Value of ^{18}F-FDG PET/CT in discrimination between indolent and aggressive non-Hodgkin's lymphoma: A study of 328 patients

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Abstract

Objective: Non-Hodgkin's lymphoma (NHL) cases with inconclusive biopsy findings are not infrequently referred for fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT). We searched for maximum standardized uptake value (SUVmax) cut-off values that could discriminate between indolent and aggressive NHL in conventional non-time of flight (non-TOF) ^{18}F-FDG PET/CT and TOF ^{18}F-FDG PET/CT. **Subjects and Methods:** Retrospectively, 328 patients were selected by the following inclusion criteria: biopsy-proven NHL with no more than one histopathological type; new cases with less than 90 days between obtaining biopsy and ^{18}F-FDG PET/CT scanning; recurrent cases with time interval more than six months since the last therapy with no history of transformation; and blood glucose less than 150mg/dL. Two hundred forty six (246) selected patients were scanned with non-TOF PET/CT, and 82 patients were scanned with TOF ^{18}F-FDG PET/CT. **Results:** The SUVmax of NHL tends to be higher in TOF ^{18}F-FDG PET/CT than non-TOF ^{18}F-FDG PET/CT. New aggressive NHL had significantly higher SUVmax than new indolent NHL in both, non-TOF ^{18}F-FDG PET/CT (13.6±7.7g/mL vs. 5.3±3.4g/mL, P<0.0001) and TOF ^{18}F-FDG PET/CT (20.5±9.8g/mL vs. 6.6±4.7g/mL, P<0.0001). A receiver operating characteristic curve analysis for new cases in non-TOF ^{18}F-FDG PET/CT (n=204), demonstrated SUVmax of 10g/mL as the most balanced cut-off between aggressive and indolent NHL, with the area under the curve (AUC) of 86%, specificity of 94%, and sensitivity of 71%. While SUVmax of 13g/mL was the most balanced cut-off for new cases in TOF ^{18}F-FDG PET/CT (n=57), with AUC of 91%, specificity of 95.5%, and sensitivity of 77%. **Conclusion:** Both SUVmax> 10g/mL in non-TOF ^{18}F-FDG PET/CT and >13g/mL in TOF ^{18}F-FDG PET/CT were highly suggestive of an aggressive nature of NHL, while there was an overlap between indolent and aggressive NHL in the lower SUV max levels.

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Introduction

Fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has become a routine in the evaluation and management of lymphomas [1-7]. Scanning lymphoma patients constitutes 50% of the workload of ^{18}F-FDG PET/CT studies in some centers [6]. Currently, ^{18}F-FDG PET/CT with time of flight (TOF)-based image reconstruction is increasingly used due to its advantages in the detection of small lesions, the use of a lower injected dose or shorter acquisition time, and improvement of image quality [8-12]. All medical imaging manufactures incorporated TOF technology in their whole body ^{18}F-FDG PET/CT [12].

Approximately 2.1% of world population will be diagnosed with non-Hodgkin's lymphoma (NHL) at some point during their lifetime [13]. Non-Hodgkin's lymphoma is divided into different histological types with an indolent behavior in 40% of patients and an aggressive nature in 60% [14]. The indolent NHL includes; follicular lymphoma (grade I and II), marginal zone B-cell lymphoma, small lymphocytic lymphoma, lymphoplasmacytic lymphoma, some cases of mantle cell lymphoma and mycosis fungoides. The aggressive NHL includes: diffuse large B-cell lymphoma, follicular lymphoma (grade III), some cases of mantle cell lymphoma, peripheral T-cell lymphoma, anaplastic large cell lymphoma, highly aggressive NHL; Burkitt's lymphoma, B lymphoblastic lymphoma, T lymphoblastic lymphoma and adult T-cell lymphoma [15]. Determination of the histopathological subtype of NHL is crucial for treatment plan and prognosis. Survival of untreated indolent NHL is measured in years while survival of untreated aggressive NHL in months [15]. Biopsy is used for this purpose, but it frequently gives equivocal inconclu-

sive results that may contradict clinical presentation of cases [16, 17].

Many studies reported that ^{18}F-FDG is taken avidly by aggressive NHL and weakly by indolent NHL [18-21]. The main aim of the current study was to find well-balanced cut-offs of ^{18}F-FDG uptake that can discriminate between indolent and aggressive NHL to support biopsy findings in the challenging equivocal cases in conventional non-time of flight (non-TOF) ^{18}F-FDG PET/CT and TOF ^{18}F-FDG PET/CT. The other aim was to check whether the detection rate of NHL subtypes in non-TOF PET differs from that in TOF ^{18}F-FDG PET/CT.

Subjects and Methods

Patients

A retrospective analysis was done for all NHL patients who underwent ^{18}F-FDG PET/CT in the period between January 2008-December 2016 at our institution. This study was approved by our institutional review board. Three hundred and twenty eight patients were selected by the following inclusion criteria: biopsy-proven NHL with no more than one histopathological type; pretreatment (new) cases with less than 90 days between obtaining biopsy and ^{18}F-FDG PET/CT scanning; recurrent cases with time interval more than six months since the last therapy with no history of transformation; blood glucose less than 150mg/dL.

Fifty five percent (181/328) of our patients had aggressive NHL, and 45% (147/328) had indolent NHL. In aggressive NHL, males were 56% (101/181), and females were 44% (80/181). In indolent NHL, females were 56% (83/147), and males were 44% (64/147). In aggressive NHL, age was 61±16.5 years (y) (range 20-89y), in indolent NHL age was 61.9±12.8y (range 26-87y). In aggressive NHL, 83.4% (151/181) were new cases, and 16.5% (30/181) were recurrent. In indolent NHL, 75% (110/147) were new, and 25% (37/147) were recurrent cases.

The ^{18}F-FDG PET/CT examination was performed with 2 types of scanning. Two hundred and forty six patients were scanned between January 2008-December 2014 with non-TOF ^{18}F-FDG PET/CT in which the images were reconstructed by using non-TOF based ordered subset expectation maximization (OSEM) related algorithm, and 82 patients were scanned between January 2015-December 2016 with TOF ^{18}F-FDG PET/CT with TOF-based OSEM. After at least four hours of fasting, mean blood glucose in aggressive vs indolent NHL cases was 99.5±15mg/dL vs. 97.6±14mg/dL (P=0.3). Fluorine-18-FDG was intravenously injected (3.7MBq of ^{18}F-FDG/kg of body weight). The mean of doses given to aggressive vs indolent NHL cases were 214±57MBq vs. 219±50MBq (P=0.4). The time between injection of ^{18}F-FDG and ^{18}F-FDG PET/CT scanning was one hour.

In both, non-TOF ^{18}F-FDG PET/CT and TOF ^{18}F-FDG PET/CT studies a multi-slices, non-enhanced CT whole body scan (120kVp, 50mAs) was acquired from the parietal area of the skull to mid-thighs, for attenuation correction and anatomical localization. Thereafter in both scanners, three-dimensional emission whole body scans were acquired from the parietal area of the skull to mid-thigh with two minutes per bed position for 11 bed positions.

The non-TOF ^{18}F-FDG PET/CT scanner was Gemini GXL; Philips, with gadolinium-based crystals, timing resolution of 7.5ns, transaxial field of view (FOV) of 57.6cm in diameter, axial FOV of 18cm and spatial resolution of 5.2mm and 6mm at 1cm and 10cm from the center of FOV, respectively. Time of flight ^{18}F-FDG PET/CT scanner was Discovery 710; GE Healthcare, with lutetium-yttrium based-crystals, and timing resolution of 4.9ns, transaxial FOV of 70cm, axial FOV of 15.7cm and spatial resolution of 4.7mm and 5.2mm at 1cm and 10cm from the center of FOV, respectively.

Analysis of ^{18}F-FDG uptake

Maximum standardized uptake value (SUVmax) calculation was based on the body weight. SUV=[decay corrected activity (kBq)/tissue volume (mL)]/[injected FDG activity (kBq)/body weight (g)]. Abnormal foci were lesions with SUVmax of ^{18}F-FDG ≥2.5g/mL [3]. In the majority of cases, our decision was merely based on this SUVmax threshold, and in the minority of cases (with lesions with high normal ^{18}F-FDG uptake) was based on SUVmax threshold and on comparing the SUVmax of the lesions with SUVmax of the blood pool and liver. The SUVmax of the area with the highest uptake was recorded for the calculation of the cut-offs. We included the lesions with the highest uptake regardless of their size and used SUVmax rather than SUVmean in order to decrease partial volume effect [22].

Statistics

Excel spreadsheet software (2013, Microsoft Corporation, Redmond, WA, USA) and JMP Pro12.2.0 (2016-SAS, USA) were used. The t-test was used for testing the statistical significance of the difference in SUVmax. Receiver operating characteristics (ROC) curve was used to determine the cut-off value between indolent and aggressive NHL. The aggressive NHL was considered as the positive finding in the ROC curve. The cut-off was selected by the highest [sensitivity-(1-specificity)], that is the highest sum of sensitivity and specificity, which represents the nearest point to the upper right corner of the ROC Figure. The detection rate was presented by the number of the detected cases of a specific NHL subtype by ^{18}F-FDG PET/CT as a numerator and the total cases of that specific NHL subtype as a denominator. Fisher's test was used to measure the difference in the detection rates of NHL subtypes by non-TOF versus TOF ^{18}F-FDG PET/CT. Maximum standardized uptake value and other numerical data were written as a mean±standard deviation. P value was set as significant if less than 0.05.

Results

The SUVmax of NHL cases (regardless of being aggressive or indolent, and regardless of being new or recurrent) tend to be higher in TOF ^{18}F-FDG PET/CT than non-TOF ^{18}F-FDG PET/

Table 1. *Differences in SUVmax of new NHL between non-TOF ^{18}F-FDG PET/CT (n=204) and TOF ^{18}F-FDG PET/CT (n= 57)*

New NHL	non-TOF ^{18}F-FDG PET/CT		TOF ^{18}F-FDG PET/CT		P value
	n	SUVmax (g/mL)	n	SUVmax (g/mL)	
DLCL	90	14.8±7.8	26	21.6±10.6	0.0005
FL III	12	8.6 ±5.6	0		
PTCL-NOS	5	7.5±5.2	3	14.5±6.7	0.1
NK/TCL	2	17.0±2.4	2	20.0±4.2	0.4
PCTCL	1	18.1	2	20.8±12	
ALTCL	1	11.2	2	15.1±1.9	
AIBTCL	2	6.6±3.8	0		
TLL	2	11.5±11.8	0		
IVLBCL	1	6.6	0		
FL I, II	49	6.5±2.8	10	8.6 ±4.9	0.06
MZL(MALT)	26	3.1±2.3	10	4.4±3.4	0.1
MZL(non-MALT)	7	3.2±2.0	1	12.5	
LPL	4	8.5±7.6	0		
SLL	2	3.1±0.1	1	3.4	

SUVmax: maximum standardized uptake value; NHL: non-Hodgkin's lymphoma; TOF: time of flight; ^{18}F-FDG PET/CT: fluorine-18-fluoro-deoxyglucose-positron emission tomography/computed tomography; DLCL: diffuse large cell lymphoma; FL III: follicular lymphoma grade III; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; NK/TCL: natural killer/T-cell lymphoma; PCTCL: primary cutaneous T-cell lymphoma; ALTCL: anaplastic large T-cell lymphoma; AIBTCL: angioimmunoblastic T-cell lymphoma; TLL: T-lymphoblastic lymphoma; IVLBCL: intravascular large B-cell lymphoma; FL I, II : follicular lymphoma grade I and II; MZL: marginal zone lymphoma; MALT: mucosa associated lymphoid tissue lymphoma; LPL: lymphoplasmacytic lymphoma; SLL: small lymphocytic lymphoma

CT (Tables 1, 2). The mean of increment in SUVmax in TOF ^{18}F-FDG PET/CT was 31.5%. The highest increment (37.5%) was in mucosa-associated lymphoid tissue lymphoma (MALT), and the lowest (23%) was in grade I and II of the follicular lymphomas (FL I and II). The increment was 35% in diffuse large cell lymphomas (DLCL), 31% in T-cell lymphomas (TCL), and 31% in grade III follicular lymphomas (FL III).

New aggressive NHL had significantly higher SUVmax than new indolent NHL in both, non-TOF and TOF ^{18}F-FDG PET/CT; SUVmax for non-TOF ^{18}F-FDG PET/CT (13.6±7.7 g/mL vs. 5.3±3.4g/mL, P<0.0001), and for TOF ^{18}F-FDG PET/CT (20.5±9.8g/mL vs. 6.6±4.7g/mL, P<0.0001) (Figures 1 and 2). The most balanced SUVmax cut-off value between new aggressive NHL (n=116) and new indolent NHL (n=88) scanned by the non-TOF ^{18}F-FDG PET/CT was 10g/mL according to the ROC curve, with the area under the curve (AUC) of 86%, a specificity of 94%, and a sensitivity of 71% (Figure 3). A higher SUVmax cut-off was detected in cases scanned by TOF ^{18}F-FDG PET/CT; the most balanced SUVmax cut-off between new aggressive NHL (n= 35) and new indolent NHL (n=22) was 13g/mL, with AUC of 91%, specificity of 95.5%, and sensitivity of 77% (Figure 4). In both; non-TOF ^{18}F-FDG PET/CT and TOF ^{18}F-FDG PET/CT studies, as the SUVmax cut-off value increases, the specificity also increases but the sensitivity decreases (Table 3 and Table 4).

A value of 10g/mL as SUVmax cut-off in non-TOF ^{18}F-FDG PET/CT, falsely characterized 34 patients (34/116 of new aggressive NHL which scanned by non-TOF ^{18}F-FDG PET/CT) as indolent while they had a biopsy-proven aggressive NHL (false negative=FN). Twenty two FN cases were DLCL (22/90 of new DLCL). Nasopharynx was the most worrisome area; there were four cases of DLCL in the nasopharynx, three of them were FN. Other DLCL FN cases were: two out of five DLCL in the cerebrum, 2/6 in the inguinal lymph nodes (LN), 2/12 in the stomach, 1/12 in the neck LNs, and 12 FN DLCL in other organs. Six FN cases were FL III (6/12 of new FL III). The neck LN was the most worrisome area; four out of six cases of FL III in the neck LN were FN. Other FL III FN

Table 2. *Differences in SUVmax of recurrent NHL between non-TOF ^{18}F-FDG PET/CT (n=42) and TOF ^{18}F-FDG PET/CT (n=25)*

New NHL	non-TOF^{18}F-FDG PET/CT		TOF^{18}F-FDG PET/CT		P value
	n	SUVmax (g/mL)	n	SUVmax (g/mL)	
DLCL	9	12.5±14.4	9	19.3±11.1	0.27
FL III	2	9.0 ± 0.3	3	13.0±6.1	0.4
PTCL-NOS	0		1	24.9	
ALTCL	1	2	1	19	
TLL	3	9.7±10.3	0		
ATCL	1	6	0		
FL I, II	18	7.4±3.1	8	9.3±3.4	0.1
MZL (MALT)	4	5.4±2.6	3	9.4±4.7	0.2
MZL (Non MALT)	2	3.7±0.4	0		
SLL	2	3.1±3.1	0		0.06

SUVmax: maximum standardized uptake value; NHL: non-Hodgkin's lymphoma; TOF: time of flight; 18F-FDG PET/CT: fluorine-18-fluorodeoxyglucose positron emission tomography /computed tomography; DLCL : diffuse large cell lymphoma; FL III: follicular lymphoma grade III; PTCL-NOS: peripheral T-cell lymphoma not otherwise specified; ALTCL: anaplastic large T-cell lymphoma; TLL: T-lymphoblastic lymphoma; ATCL: adult T-cell lymphoma; FL I , II: follicular lymphoma grade I and II; MZL: marginal zone lymphoma; MALT: mucosa associated lymphoid tissue lymphoma; SLL: small lymphocytic lymphoma

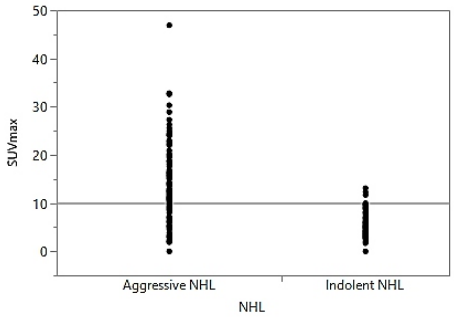

Figure 1. Distribution of SUVmax of ^{18}F-FDG in new aggressive and new indolent non-Hodgkin's lymphoma (NHL) in conventional non-time of flight ^{18}F-FDG PET/CT of 204 patients, demonstrating a higher SUVmax in aggressive NHL. However, in the lower SUVmax levels there is an overlap between aggressive and indolent NHL.

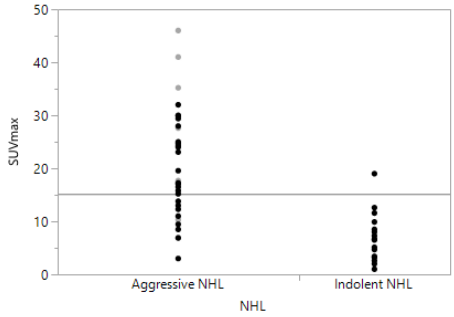

Figure 2. Distribution of SUVmax of ^{18}F-FDG in new aggressive and new indolent non-Hodgkin's lymphoma (NHL), in time of flight ^{18}F-FDG PET/CT of 57 patients, demonstrating a higher SUVmax for aggressive NHL. However, in the lower SUVmax levels, there is an overlap between aggressive and indolent NHL

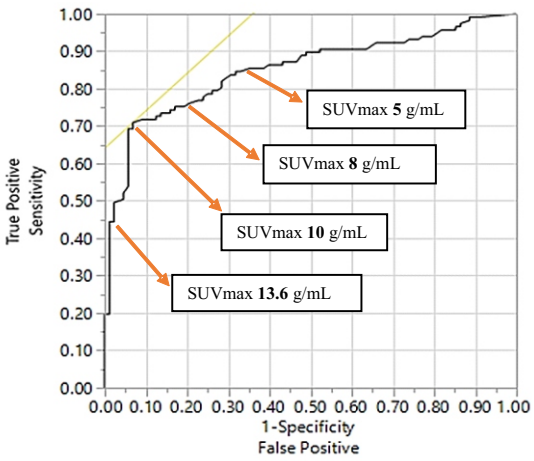

Figure 3. Receiver operating characteristic curve demonstrating SUVmax of 10g/mL as the most balanced cut-off between new aggressive and new indolent non-Hodgkin's lymphoma (n=204) which were scanned by conventional non-time of flight ^{18}F-FDG PET/CT with area under curve of 86%, specificity of 94%, and sensitivity of 71%. The most balanced cut-off is that with the highest [sensitivity-(1-specificity)], that is the highest sum of sensitivity and specificity, which represents the nearest point to the upper right corner of the ROC Figure. The other cut-offs below and above the most balanced one were selected from the ROC table and were added to the original ROC Figure to show the difference in the sensitivity, specificity between those less balanced cut-offs and the most balanced one.

cases were: 1/3 in the abdominal LN and 1/2 in the inguinal LN. Five FN cases were TCL (5/13 of new TCL). Two cases of TCL FN were angioimmunoblastic TCL (2/2 of new angioimmunoblastic TCL), and three cases of FN TCL were peripheral

TCL-not otherwise specified (PTCL-NOS) (3/5 of new PTCL-NOS). No FN cases were observed in the other subtypes of TCL. There was only one case of the rare intravascular NHL in our study. It was in the uterus and misclassified as indolent.

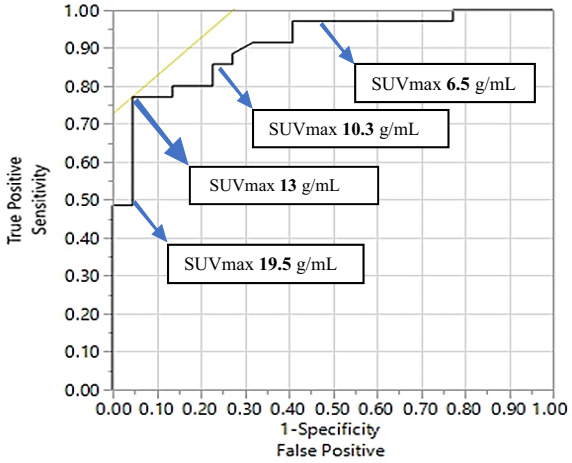

Figure 4. Receiver operating characteristic curve demonstrating SUVmax of 13g/mL as the most balanced cut-off between new aggressive and new indolent non-Hodgkin's lymphoma (n=57) which were scanned by time of flight ^{18}F-FDG PET/CT, with area under curve of 91%, specificity of 95.5%, and sensitivity of 77%. The most balanced cut-off is that with the highest [sensitivity-(1-specificity)], that is the highest sum of sensitivity and specificity, which represents the nearest point to the upper right corner of the ROC Figure. The other cut-offs below and above the most balanced one were selected from the ROC table and were added to the original ROC figure to show the difference in the sensitivity, specificity between those less balanced cut-offs and the most balanced one.

Table 3. *Comparison of multiple SUVmax cut-offs between new aggressive and new indolent NHL in non-TOF ^{18}F-FDG PET/CT*

SUVmax (g/mL)	Specificity	Sensitivity	TP	TN	FP	FN
13.6	100%	44%	52	87	0	65
10	94%	71%	83	82	5	34
8.0	80%	76%	89	70	17	28
5	54%	87%	102	47	40	15

SUVmax: maximum standard uptake value; NHL: non-Hodgkin's lymphoma; TOF: Time of flight; ^{18}F-FDG PET/CT: fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; TP:True positive; TN: Truenegative; FP: False positive; FN: False negative

Five cases of new indolent NHL scanned by non-TOF ^{18}F-FDG PET/CT were FP and classified as aggressive (5/88 of new indolent NHL). All FP cases were FL I or II (5/49 of new FL or II). False positive cases were situated: 2/12 in the abdominal LN, 1/13 in the neck LN, 1/1 in the oropharynx and 1/1 in the ileum.

When 13g/mL was applied as SUVmax cut-off for TOF ^{18}F-FDG PET/CT cases, 8/35 of new aggressive NHL were FN. Six FN cases were DLCL (6/26 of new DLCL). The FN DLCL cases were: 2 in the neck LN, 1 in each of the stomach, the breast, the lung and the nasopharynx. Two of FN were TCL (2/9 of new TCL); one case was PTCL-NOS in neck LN (1/3 of new PTCL-NOS) and 1 case was primary cutaneous TCL (PCTCL) in the skin (1/2 of new PCTCL). There was only one FP case when using 13 g/mL as SUVmax cut-off in TOF ^{18}F-FDG PET/CT; it was FL II located in the thyroid.

Table 4. *Comparison of multiple SUVmax cut-offs between new aggressive and new indolent NHL in TOF ^{18}F-FDG PET/CT*

SUVmax (g/mL)	Specificity	Sensitivity	TP	TN	FP	FN
19.5	100%	48.5%	17	22	0	18
13	95.5%	77%	27	21	1	8
10.3	77%	85.7%	30	17	5	5
6.5	50%	97%	34	11	11	1

SUVmax: maximum standard uptake value; NHL: non-Hodgkin's lymphoma; TOF: Time of flight; ^{18}F-FDG PET/CT: fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography; TP:True positive; TN: Truenegative; FP: False positive; FN: False negative

No significant differences were found in the detection rates of NHL subtypes (new and recurrent) between non- TOF ^{18}F-FDG PET/CT and TOF ^{18}F-FDG PET/CT, when using SUVmax of 2.5 as the normal upper limit (Table 5).

Discussion

The current study demonstrated that SUVmax of 10g/mL in non-TOF ^{18}F-FDG PET/CT could predict the aggressive nature of NHL with specificity of 94% and sensitivity of 71%. These results were confirmative for the findings of previous smaller studies; Schöder et al. (2005) [19] in a study of 69 patients, showed that SUVmax of 10g/mL in non-TOF PET/CT was a reasonably balanced cut-off with specificity of 81% and sensitivity of 71%. The current study demonstrated the same cut-off with similar sensitivity (71%) but with higher specificity (94% vs. 81%). The same cut-off was also reported by Ngeow at al. (2009) [20] in a study of 74 patients with NHL.

The current study demonstrated a higher SUVmax cut-off in TOF ^{18}F-FDG PET/CT; SUVmax of 13g/mL was the most balanced cut-off that can predict the aggressive nature of NHL with specificity of 95.5% and sensitivity of 77%. To our knowledge, there were no previous studies investigated this issue in TOF ^{18}F-FDG PET/CT.

Overall, TOF ^{18}F-FDG PET/CT is a better as a test than non-TOF ^{18}F-FDG PET/CT; AUC was 91% vs 86% respectively. This could be attributed to the higher precision (less variability) of the measurements of the ^{18}F-FDG uptake in the same patients or across patients when using TOF-reconstruction [23], so SUVmax in TOF ^{18}F-FDG PET/CT is closer to the real uptake of the lesion.

These cut-off values are not only useful in new NHL cases with

Table 5. *Detection rates for NHL subtypes in non-TOF ^{18}F-FDG PET/CT and TOF ^{18}F-FDG-PET/CT*

NHL classification according to world health organization	Detection rate non-TOF ^{18}F-FDG PET/CT	Detection rate TOF ^{18}F-FDG PET/CT
Diffuse large cell lymphoma	98/99	35/35
Follicular lymphoma grade 3	11/14	3/3
Peripheral T-cell lymphoma, not otherwise specified	4/5	4/4
Anaplastic large T-cell lymphoma	2/2	3/3
Extranodal natural killer/T-cell lymphoma, nasal type	2/2	2/2
T-lymphoblastic lymphoma	5/5	-
Primary Cutaneous T-cell lymphoma	1/1	2/2
Angioimmunoblastic T-cell lymphoma	2/2	-
Adult T-cell lymphoma	1/1	-
Intravascular large B-lymphoma	1/1	-
Follicular lymphoma grade 1 and 2	64/67	17/18
Mucosa-associated lymphoid tissue lymphoma	21/30	10/13
Nodal marginal zone B-cell lymphoma	7/9	1/1
Small lymphocytic lymphoma	4/4	1/1
Lymphoplasmacytic lymphoma	4/4	-

NHL: non-Hodgkin's lymphoma; TOF: Time of flight; ^{18}F-FDGPET/CT:fluorine-18-fluorodeoxyglucosepositronemissiontomography/computed tomography

inconclusive biopsy findings, but could also be useful in already diagnosed or recurrent indolent NHL, where unexpectedly high SUVmax above the cut-offs may indicate transformation to an aggressive form. Biopsy of the hottest uptake area of the disease is highly recommended in such cases.

However, because of the overlap between indolent and aggressive NHL in the lower SUVmax levels; <10g/mL in TOF ^{18}F-FDG PET/CT and <13g/mL in TOF ^{18}F-FDG PET/CT (Figures 1 and 2), and the considerable FN rate, we suggest using these cut-offs only as the last resort when clinical and immunohistopathological findings are inconclusive.

These cut-offs (in both TOF and non-TOF ^{18}F-FDG PET/CT) falsely characterized 42 aggressive NHL cases as indolent, the highest FN rate was in FLIII (6/12), and lowest was in DLCL (28/116). Some areas of the body more frequently showed lesions with FN findings: the nasopharynx in cases of DLCL, and the neck LN in cases of FL III or TCL. In the cerebrum, there were six cases of DLCL, two of them were FN, but the brain is not a worrisome area for potential misclassification that leads to missing the chance for treatment and cure because most primary central nervous lymphomas are aggressive and rarely indolent [24]. Furthermore, NHL cases in the brain are always treated cautiously, even in cases with equivocal biopsy findings [25].

The current study showed higher SUVmax in TOF ^{18}F-FDG PET/CT than in non-TOF PET/CT. This is in concordance with other studies that reported higher SUV in TOF PET/CT than in non-TOF ^{18}F-FDG PET/CT [11, 26, 27].

No significant differences were found in the detection rates (DR) of NHL subtypes between non-TOF and TOF ^{18}F-FDG PET/CT (Table 5). This could be attributed to the smaller effect of TOF-based reconstruction on ^{18}F-FDG uptake of lesions with SUV<5g/mL as shown by a previous study [28], which reported no significant differences in DR between TOF and non-TOF in tumors with SUV<5g/mL, while other studies demonstrated TOF PET to be consistently better than non-TOF PET in lesion detectability [29, 30].

In total (new and recurrent, non-TOF and TOF ^{18}F-FDG PET/CT studies); aggressive NHL cases were detected in 98% (177/181), nearly the same was reported in previous studies; DR of 97% [31, 32]. In the current study, FL III was detected in 14/17. Despite that FL III is regarded as an aggressive NHL, DR for it was less than DR for the indolent FL I or II; 14/17 vs. 81/85. Such a difference was also reported in a previous study; 33/37 vs. 71/72 [31]. For TCL, the DR was 28/29, this was in concordance with previous studies; which reported DR of 122/135 [33], 36/41 [34], and 33/38 [31].

There were six cases of indolent FL in the gastrointestinal tract (GIT), 4/6 of which were in the duodenum. Such predilection of FL in GIT for the duodenum was previously reported [35]. Duodenal FL was only recently classified as a specific category by the last World Health Organization classification, in 2016 [36]. In the current study, the DR for duodenal FL was 2/4, a lower DR was previously reported; 12/34 [37].

The lowest DR was for MALT lymphomas 31/43, about two-thirds of missed cases were in the stomach. Previous studies showed varied DR for MALT; 43/52 [32], 27/50 [31], 19/35[38], and 63/222 [39]. We studied 5 cases of SLL which had the lowest uptake among all NHL, DR was 5/5. Other studies demonstrated DR for SLL of 2/2 [20], 24/29 [31], and 384 positive scans out of 526 scans in 272 patients [40].

Currently, we used visual analysis and comparison of SUV of the lymphoma lesions with normal uptake in the mediastinum and the liver in the same patient. Deauville scores

are considered more valuable than the mere use of SUV in the assessment of treatment response in lymphoma [41]. However, Deauville scores cannot be used to differentiate between indolent and aggressive NHL as we compare two malignant lesions, which usually have higher ^{18}F-FDG uptake than that in the mediastinum and the liver. However, tumor/liver ratio for differentiation between indolent and aggressive NHL could be suggested for accuracy assessment in further studies.

Limitation of the study

The current study used SUVmax, which although being the most widely used parameter, varies between centers and scanners [42, 43] as it is susceptible to multiple factors particularly image noise [44]. However, SUVmax is better than SUVmean in this matter [45]. Also we included all lesions with the highest uptake regardless of their size, so there was a possibility of partial volume effect, however, we used SUVmax rather than SUV mean to decrease this effect [22] and it is worth mentioning that the size of the lesions could affect the SUV only up to 5% [46].

In conclusion, SUVmax>10g/mL in non-TOF ^{18}F-FDG PET/CT and >13g/mL in TOF ^{18}F-FDG PET/CT were highly suggestive of an aggressive nature of NHL, while there was an overlap between indolent and aggressive NHL in the lower SUVmax levels.

Acknowledgment

All procedures performed in this study were in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. This study was approved by the institutional review board (authorization number 17162).

The authors declare that they have no conflicts of interest.

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Alexander the Great. Afganistan was ruled by his generals, Selephkos and others for about 280 years.