Investigation of FDG-PET/CT imaging to guide biopsies in the detection of histological transformation of indolent lymphoma

Positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) has been successfully evaluated in the management of non-Hodgkin's lymphoma (NHL).[1–3] Histological transformation (HT) of indolent lymphoma is a dramatic event that occurs in 5-10% of the patients and carries a dismal prognosis.[4,5] Previous studies prove that indolent lymphoma entities show a lower FDG uptake when compared with aggressive lymphomas.[6–8] We therefore postulated that FDG-PET/CT identifies aggressive transformation sites and can guide biopsies.

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From January 2005 to January 2007, all indolent lymphoma adult patients presenting with clinical and/or biological signs of HT were included in a monocentric prospective study. HT was suspected if at least one of the following parameters was present: B symptoms, localized tumor mass enlargement, unexplained high levels of lactate dehydrogenase (LDH) or β2 microglobulin in the serum. Mass was considered to be voluminous on CT images when one diameter was > 5 cm. FDG-PET/CT was systematically performed on integrated PET/CT systems (Discovery LS, GE Healthcare, Waukesha, WI, USA). FDG-PET/CT images were analyzed visually and semi-quantitatively, using maximal standardized uptake values (SUVmax). A SUVmax gradient was calculated (i.e. the difference between the highest and the lowest SUVmax). Biopsy was performed in the accessible site of highest SUVmax. All tissue specimens were then analyzed by local anatomopathologists and classified according to the WHO classification.[9] HT was confirmed if the histological and immunophenotypical analysis showed diffuse large B lymphoma (DLBCL). Hodgkin disease (HD) was interpreted as HT in case of chronic lymphocytic leukemia (CLL), and as composite lymphoma if associated with other indolent lymphoma subtypes. The local ethics committee approved the protocol and informed consent was obtained. Group comparisons were made using the non-parametric Mann-Whitney test for quantitative variables and Fisher's exact

Table 1. Patient characteristics.

							Characteristics of FDG-PET guided-biopsies			
N	*Age*	*Sex*	*Subtypes of indolent lymphoma*	*Signs and symptoms*	*Involvement*	*Uptake intensity*	*Site of biopsy*	*Size*	*Maximal SUV*	*Histology*
1	59	M	FL	LDH, Bs	N&EN	3.9-24.5	N	L	24.5	DLBCL
2	72	M	CLL	Bs	N	2.2-23.2	N	S	23.2	DLBCL
3	69	F	FL	Bs,LNE	N	3.9-41.2	N	L	41.2	DLBCL
4	72	M	WM	Bs,LNE	N&EN	5.5-14.0	N	L	14.0	DLBCL
5	50	F	FL	LNE	N&EN	9.4-22.7	N	S	22.7	DLBCL
6	75	F	FL	LNE	N&EN	12.4-18.5	N	S	18.5	DLBCL
7	50	F	FL	LNE	N	9.0-17.0	N	L	17.0	DLBCL
8	63	F	CLL	Bs,LNE	N	2.5-18.9	N	L	16.9	DLBCL
9	62	M	FL	Bs,LNE	N	10.6-30.6	N	L	17.7	DLBCL
10	64	F	CLL	LNE, LDH, Bs	N	2.2-16.1	N	L	14.1	DLBCL
11	54	F	FL	Bs, LNE	N	5.4-39.0	N	L	39.0	DLBCL
12	57	M	FL	Bs,LNE	N	7.1-17.7	N	L	14.6	DLBCL
13	77	F	FL	LNE, LDH	N	17	spleen	L	17.0	DLBCL
14	71	F	MZL	LNE	N	2.8-16.2	N	S	16.0	DLBCL
15	57	M	FL	LNE	N&EN	4.5-11.7	duodenum	L	11.7	DLBCL
16	79	M	CLL	LNE	N	2.8-14.0	N	L	14.0	HL
17	61	M	FL	Bs,LNE	N	3.2-24.4	N	L	14.6	HL
18	56	F	FL	LNE	N	5.5-8.0	N	S	8.0	FL
19	81	F	CLL	LNE	N	2.3-7.7	N	S	7.7	CLL
20	76	F	CLL	LNE, Bs, LDH	N&EN	4.6-6.1	Subcutaneous	S	4.8	CLL
							Bone	S	6.1	CLL
21	50	M	CLL	Bs,LNE	N	2.9-3.8	N	S	3.8	CLL
22	67	M	CLL	Bs,LNE	N	5.8-10.6	N	L	10.6	CLL
23	52	F	FL	Bs,LNE	N	4.0-7.1	N	S	7.1	FL
24	73	F	CLL	LNE	N	1.7	N	S	1.7	CLL
25	65	F	FL	LNE	N&EN	5.0-12.2	bone	L	7.8	FL
26	50	F	FL	LNE	N	9.3-11.5	N	S	9.9	FL
27	62	F	FL	Bs,LNE	N	6.8-12.9	N	L	12.9	FL
28	68	M	WM	LDH, Bs	N	4.0-7.0	EN	S	7.0	WD
29	56	F	FL	LNE	N	5.5-17.0	N	S	17.0	FL
30	63	M	FL	LNE	N&EN	3.0-12.5	lung	S	12.5	FL
31	38	F	FL	LNE	N&EN	2.0-8.6	lung	S	8.6	FL
32	66	F	FL	LNE	N	3.0-8.7	N	S	8.7	FL
33	78	H	MZL	LNE	N	3.8-13.3	N	S	13.3	MZL
34	70	M	CLL	LNE	N	3.2-4.0	bone	S	3.8	CLL
35	63	F	FL	LNE	N	9.9	N	L	9.9	FL
36	62	M	MZL	LNE	N	3.1-3.9	N	L	3.9	MZL
37	47	M	FL	LNE	N	5.2-7.1	N	S	7.1	FL
38	76	F	FL	LNE	N	5.9-13.6	N	L	13.6	FL

FL: follicular lymphoma; CLL: chronic lymphocytic leukemia; WM: Waldenström macroglobulinemia; MZL: marginal zone lymphoma; Bs: B symptoms; LNE: lymph nodes enlargement; N: nodal; EN: extra-nodal; L: large (more than 5 cm); S: small (less than 5 cm); DLBCL: diffuse large B cell lymphoma; HL: Hodgkin's lymphoma.

test for qualitative variables. To avoid overfitting, *leave-one-out* (LOO) cross validation was used. The global significance of ROC curves was assessed using κ tests. The study included 22 females and 16 males (Table 1). The median age was 63 years [38-81]. The initial indolent lymphoma histopathological subtypes were: follicular lymphoma (FL) in 23 cases, CLL in 10 cases, Waldenström macroglobulinemia (WM) in 2 cases and marginal zone lymphoma (MZL) in 3 cases. The size of biopsied lesions on CT was >5 cm in 19 cases (50%). FDG-PET/CT images showed abnormal FDG uptakes in all cases (29 nodal, 9 nodal and extra-nodal diseases). SUVmax ranged from 1.7-41.2. Important intra and inter-individual variations were observed (Table 1). The median SUVmax gradient was 7.3 (range, 0.8-37.3). The median minimal SUVmax was 5.5 (range, 2.0-17.0) in FL patients vs. 2.9 (1.7-5.8) in non-FL patients (p<0.001). The median maximal SUVmax was 13.6 (range, 7.1-41.2) in FL patients vs. 9.2 (1.7-23.2) in non-FL patients (p<0.028). The median SUVmax was 18.5 (range, 11.7-41.2) in HT patients vs. and 8.6 (range, 1.7-17.0) in non-HT patients (p<0.0001). The median gradient of SUVmax was 13.7 (range, 6.1-37.3) in HT patients with HT vs. 4.8 (range, 0.8-11.5) in non-HT patients (p<0.0001). FDG-PET/CT-guided-biopsy was systematically performed in the highest SUVmax (range from 1.7-41.2) abnormal sites. Histopathological analysis showed a HT in 17 cases: 15 DLBCL cases (cases 1-15), 1 HD case (case 16) and 1 composite lymphoma case (case 17). Histopathological analysis showed no HT in 21 cases (cases 18-38), none of which presented HT after inclusion in the protocol (median follow-up, 12 months, range 6-24).

ROC curve analysis was applied to determine if SUVmax could segregate HT from low-grade lymphoma. Statistical analysis determined that, for each *training* set (n-1 patient), the SUVmax threshold of 14 was the best compromise regarding correctly classified frequency. Therefore, with a threshold of 14, the *test* patient (n=1) was correctly classified 36 times out of 38 repetitions (94.7%). Sensitivity and positive predictive value (PPV) made up 93.9%, and specificity and negative predictive value (NPV) 95.3%. A SUVmax >17 enhanced PPV, which rose to 100%. Indeed, all of the 7 patients with SUVmax > 17 showed HT. Conversely, a threshold <11.7 enhanced NPV, In fact, none of the 14 patients with SUVmax <11.7 showed HT.

Our study confirms that FDG-PET/CT can be used as an accurate guide for biopsies in suspected transformed tissues. In addition, statistical analysis proved tumor size was not predictive of HT (p=0.094). Furthermore, we show that a SUVmax < than 11.7 is always associated with indolent lymphoma, whereas a SUVmax >17 is always associated with HT. The FDG uptake gradient, observed on metabolic imaging recorded at initial DLBCL staging, could suggest transformation of unidentified low-grade lymphoma patients. Our study is in agreement with previous reports. For instance, Schöder *et al*. reported that FDG uptake was significantly lower in indolent lymphoma, with SUVmax ranging between 2.3-13 (mean 6.7, SD 2.9), than in aggressive lymphoma (SUVmax range 3.2-43, mean 17.2, SD 9.7).[7] The probability of aggressive disease rose as the SUV increased. Schöder's study was a retrospective analysis with images acquired by different PET cameras. More recently, Bruzzi *et al*. reported a retrospective FDG-PET/CT assessment study, performed with the same PET/CT system, to identify HT in 37 CLL patients.[10] With a SUVmax threshold of 5, HT was detected with a sensitivity, a specificity, a PPV and an NPV of 91%, 80%, 53% and 97% respectively. The relatively high number of false positive findings (9 cases) was probably related to the low threshold, which only allowed for good sensitivity and NPV. Our study is more accurate, because all the patients showed clinical or biological signs of transformation. In line with Bruzzi's publication, we believe that it is appropriate to choose a lower cut-off in CLL patients than in FL patients, since FDG uptake is higher in FL patients than in non-FL patients. Furthermore, SUV is a semi-quantitative method to measure the accumulation of radiotracers in tissues. The resulting value varies according to biological factors (glycemia, steroids, uptake period duration, injected activity) and reconstruction parameters.[11] In conclusion, indolent lymphoma patients showing HT symptoms should systematically undergo FDG-PET/CT investigation before biopsies are performed. Biopsies should be performed in the SUVmax site. However, histological analysis remains the gold standard to confirm HT.

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