Chapter 2

18F-Fluorodeoxyglucose (18F-FDG) or 18F-fluorothymidine (18F-FLT) to detect transformation of follicular lymphoma.

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Published in Journal of Nuclear Medicine, 2015:56(2):216-221

Abstract

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 18F-FDG has utility as biomarker of transformation. However, quantitative thresholds may require inclusion of homogeneous NHL subtypes to account for differences in tracer uptake per subtype. Moreover, since proliferation is a hallmark of transformation, 18F-FLT might be superior to 18F-FDG in this setting. To define the best tracer for detection of transformation of FL, we performed a prospective a head-to-head comparison of 18F-FDG and 18F-FLT in patients with FL and transformed FL.

Methods: 18F-FDG- and 18F-FLT-PET scans were performed in 17 patients with FL and 9 patients with transformed lymphoma. We measured highest SUVmax, defined as the lymph node with the highest uptake per patient and SUVrange, defined as the difference between the SUVmax of the lymph node with the highest and lowest uptake per patient. To reduce partial volume effects only lymph nodes larger than 3cc (A50 isocontour) were analyzed. Scans were made 1 hour after injection of 185 MBq of 18F-FDG or 18F-FLT. To determine the discriminative ability of SUVmax and SUVrange of both tracers for transformation of FL, ROC curve analysis was performed.

Results: Highest SUVmax was significantly higher for TF compared to FL for both 18F-FDG and 18F-FLT ($p<0.001$). SUVrange was significantly higher for TF as compared to FL for 18F-FDG ($p=0.029$) and not for 18F-FLT ($p=0.075$). The ability of 18F-FDG to discriminate between FL and TF was superior to that of 18F-FLT for both the highest SUVmax ($p=0.039$) and SUVrange ($p=0.012$). The cut-off value for highest SUVmax of 18F-FDG aiming at 100% sensitivity with a maximum specificity was found to be 14.5 (corresponding specificity 82%). For 18F-FLT these values were 5.1 and 18%, respectively. When applying the same method to SUVrange, cut-off values were 5.8 for 18F-FDG (specificity 71%) and 1.5 for 18F-FLT (specificity 36%).

Conclusion: our data suggest that 18F-FDG PET is a better biomarker for transformed FL than 18F-FLT PET. The proposed thresholds of highest SUVmax and SUVrange should be prospectively validated.

(this trial was registered: NTR code 1487)

Introduction

Follicular lymphoma (FL) is the most common form of indolent B-cell non-Hodgkin's lymphoma accounting for about 30% of all non-Hodgkin's lymphomas. Its clinical course varies and is characterized by repeated but transient responses to therapy. Histological transformation into an aggressive lymphoma occurs in 17%, 28% and 37% of FL patients after 5,10 and 15 years respectively, with an apparent plateau at 15 years after which transformation rarely seems to occur (1). There is increasing evidence that autologous consolidation of transformed lymphoma 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 transformed lymphoma. Transformation can be heralded by rapid growth of lymph nodes, an elevated lactate dehydrogenase (LDH) and/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 (DLBCL) in a patient diagnosed with FL. Therefore, it is mandatory to biopsy at the slightest suspicion of transformation. However, since 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 Positron Emission Tomography (PET) as this technique allows for whole body tissue characterization, enabling determination of areas of high metabolic or proliferative activity. Currently, 18-fluorodeoxyglucose (18F-FDG) PET is used for staging and response evaluation both in aggressive, as well as in more indolent types of lymphoma (8). There is a clear trend towards higher 18F-FDG uptake in more aggressive histological subtypes. Therefore a high uptake in an indolent lymphoma could support the suspicion of transformation. However, there is a considerable overlap in 18F-FDG uptake between aggressive and indolent lymphomas potentially impairing its utility to detect transformation (9-11). In order to overcome this, alternative tracers might be useful. Conceptually, fluorothymidine (18F-FLT) reflects proliferation more closely than 18F-FDG (12,13). The limited data on 18F-FLT-PET in patients with transformed FL suggest a higher 18F-FLT uptake in aggressive lymphoma as compared to indolent lymphoma, albeit with overlap (14,15).

Studies on the role of PET in detection of transformation typically comprise a spectrum of histological subtypes, reporting considerable variability in uptake of 18F-FDG. However, since 18F-FDG uptake may strongly vary among histological subtypes of

indolent lymphoma (16) and their transformation (10), thresholds of 18F-FDG uptake (SUV) to detect transformation may be a function of the subtype.
In order to define the best discriminative tracer for the detection of transformation of FL, we performed a prospective study with a head to head comparison of 18F-FDG and 18F-FLT in a homogeneous patient group consisting of patients with FL and transformation of FL only. In addition to maximum tracer uptake the intra-patient variability of tracer uptake was determined as this parameter might be a more accurate indicator for transformation.

Materials and methods

Patients with untreated histologically proven FL and patients with histologically proven transformation of FL (TF) were eligible. FL patients underwent a biopsy to establish the diagnosis, defined according to the WHO classification 2008 and were included based on this histology. Since it is unethical to obtain a biopsy of all involved lymph nodes in FL patients to rule out histological 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: no need for therapy for at least one year after inclusion in the study OR a complete remission (CR) or partial remission (PR) on CT scan after therapy for indolent lymphoma (i.e. therapy without anthracyclins) and a subsequent treatment-free period of more than three months.
In TF patients a biopsy was taken because of clinical symptoms suggesting transformation (B symptoms, localized tumor mass growth or elevated LDH). Transformation was defined as (areas of) DLBCL in a biopsy obtained from a patient previously diagnosed with FL.
The treating haematologist was blinded to all data except for the staging results (qualitative assessment) of the 18F-FDG scan, in the context of standard patient care.
Patients were included when they had at least one 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) other types of indolent NHLs 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 a 18F-FDG as well as a 18F-FLT PET-CT within one week, in random order, depending on logistics. After at least six hours of fasting, patients were injected with ~ 185 MBq 18F-FDG or 18F-FLT iv. All studies were performed on a Gemini TOF-64 PET-CT scanner (Philips Medical Systems, Best, The Netherlands). Low-dose CT was collected using a beam current of 30 to 50 mAs at 120 keV. Images (3 minutes per bed position) covered the mid-thigh to skull vertex trajectory, starting 60 minutes post injection. Plasma glucose levels were routinely obtained before 18F-FDG PET-CT. Calibration and scanning procedures complied with the EANM guidelines (17).

CT was 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 post reconstruction image resolution was 7 mm FWHM. PET images were evaluated by two independent observers. Nodal 18F-FDG uptake was classified as positive if uptake exceeded that of liver. 18F-FLT uptake was positive if uptake was enhanced compared to local background.

18F-FDG and 18F-FLT uptake as defined with SUV (SUVmax, SUV A50%, SUV A70%) were measured of all visually positive lymph nodes of at least 3cc (as defined with A50 VOI isocontouring, to account for partial volume effects) (18,19)

Tumor volumes of interest (VOI) were defined using a 3D region growing algorithm, as described previously (20). This algorithm is based on the 3D search algorithm in the IDL software package version 6.3 (Interactive Data Language, Research Systems Inc., Boulder, USA). In short, the program first searched for the location of the maximum voxel value within a (semi-automatically or manually) predefined region. Next, using this maximum value and its location as starting point, a 3D VOI was defined automatically using a 3D region growing algorithm, including all voxels above a specified threshold. This threshold was set at 50 and 70% of the sum of maximum and background values. 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 (pre-)defined tumor volume. This initial estimate is based on the 70% of maximum pixel value 3D isocontour (21,22). SUVs were normalized to body weight and to serum glucose for 18F-FDG.

Since 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 SUVmax of the most avid lymph node (highest SUVmax) we calculated the SUVrange, 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 non-parametric Mann Whitney U test. Discriminative ability of highest SUVmax and SUVrange to distinguish absence and presence of transformation were quantified by means of the area under the receiver operating characteristic (ROC) curve, using our definition of transformation (see before) as the reference test. From this ROC curve analysis we also determined a cut-off value for detection of transformation. The cut-off value chosen was the smallest cut-off 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 SUVmax between the FL and TF groups. The planned number of 17 per group would provide 80% power to detect a difference of one standard deviation (approximately 5 units) in mean SUVmax assuming two-sided testing at a significance level of 5%. In order to protect patients from both the physical and radiation burden of two consecutive PET scans the institutional review board requested an analysis after inclusion of half of the transformed lymphoma patients. The 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 IBM SPSS statistical package 20.0, except for comparison of AUCs between FDG and FLT which was performed in SAS version 9.2.

Results

From November 2008 until June 2011, we included 17 patients with FL and 9 with histologically proven transformation of FL (TF). Median clinical follow-up of all patients was 31.5 months (range:14-43). Follow-up time was similar for FL and TF patients (p=0.79, table 1). All patients with FL histology at time of PET-CT satisfied our definition of FL during their subsequent disease course : 6 did not need immediate treatment, two of them eventually required treatment during follow-up (after 17 and 21 months, respectively), and one of them was diagnosed with TF after 21 months (sudden increase

of a previously stable lymph node). The remaining 11 FL patients reached CR on CT scan after chemo-immunotherapy, with a median response duration of 30 months (range 14-43). All FL patients were alive at last follow-up.
Eight out of nine TF patients reached CR on PET-CT after induction therapy, seven of whom were eligible for consolidation with autologous stem cell transplantation. Of these seven patients only one patient relapsed after 30 months. The patient without consolidation died of secondary acute myeloid leukemia 34 months after her treatment. In the single patient who obtained a partial remission (PR) only on PET-CT after induction therapy, the autologous stem cell transplantation did not result in an improvement of response, and progression occurred 3 months after transplant eventually leading to death. Median PFS and OS for TF patients were both 29 months. (table 1).

For either tracer, the mean uptake interval between injection and image acquisition was 61 minutes (SD 7.9 min). During 18F-FDG PET examination, serum glucose levels ranged from 5.4 to 7.2 mmol/l, except in one diabetic TF patient who had a plasma glucose level of 16 mmol/l.
The number of visually positive lymph nodes was similar for 18F-FDG and 18F-FLT PET. We measured SUV of 259 lymph nodes in the 26 patients (median 9 per patient, range 2-23). Since results of the various SUV metrics were highly concordant for either tracer: $r=0.99$, $p<0.01$, we only report the SUVmax based data. SUV A50% can be inferred by multiplying SUVmax by 0.68.
In individual patients, the most avid lymph node was the same for 18F-FDG and 18F-FLT in only 42% (11 out of 26 patients; 5 FL and 6 TF) .

Table 1: patient characteristics

FL/TF	age (yrs)	stage	FLIPI	reason for biopsy	time FL diagnosis to scan or TF	Treatment *(treatment received for FL before transformation)*	response (months)	follow up (months)
FL	54	3	int	diagn	48 months	W&W		34
FL	42	4	int	diagn	14 months	W&W		30
FL	62	3	int	diagn	48 months	W&W		35
FL	59	2	low	diagn	3 months	W&W, TF after 21 months		31
FL	55	3	low	diagn	2 months	W&W, R-L after 21 months		24
FL	47	4	int	diagn	1 month	W&W, R-CVP after 17 months		21
FL	56	3	low	diagn	1 month	R-L	42	42
FL	63	4	high	LM	20 yrs	R-L	43	43
FL	54	3	int	diagn	1 week	R-L	42	42
FL	59	4	high	diagn	4 months	R-L	18	42
FL	78	3	int	diagn	11 months	R-L	27	27
FL	38	4	int	diagn	3 months	R-CVP	41	41
FL	49	3	int	LM	2 months	R-CVP	32	32
FL	34	2	low	diagn	4 months	R-CVP	30	30
FL	37	3	high	diagn	2 weeks	R-CVP and R maintenance	28	28
FL	47	4	int	diagn	11 months	R-CVP	24	24
FL	80	3	high	diagn	2 days	3 x R-CVP and 3 x R-L	14	14
TF	64	4		LM	20 yrs	R-CHOP, died of AML *(RT, L)*	36	36
TF	67	3		LM	0.9 yrs	R-CHOP *(W&W)*	29	29
TF	49	3		BS	3 yrs	R-CHOP, Z-BEAM and AuSCT *(R-CVP)*	42	42
TF	58	3		ELD	5.3 yrs	R-CHOP, Z-BEAM and AuSCT *(CVP, F)*	40	40
TF	42	3		LM	2.5 yrs	R-CHOP, Z-BEAM and AuSCT *(R-CVP)*	38	38
TF	60	4		ELD	15 yrs	R-CHOP, Z-BEAM and AuSCT *(L)*	30	35
TF	63	4		LM	3 yrs	R-CHOP, Z-BEAM and AuSCT *(R-L)*	16	16
TF	62	3		LM	7 yrs	R-DHAP/VIM/DHAP, Z-BEAM and AuSCT *(L)*	23	23
TF	61	3		LM	2 months	R-DHAP/VIM/DHAP, Z-BEAM and AuSCT *(W&W)*	3*	3

FL=follicular lymphoma, TF=transformation of FL, FLIPI=follicular lymphoma international prognostic index, int=intermediate, diagn=diagnosis, LM=large mass, BS=B symptoms, ELD=elevated LDH
W&W=watch and wait
R= rituximab
L= chlorambucil
CVP= cyclophosphamide, vincristine and prednisone
CHOP=cyclophosphamide, doxorubicine, vincristine, prednisone
RT=radiotherapy
F=fludarabine
DHAP=high dose cytarabine, cisplatinum, dexamethasone
VIM=etoposide, iphosphamide, methotrexate
Z=Zevalin=90Yttrium ibritumomab tiuxetan
BEAM=carmustine, etoposide, cytarabine, melphalan
AuSCT=autologous stem cell transplantation
*: died of progression, 3 months after AuSCT

The highest intrapatient SUVmax was significantly higher for TF compared to FL for both 18F-FDG and 18F-FLT (table 2; both p<0.001). However, there was a considerable overlap between the SUVmax of TF and FL, for both tracers (fig 1). The intrapatient SUVrange of 18F-FDG was significantly higher for TF as compared to FL (table 2; p=0.029), but not for 18F-FLT (table 2; p=0.075). Values for each individual patient are depicted in figure 1.

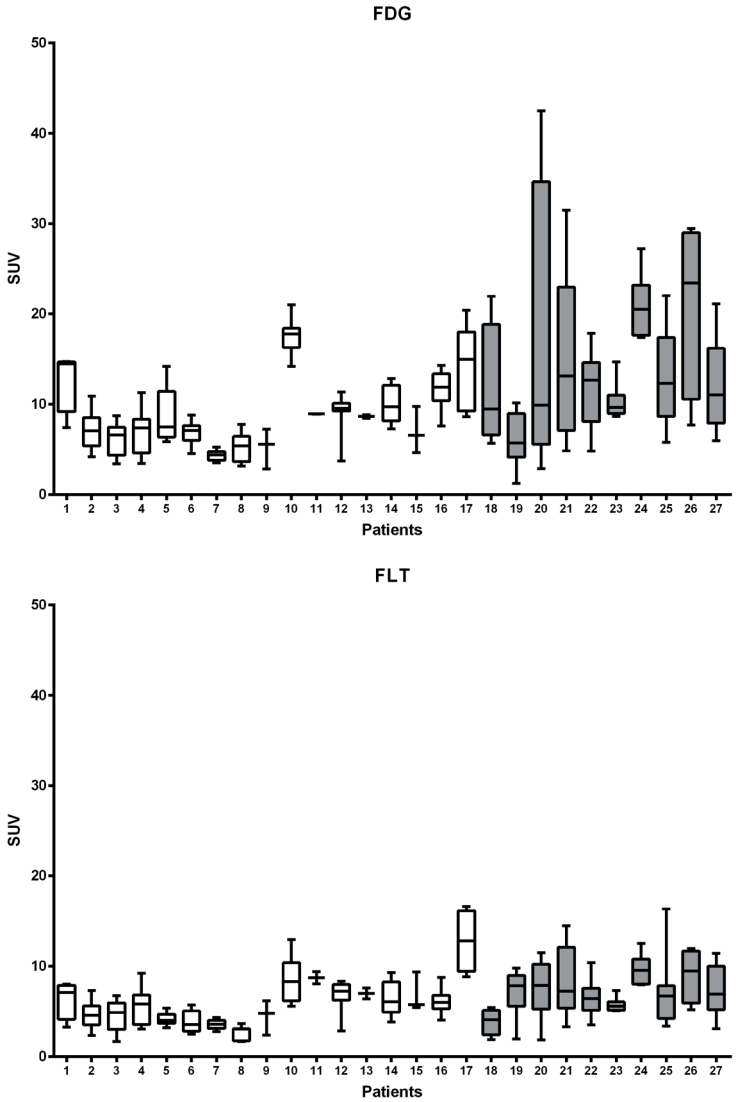

Figure 1: Intrapatient variability in uptake for 18F-FDG (A) and 18F-FLT (B) for FL (white boxes) and TF (hatched boxes)The whiskers represent the lowest and highest SUVmax in that patient, the difference between those measures is the SUVrange

In ROC analysis we found the ability of 18F-FDG to discriminate between FL and TF was superior to that of 18F-FLT for the highest SUVmax (table 3; p=0.039) as well as for the SUVrange (table 3, p=0.012). The cut-off value for highest SUVmax of 18F-FDG aiming at 100% sensitivity with a maximum specificity was 14.5, with a corresponding specificity of 82% (for 18F-FLT: 5.1 and 18%, respectively). When applying the same method to the intrapatient SUVrange, cut-off values were 5.8 for 18F-FDG (corresponding specificity 71%) and 1.5 for 18F-FLT (corresponding specificity 36%).

Table 2: Comparison of SUV measures between FL and TF groups

SUV measures		FL	TF	p
18F-FDG				
Highest SUVmax				<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	
18F-FLT				
Highest SUVmax				0.029
	median	8.0	11.5	
	range	3.6-16.1	5.5-16.3	
SUVrange				0.075
median		3.9	4.7	
range		0.0-7.4	1.5-12.5	

Table 3: Comparison of discriminative ability (AUCs) of 18F-FDG and 18F-FLT

AUC per SUV measure	18F-FDG	18F-FLT	p
Highest SUVmax			0.039
AUC	0.97	0.76	
95% confidence interval for AUC	0.91-1.00	0.54-0.98	
SUVrange			0.012
AUC	0.97	0.72	
95% confidence interval for AUC	0.90-1.00	0.50-0.93	

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 18F-FDG and 18F-FLT in a homogeneous group of patients with

either FL or histologically proven transformation of FL suggests that using the highest SUVmax or the SUVrange, 18F-FDG is superior to 18F-FLT in detection of transformation of FL. Using thresholds maximizing sensitivity 18F-FDG's highest SUVmax and SUVrange correctly identified all transformed patients, misclassifying 3 and 5 FL patients as TF, respectively. In contrast, the highest SUVmax and SUVrange of 18F-FLT were not suited to detect transformation: here, aiming at detecting all transformed patients, 14 and 12 FL patients were erroneously classified as TF, respectively.
Other studies using 18F-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 SUVmax or SUVrange. (9-11) For example, our median 18F-FDG highest SUVmax 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). 18F-FDG avidity seems to be related to the histological subtype of indolent lymphoma and its transformation (16,23,24). Noy et al. reported higher 18F-FDG uptake in transformed FL than in transformed marginal zone lymphoma 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 (17).

Because of biological reasons, we hypothesized that 18F-FLT would be superior to 18F-FDG in detecting transformation. 18F-FLT has been reported as a specific biomarker of proliferation (12,13,15). However, we could neither determine a cut-off value for highest SUVmax nor did we find a significant difference between the SUVrange 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 18F-FDG and 18F-FLT uptake confirms that these tracers reflect different biological processes. The poor performance of 18F-FLT may question its specificity for proliferation. In an earlier study on FL patients we showed that 18F-FLT uptake was poorly associated with Ki67 expression. The observed high 18F-FLT uptake in FL may also be due to 18F-FLT being a substrate for DNA repair (25). The reverse of this hypothesis would be that TF shows a lower uptake than expected based on proliferation. It has been shown that 18F-FLT uptake is underestimated if the tumor relies primarily upon "de novo" thymidine synthesis, thereby bypassing the thymidine salvage pathway that is also used by 18F-FLT (26). It is not known to what extent TF use this "de novo" pathway and consequently show

lower 18F-FLT uptake although they are highly proliferative. Moreover, in preclinical models high intrinsic thymidine levels can also inversely affect 18F-FLT uptake, leading to less uptake despite a high tumor proliferation rate. The clinical impact of this phenomenon remains to be determined (27).

In our original study protocol we had not specified an alpha-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 18F-FLT, it was decided to end the study prematurely.

Obviously, our data and thresholds need to be validated, for example by prospectively implementing 18F-FDG PET routinely upon suspected FL transformation. We speculate that in such 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) since it was unethical to delay treatment until both PET-CT scans had been made. 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 SUVmax and SUVrange (9). Based on our data we suggest that for optimal detection of transformation of FL, the PET-CT should be performed before the biopsy. At that moment the diagnostic accuracy is optimal, moreover, given the high intra-individual heterogeneity in uptake, the PET will be helpful in the decision 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 18F-FDG PET is a better biomarker of transformation of FL than 18F-FLT PET. Our proposed SUV-based thresholds indicating transformation of FL should be prospectively validated in a real life clinical setting that is compliant with prevailing guidelines for quantitative 18F-FDG PET.

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