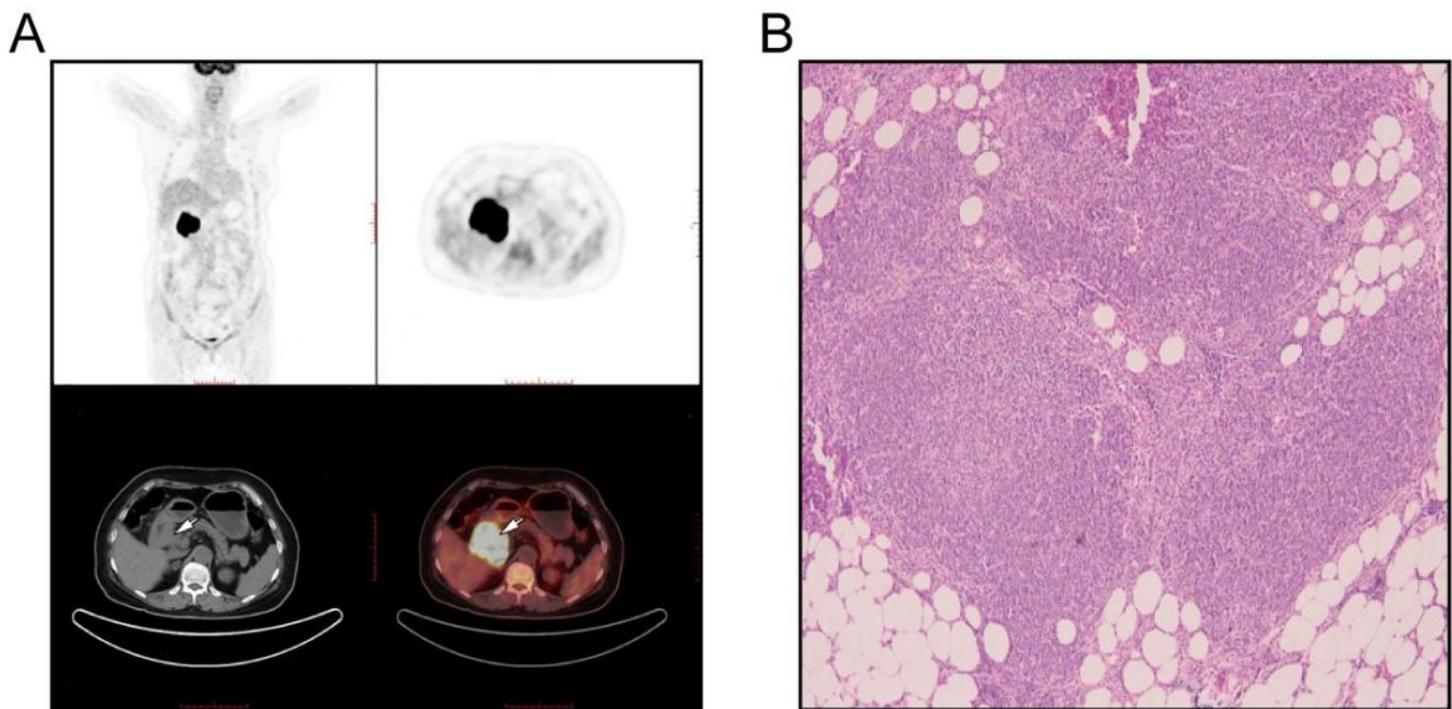


Figure 2

The highest lesion was measured in the abdominal lymph nodes of a patient with DLBCL. PET-CT clearly showed the lesions and it has strong FDG uptake. Maximum standardized uptake value (SUVmax) is 51. (B) The final pathological result of this patient proved to be diffused large B-cell lymphoma (DLBCL).

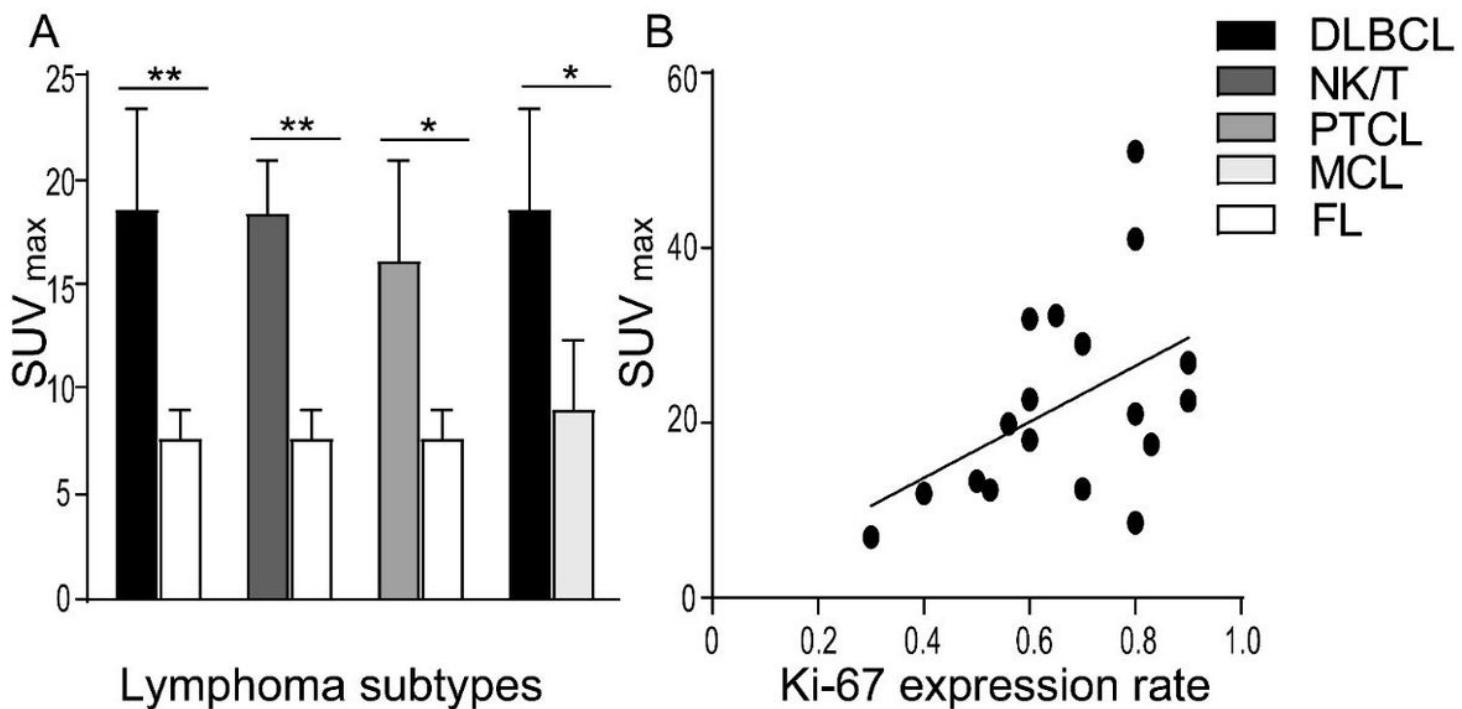


Figure 3

Maximum standardized uptake value (SUVmax) has significant value for differential diagnosis of different pathological types of non-Hodgkin's lymphoma (NHL) and is a promising indicator for prognostic in patients with diffused large B-cell lymphoma (DLBCL). (A) Among NHL, the mean SUVmax of each pathological group differed significantly between DLBCL and follicular lymphoma (FL) ($p=0.0004$), FL and natural killer/T-cell lymphoma ($p=0.0078$), FL and peripheral T-cell lymphoma (PTCL) ($p=0.0117$), and DLBCL and mantle cell lymphoma (MCL) ($p=0.0294$). (B) The SUVmax value exhibited a fair correlation with the expression rate of proliferation marker Ki-67 in patients with DLBCL ($r=0.33$, $p=0.018$). * $P \leq 0.05$, ** $P \leq 0.01$.