^{18}F-FDG or 3′-Deoxy-3′-^{18}F-Fluorothymidine to Detect Transformation of Follicular Lymphoma

Marielle J. Wondergem[1], Saiyada N.F. Rizvi[2], Yvonne Jauw[1], Otto S. Hoekstra[2], Nikie Hoetjes[2], Peter M. van de Ven[3], Ronald Boellaard[2], Martine E.D. Chamuleau[1], Saskia A.G.M. Cillessen[4], Josien C. Regelink[5], Sonja Zweegman[1], and Josée M. Zijlstra[1]

[1]Department of Hematology, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Nuclear Medicine, VU University Medical Center, Amsterdam, The Netherlands; [3]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands; [4]Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands; and [5]Department of Hematology, Meander Medisch Centrum, Amersfoort, The Netherlands

Considering the different treatment strategy for transformed follicular lymphoma (TF) as opposed to follicular lymphoma (FL), diagnosing transformation early in the disease course is important. There is evidence that ^{18}F-FDG has utility as a biomarker of transformation. However, quantitative thresholds may require inclusion of homogeneous non-Hodgkin lymphoma subtypes to account for differences in tracer uptake per subtype. Moreover, because proliferation is a hallmark of transformation, 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) might be superior to ^{18}F-FDG in this setting. To define the best tracer for detection of TF, we performed a prospective a head-to-head comparison of ^{18}F-FDG and ^{18}F-FLT in patients with FL and TF. **Methods:** ^{18}F-FDG and ^{18}F-FLT PET scans were obtained in 17 patients with FL and 9 patients with TF. We measured the highest maximum standardized uptake value (SUV_{max}), defined as the lymph node with the highest uptake per patient, and SUV_{range}, defined as the difference between the SUV_{max} of the lymph node with the highest and lowest uptake per patient. To reduce partial-volume effects, only lymph nodes larger than 3 cm^3 (A50 isocontour) were analyzed. Scans were acquired 1 h after injection of 185 MBq of ^{18}F-FDG or ^{18}F-FLT. To determine the discriminative ability of SUV_{max} and SUV_{range} of both tracers for TF, receiver-operating-characteristic curve analysis was performed. **Results:** The highest SUV_{max} was significantly higher for TF than FL for both ^{18}F-FDG and ^{18}F-FLT ($P < 0.001$). SUV_{range} was significantly higher for TF than FL for ^{18}F-FDG ($P = 0.029$) but not for ^{18}F-FLT ($P = 0.075$). The ability of ^{18}F-FDG to discriminate between FL and TF was superior to that of ^{18}F-FLT for both the highest SUV_{max} ($P = 0.039$) and the SUV_{range} ($P = 0.012$). The cutoff value for the highest SUV_{max} of ^{18}F-FDG aiming at 100% sensitivity with a maximum specificity was found to be 14.5 (corresponding specificity, 82%). For ^{18}F-FLT, these values were 5.1 and 18%, respectively. When the same method was applied to SUV_{range}, the cutoff values were 5.8 for ^{18}F-FDG (specificity, 71%) and 1.5 for ^{18}F-FLT (specificity, 36%). **Conclusion:** Our data suggest that ^{18}F-FDG PET is a better biomarker for TF than ^{18}F-FLT PET. The proposed thresholds of highest SUV_{max} and SUV_{range} should be prospectively validated.

Key Words: follicular lymphoma; transformed lymphoma; positron emission tomography; ^{18}F-FDG; ^{18}F-FLT

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Follicular lymphoma (FL) is the most common form of indolent B cell non-Hodgkin lymphoma, accounting for about 30% of all non-Hodgkin lymphomas. Its clinical course varies and is characterized by repeated but transient responses to therapy. Histologic transformation into an aggressive lymphoma occurs in 17%, 28%, and 37% of FL patients after 5, 10, and 15 y, respectively, with an apparent plateau at 15 y, after which transformation rarely seems to occur (*1*). There is increasing evidence that autologous consolidation of transformation of FL (TF) patients as first-line treatment may improve survival (*2–4*). Furthermore, retrospective analyses suggest that patients can be cured more often when transformation is diagnosed at an early stage (*5,6*). Consequently, correct and early diagnosis is a prerequisite for adequate treatment of patients with TF. Transformation can be heralded by rapid growth of lymph nodes, an elevated lactate dehydrogenase, or development of systemic symptoms (*7*). Histology remains the gold standard, defining transformation as the presence of sheets of blastic cells or frank diffuse large B cell lymphoma in a patient diagnosed with FL. Therefore, it is mandatory to perform biopsy at the slightest suspicion of transformation. However, because transformation may not involve all lymph nodes, sampling errors can lead to a significant diagnostic delay.

This problem might be overcome by the use of PET because this technique allows for whole-body tissue characterization, enabling determination of areas of high metabolic or proliferative activity. Currently, ^{18}F-FDG PET is used for staging and response evaluation in both aggressive and more indolent types of lymphoma (*8*). There is a clear trend toward higher ^{18}F-FDG uptake in more aggressive histologic subtypes. Therefore, a high uptake in an indolent lymphoma could support the suspicion of transformation. However, there is a considerable overlap in ^{18}F-FDG uptake between aggressive and indolent lymphomas, potentially impairing its utility to detect transformation (*9–11*). To overcome this problem, alternative tracers might be useful. Conceptually, 3′-deoxy-3′-^{18}F-fluorothymidine (^{18}F-FLT) reflects proliferation more closely than ^{18}F-FDG (*12,13*). The limited data on ^{18}F-FLT PET in patients with transformed FL

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For correspondence or reprints contact: Marielle J. Wondergem, Department of Hematology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.
E-mail: m.wondergem@vumc.nl
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suggest a higher ^{18}F-FLT uptake in aggressive lymphoma than in indolent lymphoma, albeit with overlap (*14,15*).

Studies on the role of PET in the detection of transformation typically comprise a spectrum of histologic subtypes, reporting considerable variability in uptake of ^{18}F-FDG. However, because ^{18}F-FDG uptake may strongly vary among histologic subtypes of indolent lymphoma (*16*) and their transformation (*10*), thresholds of ^{18}F-FDG uptake (standardized uptake value) to detect transformation may be a function of the subtype.

To define the best discriminative tracer for the detection of TF, we performed a prospective study with a head-to-head comparison of ^{18}F-FDG and ^{18}F-FLT in a homogeneous patient group consisting of patients with FL and TF only. In addition to maximum tracer uptake, the intrapatient variability of tracer uptake was determined because this parameter might be a more accurate indicator for transformation.

MATERIALS AND METHODS

Patients with untreated histologically proven FL and patients with histologically proven TF were eligible. FL patients underwent a biopsy to establish the diagnosis, defined according to the World Health Organization classification (*17*), and were included based on this histology. Because it is unethical to obtain a biopsy of all involved lymph nodes in FL patients to rule out histologic transformation in every separate lymph node, we defined FL as a pathologically proven diagnosis of FL in a lymph node, confirmed retrospectively by a clinical course fitting FL. The clinical course comprised no need for therapy for at least 1 y after inclusion in the study OR a complete remission or partial remission on CT scan after therapy for indolent lymphoma (i.e., therapy without anthracyclines) and a subsequent treatment-free period of more than 3 mo.

In TF patients, a biopsy was taken because of clinical symptoms suggesting transformation (B symptoms, localized tumor mass growth, or elevated lactate dehydrogenase). Transformation was defined as (areas of) diffuse large B cell lymphoma in a biopsy obtained from a patient previously diagnosed with FL.

The treating hematologist was masked to all data except for the staging results (qualitative assessment) of the ^{18}F-FDG scan, in the context of standard patient care.

Patients were included when they had at least 1 lymph node with a diameter of at least 2 cm (measured on CT scan or ultrasound). Patients were excluded if treatment was started before PET/CT or if they had (transformation of) types of indolent non-Hodgkin lymphomas other than FL. In accordance with the Declaration of Helsinki, all patients gave written informed consent to participate in this single-center study, which was approved by the institutional review board. This trial was registered in the Dutch trial register (NTR code 1487).

PET

Each patient underwent ^{18}F-FDG as well as ^{18}F-FLT PET/CT within 1 wk, in random order, depending on logistics. After at least 6 h of fasting, patients were injected with approximately 185 MBq of ^{18}F-FDG or ^{18}F-FLT intravenously. All studies were performed on a Gemini TOF-64 PET/CT scanner (Philips). Low-dose CT was collected using a beam current of 30–50 mAs at 120 keV. Images (3 min per bed position) covered the mid thigh to skull vertex trajectory, starting 60 min after injection. Plasma glucose levels were routinely obtained before ^{18}F-FDG PET/CT. Calibration and scanning procedures complied with the guidelines of the European Association of Nuclear Medicine (*18*).

CT images were reconstructed using an image matrix size of 512 × 512, resulting in voxel sizes of 1.17 × 1.17 mm and a slice thickness of 5 mm. For PET, data were reconstructed by means of a raw action ordered-subset expectation maximization algorithm using default reconstruction parameters. Time-of-flight information was used during reconstruction. Reconstructed images had an image matrix size of 144 × 144, a voxel size of 4 × 4 mm, and a slice thickness of 4 mm. The postreconstruction image resolution was 7 mm in full width at half maximum.

PET images were evaluated by 2 independent observers. Nodal ^{18}F-FDG uptake was classified as positive if uptake exceeded that of liver. ^{18}F-FLT uptake was positive if uptake was enhanced, compared with local background.

^{18}F-FDG and ^{18}F-FLT uptake as defined with standardized uptake value (SUV) (maximum SUV [SUV_{max}] and 50% and 70% of the sum of maximum and background values [SUV A50% and SUV A70%, respectively]) were measured for all visually positive lymph nodes of at least 3 cm^3 (as defined with A50 volume-of-interest isocontouring, to account for partial-volume effects) (*19,20*).

Tumor volumes of interest were defined using a 3-dimensional (3D) region-growing algorithm, as described previously (*21*). This algorithm is based on the 3D search algorithm in the IDL software package (Interactive Data Language, version 6.3; Research Systems Inc.). In short, the program first searched for the location of the maximum voxel value within a (semiautomatically or manually) predefined region. Next, using this maximum value (SUV_{max}) and its location as a starting point, a 3D volume of interest was defined automatically using a 3D region-growing algorithm, including all voxels above a specified threshold. This threshold was set at SUV A50% and SUV A70%. The local background value was derived automatically using a 3D shell of 1 voxel thickness at 1.5 cm from the border of the initially estimated or predefined tumor volume. This initial estimate was based on the 70% of maximum pixel value 3D isocontour (*22,23*). SUVs were normalized to body weight and to serum glucose for ^{18}F-FDG.

Because transformation in patients with FL might not occur in all lymph nodes simultaneously, we hypothesized that the intrapatient variability of tracer uptake might reflect the process of transformation. For either tracer, and for each patient, apart from measuring the SUV_{max} of the most avid lymph node (highest SUV_{max}) we calculated the SUV_{range}, defined as the difference between maximum and minimum uptake within an individual patient.

Statistics

Correlations were calculated using the Pearson r method. To compare follow-up times and SUVs between FL and TF groups, we used the nonparametric Mann–Whitney *U* test. The discriminative ability of the highest SUV_{max} and SUV_{range} to distinguish the absence and presence of transformation were quantified by means of the area under the receiver-operating-characteristic curve, using our definition of transformation (see the "Materials and Methods" section) as the reference test. From this receiver-operating-characteristic curve analysis, we also determined a cutoff value for detection of transformation. The cutoff value chosen was the smallest cutoff value for which sensitivity in the sample was 100% (i.e., maximizing specificity under the restriction of no false-negatives).

Sample size was based on the comparison of mean SUV_{max} between the FL and TF groups. The planned number of 17 per group would provide 80% power to detect a difference of 1 SD (~5 units) in mean SUV_{max}, assuming 2-sided testing at a significance level of 5%. To protect patients from both the physical and the radiation burden of 2 consecutive PET scans, the institutional review board requested an analysis after inclusion of half of the TF patients. This paper presents the results of the study after inclusion of 9 (of a planned number of 17) TF patients. By that time the planned inclusion of 17 FL patients had already been completed. Statistical analyses were performed using the SPSS statistical package (version 20.0; IBM), except for comparison of areas under the curve (AUCs) between ^{18}F-FDG and ^{18}F-FLT, which was performed in SAS (version 9.2; SAS Institute Inc.).

RESULTS

From November 2008 until June 2011, we included 17 patients with FL and 9 with histologically proven TF. Median clinical follow-up of all patients was 31.5 mo (range, 14–43 mo). Follow-up time was similar for FL and TF patients ($P = 0.79$, Table 1). All patients with FL histology at the time of PET/CT satisfied our definition of FL during their subsequent disease course: 6 did not need immediate treatment, 2 of them eventually required treatment during follow-up (after 17 and 21 mo), and 1 of them was diagnosed with TF after 21 mo (sudden increase of a previously stable lymph node). The remaining 11 FL patients reached complete remission on CT scan after chemoimmunotherapy, with a median response duration of 30 mo (range, 14–43 mo). All FL patients were alive at last follow-up.

Eight of 9 TF patients reached complete remission on PET/CT after induction therapy, 7 of whom were eligible for consolidation with autologous stem cell transplantation. Of these 7 patients, only 1 patient relapsed after 30 mo. The patient without consolidation died of secondary acute myeloid leukemia 34 mo after her treatment. In

TABLE 1
Patient Characteristics

FL/TF	Age (y)	Stage	FLIPI	Reason for biopsy	Time FL diagnosis to scan or TF	Treatment (treatment received for FL before transformation)	Response (mo)	Follow-up (mo)
FL	54	3	Intermediate	Diagnosis	48 mo	W&W		34
FL	42	4	Intermediate	Diagnosis	14 mo	W&W		30
FL	62	3	Intermediate	Diagnosis	48 mo	W&W		35
FL	59	2	Low	Diagnosis	3 mo	W&W, TF after 21 mo		31
FL	55	3	Low	Diagnosis	2 mo	W&W, R-L after 21 mo		24
FL	47	4	Intermediate	Diagnosis	1 mo	W&W, R-CVP after 17 mo		21
FL	56	3	Low	Diagnosis	1 mo	R-L	42	42
FL	63	4	High	LM	20 y	R-L	43	43
FL	54	3	Intermediate	Diagnosis	1 wk	R-L	42	42
FL	59	4	High	Diagnosis	4 mo	R-L	18	42
FL	78	3	Intermediate	Diagnosis	11 mo	R-L	27	27
FL	38	4	Intermediate	Diagnosis	3 mo	R-CVP	41	41
FL	49	3	Intermediate	LM	2 mo	R-CVP	32	32
FL	34	2	Low	Diagnosis	4 mo	R-CVP	30	30
FL	37	3	High	Diagnosis	2 wk	R-CVP and R maintenance	28	28
FL	47	4	Intermediate	Diagnosis	11 mo	R-CVP	24	24
FL	80	3	High	Diagnosis	2 d	3 × R-CVP and 3 × R-L	14	14
TF	64	4		LM	20 y	R-CHOP, died of AML (RT, L)	36	36
TF	67	3		LM	0.9 y	R-CHOP (W&W)	29	29
TF	49	3		BS	3 y	R-CHOP, Z-BEAM, and AuSCT (R-CVP)	42	42
TF	58	3		ELD	5.3 y	R-CHOP, Z-BEAM, and AuSCT (CVP, F)	40	40
TF	42	3		LM	2.5 y	R-CHOP, Z-BEAM, and AuSCT (R-CVP)	38	38
TF	60	4		ELD	15 y	R-CHOP, Z-BEAM, and AuSCT (L)	30	35
TF	63	4		LM	3 y	R-CHOP, Z-BEAM, and AuSCT (R-L)	16	16
TF	62	3		LM	7 y	R-DHAP/VIM/DHAP, Z-BEAM, and AuSCT (L)	23	23
TF	61	3		LM	2 mo	R-DHAP/VIM/DHAP, Z-BEAM, and AuSCT (W&W)	3*	3

*Died of progression, 3 mo after AuSCT.

FLIPI = follicular lymphoma international prognostic index; W&W = watch and wait; R = rituximab; L = chlorambucil; CVP = cyclophosphamide, vincristine and prednisone; LM = large mass; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone; AML = acute myeloid leukemia; RT = radiotherapy; BS = B symptoms; Z = Zevalin = ^{90}Y ibritumomab tiuxetan; BEAM = carmustine, etoposide, cytarabine, melphalan; AuSCT = autologous stem cell transplantation; F = fludarabine; ELD = elevated lactate dehydrogenase; DHAP = high dose cytarabine, cisplatinum, dexamethasone; VIM = etoposide, iphosphamide, methotrexate.

TABLE 2
Comparison of SUV Measures Between FL and TF Groups

SUV measure	FL	TF	*P*
^{18}F-FDG			
Highest SUV_{max}			<0.001
Median	10.9	22.0	
Range	5.3–21.0	14.7–42.2	
SUV_{range}			<0.001
Median	4.6	15.1	
Range	0.0–7.9	6.0–37.5	
^{18}F-FLT			
Highest SUV_{max}			0.029
Median	8.0	11.5	
Range	3.6–16.1	5.5–16.3	
SUV_{range}			0.075
Median	3.9	4.7	
Range	0.0–7.4	1.5–12.5	

the single patient who obtained a partial remission only on PET/CT after induction therapy, the autologous stem cell transplantation did not result in an improvement of response and progression occurred 3 mo after transplant, eventually leading to death. Median progression-free survival and overall survival for TF patients were both 29 mo (Table 1).

For either tracer, the mean uptake interval between injection and image acquisition was 61 min (SD, 7.9 min). During ^{18}F-FDG PET examination, serum glucose levels ranged from 5.4 to 7.2 mmol/L, except in 1 diabetic TF patient who had a plasma glucose level of 16 mmol/L.

The number of visually positive lymph nodes was similar for ^{18}F-FDG and ^{18}F-FLT PET.

We measured an SUV of 259 lymph nodes in the 26 patients (median, 9 per patient; range, 2–23). Because results of the various SUV metrics were highly concordant for either tracer, $r = 0.99$, $P < 0.01$, we report only the SUV_{max}-based data. SUV A50% can be inferred by multiplying SUV_{max} by 0.68.

In individual patients, the most avid lymph node was the same for ^{18}F-FDG and ^{18}F-FLT in only 42% (11/26 patients; 5 FL and 6 TF).

The highest intrapatient SUV_{max} was significantly higher for TF than FL for both ^{18}F-FDG and ^{18}F-FLT (Table 2; both $P < 0.001$). However, there was a considerable overlap between the SUV_{max} of TF and FL, for both tracers (Fig. 1). The intrapatient SUV_{range} of ^{18}F-FDG was significantly higher for TF than FL (Table 2; $P = 0.029$) but not for ^{18}F-FLT (Table 2; $P = 0.075$). Values for each individual patient are depicted in Figure 1.

In receiver-operating-characteristic analysis, we found that the ability of ^{18}F-FDG to discriminate between FL and TF was superior to that of ^{18}F-FLT for the highest SUV_{max} (Table 3; $P = 0.039$) and for the SUV_{range} (Table 3, $P = 0.012$). The cutoff value for the highest SUV_{max} of ^{18}F-FDG aiming at 100% sensitivity with a maximum specificity was 14.5, with a corresponding specificity of 82% (for ^{18}F-FLT, 5.1 and 18%, respectively). When the same method was applied to the intrapatient SUV_{range}, the cutoff values were 5.8 for ^{18}F-FDG (corresponding specificity, 71%) and 1.5 for ^{18}F-FLT (corresponding specificity, 36%).

DISCUSSION

In view of the different treatment strategy for TF as opposed to FL, diagnosing transformation early in the course of the disease is of utmost importance. Our head-to-head comparison of ^{18}F-FDG and ^{18}F-FLT in a homogeneous group of patients with either FL or histologically proven TF suggests that when the highest SUV_{max} or the SUV_{range} is used, ^{18}F-FDG is superior to ^{18}F-FLT in the detection of TF. When thresholds maximizing sensitivity were used, ^{18}F-FDG's highest SUV_{max} and SUV_{range} correctly identified all transformed patients, misclassifying 3 and 5 FL patients as TF, respectively. In contrast, the highest SUV_{max} and SUV_{range} of ^{18}F-FLT were not suited to detect transformation: here, with the aim at detecting all transformed patients, 14 and 12 FL patients were erroneously classified as TF, respectively.

Other studies using ^{18}F-FDG in this setting included mixtures of several lymphoma subtypes, and this heterogeneity may have contributed to the lack of consistency of thresholds of highest SUV_{max} or SUV_{range} (*9–11*). For example, our median ^{18}F-FDG highest SUV_{max} for FL (10.9, Table 2) is higher than the threshold of 10 proposed by Schöder et al., excluding indolent lymphoma with a specificity of 81% (*9*). ^{18}F-FDG avidity seems to be related to the histologic subtype of indolent lymphoma and its transformation (*16,24,25*). Noy et al. reported higher ^{18}F-FDG uptake in transformed FL than in transformed marginal zone lymphoma

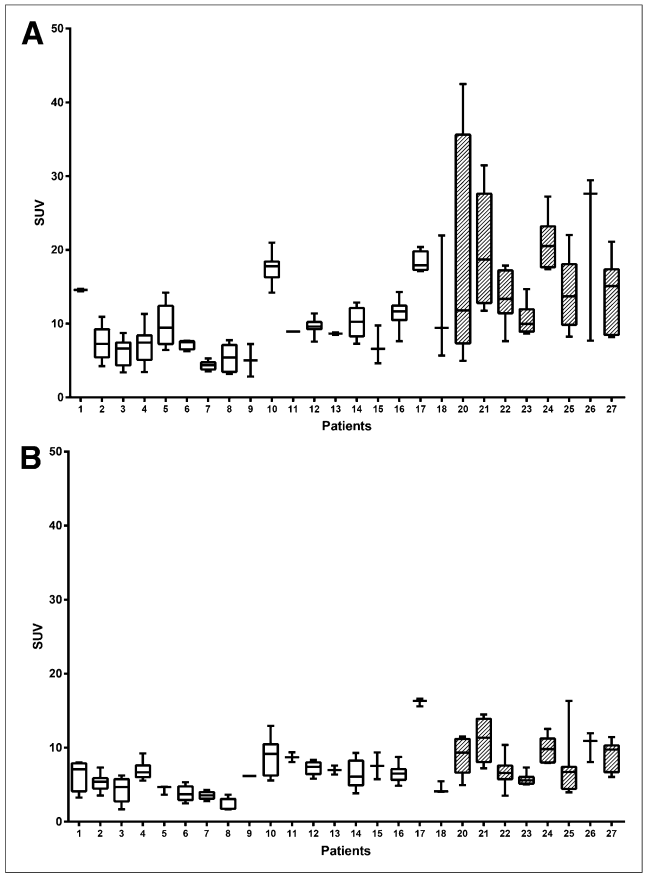

FIGURE 1. Intrapatient variability in uptake for ^{18}F-FDG (A) and ^{18}F-FLT (B) for FL (white boxes) and TF (hatched boxes). Whiskers represent lowest and highest SUV_{max} in that patient; the difference between those measures is SUV_{range}.

TABLE 3
Comparison of Discriminative Ability (AUCs) of ^{18}F-FDG and ^{18}F-FLT

AUC per SUV measure	^{18}F-FDG	^{18}F-FLT	*P*
Highest SUV_{max}			0.039
AUC	0.97	0.76	
95% confidence interval for AUC	0.91–1.00	0.54–0.98	
SUV_{range}			0.012
AUC	0.97	0.72	
95% confidence interval for AUC	0.90–1.00	0.50–0.93	

and chronic lymphocytic leukemia (*10*). We therefore suggest that thresholds indicating transformation should be investigated in homogeneous patient cohorts. Research on absolute thresholds will strongly benefit from the implementation of standardization of quantitative procedures as proposed in the guidelines of the European Association of Nuclear Medicine (*18*).

Because of biologic reasons, we hypothesized that ^{18}F-FLT would be superior to ^{18}F-FDG in detecting transformation. ^{18}F-FLT has been reported as a specific biomarker of proliferation (*12,13,15*). However, we could neither determine a cutoff value for highest SUV_{max} nor find a significant difference between the SUV_{range} of TL and FL, allowing differentiation. In our series, at optimal sensitivity, the specificity of only 36% would imply an unacceptably high proportion of patients requiring a biopsy to exclude transformation. The 58% discordance rate between nodal sites of highest ^{18}F-FDG and ^{18}F-FLT uptake confirms that these tracers reflect different biologic processes. The poor performance of ^{18}F-FLT may question its specificity for proliferation. In an earlier study on FL patients, we showed that ^{18}F-FLT uptake was poorly associated with Ki-67 expression. The observed high ^{18}F-FLT uptake in FL may also be due to ^{18}F-FLT being a substrate for DNA repair (*26*). The reverse of this hypothesis would be that TF shows a lower uptake than expected based on proliferation. It has been shown that ^{18}F-FLT uptake is underestimated if the tumor relies primarily on de novo thymidine synthesis, thereby bypassing the thymidine salvage pathway that is also used by ^{18}F-FLT (*27*). It is not known to what extent TF uses this de novo pathway, and consequently these TF show lower ^{18}F-FLT uptake although they are highly proliferative. Moreover, in preclinical models high intrinsic thymidine levels can also inversely affect ^{18}F-FLT uptake, leading to less uptake despite a high tumor proliferation rate. The clinical impact of this phenomenon remains to be determined (*28*).

In our original study protocol, we had not specified an α-spending function for the interim analysis requested by the ethics committee. In a formal interim analysis, the *P* values for comparing AUCs that were found would likely have been too large to conclude significance and so strictly we would have had to include an additional 8 TF patients. However, after weighing the burden for the additional patients and our assessment of the probability that in the final analysis a significant difference would have been found in favor of ^{18}F-FLT, it was decided to end the study prematurely.

Obviously, our data and thresholds need to be validated, for example, by prospectively implementing ^{18}F-FDG PET routinely on suspected FL transformation. We speculate that in such a setting performance might be better than we have currently observed: our study design did not allow inclusion of critically ill TF patients with high disease burden (and most likely high uptake) because it was unethical to delay treatment until both PET/CT scans had been obtained. Additionally, we cannot exclude that our threshold results were quantitatively biased by the fact that at the time of PET/CT the largest or most rapidly growing lymph node had been excised for histology in the TF patients. Such bias would likely lead to underestimated sensitivity and specificity of highest intrapatient SUV_{max} and SUV_{range} (*9*). On the basis of our data, we suggest that for optimal detection of TF, PET/CT should be performed before the biopsy. At that moment the diagnostic accuracy is optimal; moreover, given the high intraindividual heterogeneity in uptake, PET will be helpful in the decision of where to biopsy. Although no study showed biopsies of all lymph nodes in a patient, we share the opinion that the lymph node with the highest uptake is most likely the transformed lymph node, also considering data showing uptake correlating with aggressiveness (*9–11,16*).

CONCLUSION

Our data suggest that ^{18}F-FDG PET is a better biomarker of TF than ^{18}F-FLT PET. Our proposed SUV-based thresholds indicate that TF should be prospectively validated in a real-life clinical setting that is compliant with prevailing guidelines for quantitative ^{18}F-FDG PET.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. No potential conflict of interest relevant to this article was reported.

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