18F-FDG uptake of the non tumour specific sites on the PET/CT examinations of onco-haematological paediatric patients

Ph.D. thesis

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1. Introduction

Currently, according to the literature data and oncological guidelines, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) may be performed before treatment for staging (baseline PET/CT), at the end of the treatment, or during the treatment (interim PET/CT) to distinguish between those patients who can potentially be cured with reduced therapy, those who require standard or even more intensive treatment (Eichenauer et al. 2011, Brepoels et al. 2008). Hodgkin lymphoma (HL) in paediatric patients is highly curable, but these treatment results are impaired by long-term events such as second tumours, cardiopulmonary toxicity and endocrine impairment. Therefore, the treatment planning is a major objective in this specific population of patients.

Non-tumour-specific FDG uptake by organs that are not invaded by lymphoma has been reported for a long time, and is considered as a potential pitfall (Meany et al. 2007, Weineblatt et al. 1997, Levine et al. 2006). Several articles have aimed to describe the patterns of non-specific versus lymphoma-specific FDG uptake in the thymus, the spinal cord, the bone marrow and the spleen (Kaste et al. 2005, Paes et al. 2010, Salaun et al.

2009), but mainly in adults. FDG uptake by brown adipose tissue (BAT) is a well-recognised source of pitfalls also in the evaluation of lymphoma extent, in particular in the cervical region.

The actual incidence and the importance of diffuse and intense FDG uptake by non tumour invaded organs of children with onco-haematological disease might have been overlooked. This may be information that corresponds to a metabolic response, possibly related to an aspect of the disease, and may help to better define the patient's condition. The prediction of response to chemotherapy is based on the monitoring of FDG uptake in tumour lesions, but the actual incidence and significance of “non-tumour-specific” FDG uptakes is not yet clear. FDG uptake by organs without tumour invasion has been hypothesised to be the consequence of the abnormal inflammation-inducing agents produced by malignant Sternberg-Reed cells, by the HL lesion. Such inflammatory reaction in organs may provide relevant information regarding HL as an “integrator” in the case of widespread or bulky disease, reflecting the overall activity level at all HL sites, or as an “amplifier” facilitating easier detection of signals by PET.

We aimed to evaluate the frequency and intensity of visually diffuse FDG uptake by selected organs on baseline PET/CT (bPET) and interim PET/CT (iPET) images of children with HL and evaluate the correlation of the FDG uptake of these organs with the metabolic response and evolution of disease with treatment. We performed retrospective analysis in a pilot study and a validation study with larger cohort, evaluating the FDG PET/CT images of paediatric patients with diagnosis of HL. Additional studies were performed to elucidate the relation between brown adipose tissue (BAT) visualisation on FDG PET/CT at the time of diagnosis in children with oncological disease (HL or sarcoma) and the main determinants reported in adults (i.e. temperature, sex, age), and the metabolic activity of tumour lesions. (Table 1)

Table 1. Summary of the different methodologies performed

* BAT activation was determined on a per-patient basis, irrespective of the extent and intensity

	Patients involved (n)	***Diagnosis of the patients***	***Evaluation of the diffuse, non-tumour-specific sites***	***Evaluation of the tumour lesion***
Pilot study on non-tumour-specific FDG uptakes	30	Hodgkin lymphoma	Visual and quantitative analysis	Visual analysis
Validation study on non-tumour-specific uptakes	112	Hodgkin lymphoma	Visual and quantitative analysis	Quantitative analysis
Study on BAT on bPET with French cohort	135	Hodgkin lymphoma	Visual analysis*	Quantitative analysis
Study on BAT on bPET with Hungarian cohort	92	Hodgkin lymphoma; sarcoma	Visual analysis*	Quantitative analysis

2. Objectives

2.1. Objectives of the pilot study on non-tumour-specific FDG uptake in paediatric patients with Hodgkin lymphoma

In our pilot study, the first objective was to evaluate the frequency and intensity of visually diffuse FDG uptake by BAT and four selected organs on the baseline (bPET) and interim PET/CT (iPET) images of children with HL.

The second objective was to evaluate the correlation between the FDG uptake of these sites, the metabolic response of the HL sites, and evolution of the disease with treatment. For this purpose, we evaluated whether complete response (CR) was achieved at the end of the scheduled treatment or intensification was required during or at the end of the scheduled therapy in patients with refractory disease. Relapse-free survival (RFS) was determined as well.

2.2. Objectives of the validation study on non-tumour-specific FDG uptake in paediatric patients with Hodgkin lymphoma

Similar to the pilot study, the first objective of the validation study was to evaluate the frequency and intensity of visually diffuse FDG uptake by BAT and four selected organs without tumour invasion on the bPET and iPET images in a larger series of children with HL.

The second objective was to evaluate the relation between FDG uptake by the four organs without tumour invasion (SUVmax) and the HL lesions (maxSUVmax, total metabolic tumour volume [TMTV], and total lesion glycolysis [TLG]) on bPET images prior to commencing treatment.

The third objective was to evaluate the relation between FDG uptake by BAT and the four organs without tumour invasion and the remaining metabolic activity of HL on iPET after two cycles of treatment according to Deauville Score (DS).

2.3. Objective of the studies focusing on brown adipose tissue activation

In our studies focusing on brown adipose tissue (BAT) activation one objective was to elucidate the relation between BAT visualisation on bPET in children with oncological disease (HL or sarcoma) and the main determinants reported in

adults (i.e. temperature, sex, age), and non-tumour-specific FDG uptake of organs without tumour invasion.

Other objective of these studies was to evaluate the correlation between the BAT activation and the metabolic activity of the tumour lesions, and identify any significant difference between the results of the patients with HL and those with sarcoma.

3. Methods

3.1. Methods of the pilot study

Thirty children with HL (15 boys and 15 girls, age range 3–17 years, median = 14) examined between June 2006 and July 2012 with FDG PET/CT at baseline (bPET) and after two cycles of chemotherapy as an interim examination (iPET) were included in this study.

FDG PET/CT acquisitions were performed at five different PET centers across France. FDG PET/CT images of a given patient were acquired using the same machine. ^{18}F-FDG (3–5 MBq/kg of body mass) was administered intravenously to well-hydrated patients after fasting for at least 4 h. Image acquisition was commenced at least 60 min after the injection.

PET/CT reading in the pilot study

All FDG PET/CT analyses and review were performed as masked reading at the Nuclear Medicine Department of Hôpital Tenon. All images were displayed on the same workstation and examined with and without attenuation correction and with and without PET/CT fusion.

Visualisation of activated BAT was determined based on the high FDG uptake in adipose tissue corresponding to negative Hounsfield Units (HU) on CT, whereas the surrounding regions of soft tissue took up FDG with a lesser intensity.

The diffuse FDG uptake was visualised at four sites: the thymus, the bone marrow at the iliac crest, the spleen, the spinal cord at the level of the twelfth thoracic (or dorsal) vertebra (Th12). Only those sites at which the FDG uptake was diffuse and homogeneous within the organ were considered. If this criterion could not be fulfilled, such that the uptake was inhomogeneous with some more active parts within the organ, the site was considered to be probably invaded by HL and was not considered as harbouring non-specific inflammation. FDG uptake by activated BAT corresponds to very extensive and

non-contiguous foci, thus this quantification was not performed for BAT.

The metabolic disease response was also evaluated using the Deauville Criteria and the corresponding five-point scale on iPET images only (Meignan et al. 2009, Barrington et al. 2014).

Follow-up and relapse-free survival in the pilot study

It was recorded whether complete metabolic response (CR) was obtained at the end of the scheduled treatment (two, four or six cycles of chemotherapy according to the group of therapy with or without complementary radiotherapy), or if additional therapy was needed during or at the end of the scheduled treatment to obtain CR in case of refractory disease. Patients were then followed-up according to the standard procedure for paediatric HL, to confirm whether or not the patient was still in CR, and with complementary medical visits in case of suspected relapse. Relapse-free survival (RFS) was determined from the date of the end of treatment reaching CR until the date of the last medical visit if the patient was still in CR or until the visit when relapse was diagnosed.

Statistics

The non-parametric Mann–Whitney U or Wilcoxon test was used to compare quantitative data, respectively unpaired or paired, and the Fisher's exact test to compare proportions. The McNemar's test was used to compare sensitivity, specificity and predictive values of the different criteria. A p value less than 0.05 was considered significant.

Receiver operating characteristics (ROC) analysis was performed to determine the best cutoff value for the criterion according to the Youden index, and the area under the curve was compared to 0.5. The analysis of RFS was performed according to the Kaplan-Meier method.

3.2. Methods of the validation study

An independent and larger series involving the FDG PET/CT images of 112 children and adolescents with HL was collected according to a well-established practice to validate the results of the pilot study. The study design was similar to that of the pilot study: patients aged < 18 years underwent two FDG PET/CT acquisitions (at baseline before commencing treatment [bPET] and at the interim evaluation after two cycles of treatment [iPET]). The FDG PET/CT acquisitions were performed between September 2010 and February 2015 at

various PET centres in France and submitted for masked reading at Hôpital Tenon.

Differences from the study variables and end points of the pilot study

The methods used in this larger study were identical to those used in the pilot study. However, some additions were made in terms of the study variables to better reflect the metabolic mass and activity of HL lesions. In addition, some changes in the statistical analysis and the secondary objectives were also made.

Three quantitative parameters reflecting the uptake and the extent of the HL lesions on bPET, prior to interference from the treatment, were introduced in the validation study as follows: maxSUVmax, TMTV, and TLG.

In the prediction of disease outcome Deauville Score (DS) was serving as a reference.

Statistics

The non-parametric Wilcoxon test was used to compare quantitative data. The McNemar's test was used to compare sensitivity, specificity and predictive values of the different criteria. Pearson correlation was used to evaluate the

correlation of FDG uptake by HL on bPET and the FDG uptake at the sites without tumour invasion. A p value less than 0.05 was considered significant.

ROC analysis was performed by reducing the DS to two levels, “complete metabolic response” or “non-complete metabolic response”. Stepwise logistic regression was performed with combination of all quantitative variables set to predict CR.

3.3. Methods of the “BAT on bPET” studies

The first study evaluating BAT on bPET involved paediatric patients from French institutes. The data of 135 children and adolescents with HL, comprising 62 boys and 73 girls, who underwent FDG PET/CT at the time of diagnosis (baseline bPET) were analysed. The mean age of the patients at the time of undergoing FDG PET/CT was 13.6 year (median = 14.3, range 4.5–17.9 years). The patients were referred to undergo FDG PET/CT by the Paediatric Oncology Departments of various hospitals. The outside temperature values in the town and on the day of each PET/CT acquisition were obtained from the dedicated website: infoclimat.fr.

A study involving 92 paediatric patients from Hungary, comprising 48 boys and 44 girls with the mean age 12.9 years (median = 14; range 3–17 years) was performed to analyse the FDG PET/CT examination data obtained at the time of diagnosis (bPET). The patients were diagnosed with HL or sarcoma (osteosarcoma [n = 18], Ewing sarcoma [n = 4], rhabdomyosarcoma [n = 6], and monophasic synovial sarcoma [n = 1]) based on the findings of histological evaluation. Ninety-one patients underwent FDG PET/CT examination using a GE Discovery IQ5 PET/CT device; one patient underwent FDG PET/CT examination using a Siemens TruePoint HD PET/CT device. Patients were treated at the Paediatric Oncology Station, Semmelweis University, Budapest, or at the Heim Pál National Paediatric Institute, Budapest. The outside temperatures in the town and on the day of each PET/CT acquisition were obtained from the dedicated website: timeanddate.com/weather/hungary/budapest.

FDG PET/CT practice

FDG PET/CT was performed in a manner similar to that in the pilot study. The method can be summarised as follows: well-hydrated children or adolescents received an intravenous injection of FDG after fasting for at least 4 h.

Image acquisition was commenced at least 60 min after injection.

FDG PET/CT reading

All FDG PET/CT analyses and reviews were performed as masked reading at the Department of Nuclear Medicine, Hôpital Tenon, in the case of patients from France. These analyses were performed by the Department of Nuclear Medicine, Semmelweis University, in the case of Hungarian patients. The analyses were performed by a nuclear medicine physician experienced in FDG PET/CT reading. Activated BAT was detected based on the presence of a high FDG uptake in the adipose tissue corresponding to negative Hounsfield Units (HU) on CT and the lesser intensity of the FDG uptake of soft tissue in the surrounding regions. BAT activation was determined on a per-patient basis, irrespective of the extent and intensity of the hyperfunctioning foci or masses on FDG PET/CT.

The metabolic activity of the HL lesions was determined as reflected by the following variables:

- Maximum value of the SUVmax of all HL lesions (maxSUVmax) – measured only on the data of the group with 135 patients from France

- Total metabolic tumour volume (TMTV)
- Total lesion glycolysis (TLG)

A volume of interest was set around each HL lesion (lymph node or organ). TMTV was defined as the sum of the volume of all nodal and extranodal HL lesions. Bone marrow and/or spleen involvement was included in HL volume measurement only if focal uptake was observed. TLG is defined as the sum of the products of the metabolic volume divided by the SUVmean of each HL lesion.

Furthermore, similar to the pilot study, the SUVmax was measured in the structures without tumour invasion in the cohort comprising 135 patients. The sites with enhanced glucose metabolism compared with the HL activity included the liver, spinal cord at the Th12 vertebra, and iliac crest reflecting the bone marrow. Similar to the pilot study, only the sites with diffuse and homogenous FDG uptake within the organ were considered.

The TMTV and TLG of the tumour lesions were the focus of the study conducted in Hungary. The primary intention was to visualise the possible correlation between the BAT activation and the TMTV and TLG values of the tumour

lesions and identify any significant difference between the results of the patients with HL and those with sarcoma.

Statistics

The non-parametric Mann–Whitney U test was used to compare the quantitative data of the 135 paediatric patients from France. The chi-square test was used to compare proportions.

The Mann–Whitney U, chi-square, and Fisher's exact tests were used to analyse the data of the 92 patients from Hungary. The logistic regression model was fitted to further analyse the relationship between BAT activation and other variables.

A p-value of <0.05 was considered significant in both studies.

4. Results

4.1 Results of the pilot study on non-tumour-specific FDG uptake in paediatric Hodgkin lymphoma

At least one site was exhibited diffuse and intense uptake on bPET in the large majority of patients (77%). After 2

cycles of chemotherapy, on iPET this ratio decreased (23%). Quantitative analysis showed that the treatment induced a significant overall decrease in SUVmax in the thymus, bone marrow and spleen, but not in spinal cord at Th12. In contrast, an overall significant increase in the FDG uptake by the liver was observed after treatment. (Figure 1. Table 1)

In this study, the lack of increase in the FDG uptake of the liver between bPET and iPET was considered as a predictor of refractory HL (requiring additional treatment at the end of planned initial therapy to achieve CR). The predictive value of this criterion was at least as good as the visual scoring-based assessment of FDG accumulation in targeted HL lesions. The accuracy for predicting refractory HL was 87% in case of the relative variation of the liver SUVmax between bPET and iPET.

The increase >5% in the FDG uptake of the spinal cord (Th12) between bPET and iPET was indicative of a higher risk of relapse, the accuracy for predicting relaps was 73%.

Table 1. Quantitative analyses in the pilot study. *(SUVmax of the sites where FDG uptake was quantified and the influence of two cycles of chemotherapy.)*

	Baseline PET/CT SUVmax: median value [range]	**Interim PET/CT SUVmax: median value [range]** (Wilcoxon's test for paired values)	**Relative variation: Median value [range]**
Thymus (non-invaded)	1.6 [0.9,3.0]	1.2 [1.0,1.7] ($p < 0.001$)	-25% [-43%,+11%]
Bone marrow in the iliac crest (non-invaded)	1.8 [0.4,3.8]	1.2 [0.5,2.7] ($p < 0.001$)	-29% [-61%,+100%]
Spleen (non-invaded)	1.8 [0.8,4.8]	1.3 [0.8,2.7] ($p < 0.001$)	-21% [-75%,+35%]
Spinal cord at Th12 (non-invaded)	1.7 [0.7,3.4]	1.5 [0.8,3.1] ($p = 0.5$ NS)	+1% [-47%,+60%]
Liver (non-invaded)	1.7 [0.8,2.5]	1.9 [1.2,2.9] ($p = 0.002$)	+13% [-16%,+75%]

4.2. Validation study on non-tumour-specific FDG uptake in paediatric Hodgkin lymphoma

At least one site exhibited diffuse and intense uptake on bPET in the majority of patients (72%), on iPET this ratio decreased (27%). The prevalence of higher SUVmax

considerably decreased in these organs on iPET. The prevalence of hyperactivation in the spinal cord at Th12 was less on bPET (31%); however, this status persisted on iPET more frequently (17%). BAT activation was observed at bPET and iPET images in 12% and 20% of patients, respectively. Quantitative analysis revealed that treatment induced a significant overall decrease in the SUVmax in thymus, bone marrow, spleen (all $p < 0.001$), but not in the spinal cord at Th12. In contrast, the FDG uptake by the liver exhibited a significant increase after two cycles of treatment ($p < 0.001$) in 85% of cases. (Figure 1, Table 2)

The analyse of the relation between non-tumour-specific diffuse FDG uptake and the remaining metabolic activity of HL (according to the Deauville score) revealed that inadequate response can be delineated using the SUVmax of the spinal cord at Th12 or the spleen without invasion on iPET.

Table 2. Quantitative analyses in the validation study. *(SUVmax of the sites where FDG uptake was quantified and the influence of two cycles of chemotherapy.)*

	Baseline PET/CT SUVmax: median value [range]	**Interim PET/CT SUVmax: median value [range]** (Wilcoxon's test for paired values)	**Variation between bPET and iPET: increase decrease**
Thymus (non-invaded)	1.35 [0.9,4.5]	0.7 [0.7,2.7] ($p < 0.001$)	Increase (n = 2) **Decrease** (n = 17)
Bone marrow in iliac crests (non-invaded)	1.9 [0.7,10.7]	1.5 [0.7,4.1] ($p < 0.001$)	Increase (n = 21) **Decrease** (n = 79)
Spleen (non-invaded)	2.1 [1.0,7.6]	1.8 [0.7,4.1] ($p < 0.001$)	Increase (n = 24) **Decrease** (n = 64)
Spinal cord at Th12 (non-invaded)	1.7 [0.9,3.2]	1.8 [0.8,4.1] ($p = 0.06$ NS)	**Increase** (n = 50) Decrease (n = 40)
Liver (non-invaded)	1.95 [1.0,3.8]	2.3 [1.2,2.9] ($p < 0.001$)	**Increase** (n = 93) Decrease (n = 17)

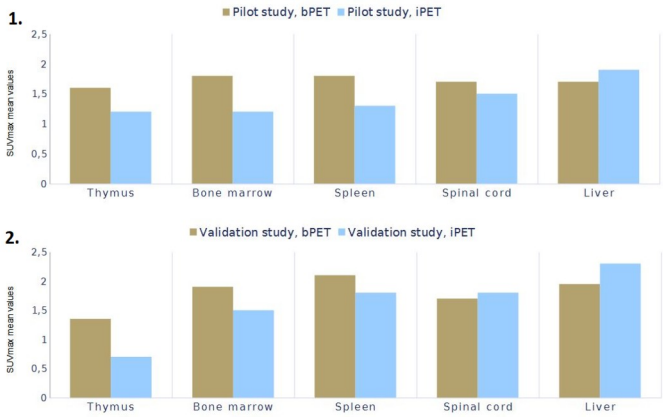

Figure 1: Comparison of FDG uptake variations of organs without tumour invasion between bPET and iPET. FDG uptake presented in SUVmax mean value, at baseline (bPET) examinations and after two cycles of treatment (iPET). **1.** Results of the quantitative analysis in the pilot study **2.** Results of the quantitative analysis in the validation study.

4.3. Results of the "BAT on bPET" studies

The prevalence of positive FDG uptake by BAT on bPET was 19% (25/135; only patients with HL) and 23.9% (22/92; patients with HL or sarcoma) in the two studies. These frequencies do not differ from studies reported previously in paediatric patients: 15% (Yeung et al. 2003); 23.8% (Cohade et al. 2003); 13.6% (Kim et al. 2008); 10% (Gilsanz et al. 2012).

We found no significant difference in the prevalence of BAT activation between boys and girls. Logistic regression analysis suggested a correlation with the age in the HL subgroup in the study involving Hungarian children (p=0.04). In the Hungarian study, 45% of the PET/CT examinations with signs of BAT activation were performed in autumn, and from all the PET/CT examinations performed in autumn 38% had signs of BAT activation.

BAT activation was not linked with the metabolic activation of the non-tumour-specific FDG uptakes of the liver, bone marrow, spleen and spinal cord at Th12 (in the study involving 135 patients with HL).

In the prevalence of BAT activation in patients with HL compare with that in patients with sarcoma, we revealed no significant difference (p = 0.12).

The findings of these studies suggest that BAT visualisation could be associated with a lower HL tumour mass (lower median values of TMTV (135 patient: p=0.07; 92 patient: p=0.06), TLG (135 patient: p=0.06; 92 patient: p=0.09). However, this result could not be confirmed when combinations of several quantitative variables were tested

simultaneously in logistic regression in the group of Hungarian paediatric patients.

Higher TMTV and TLG values were found in case of patients with sarcoma exhibiting BAT activation. However, the Mann–Whitney U test revealed no significant association in the sarcoma subgroup. This could be attributed to the limited number of patients with sarcoma.

5. Conclusions

The findings of the pilot and validation studies on non-tumour-specific FDG uptake in paediatric HL indicated that FDG uptake visually greater than that of the liver in at least one site without tumour invasion is observed in a large proportion of patients (72% and 77% in the validation and pilot studies, respectively) that decreases dramatically after two cycles of treatment (27% and 23% in the validation and pilot studies, respectively).

A significant increase in the FDG uptake of the liver between bPET and iPET confirms the conclusion of other studies in adults. Thus, the observation that liver FDG uptake varies across patients with HL during the course of treatment and disease should be considered carefully while defining the

response to therapy as a reference organ in the interim PET in HL.

The prevalence of FDG uptake visually greater than that of the liver being observed in the bone marrow and spleen without tumour invasion was significantly higher on bPET (approximately 40% in both studies). However, visual and quantified evaluations of FDG uptake revealed that this prevalence decreased after completing two cycles of treatment. The presence of homogenous lymphoma infiltration could not be excluded in the case of the diffuse spleen uptake (none of the cases had histologically-confirmed results). Notably, it reflects the activation and proliferation of macrophages probably in the inflammatory context of HL. The high FDG uptake at baseline by the spleen and the bone marrow not characteristic to HL invasion on FDG PET/CT images that decreased after two cycles of treatment is evocative of a paraneoplastic influence of HL. This hypothesis is confirmed by the close correlation of the SUVmax values of the spleen and the bone marrow of the iliac crest with the variables characterising the extent and activity of HL on bPET (TMTV and TLG).

An increase in the proportion of children with BAT activation on iPET was observed after two cycles of treatment compared with that on bPET; however, this difference did not reach the significance level in the three-fold larger cohort. The findings of the additional “BAT on bPET” studies confirmed the findings of previously published studies, derived from heterogeneous conditions, that the epidemiology of BAT activation varies between paediatric patients and adults. No significant differences were observed between boys and girls in the present study in terms of BAT visualisation. BAT activation was not linked with the metabolic activation of the liver, bone marrow, or spinal cord, which may be observed in paediatric patients owing to the presence of the HL. Nevertheless, the findings of the present study suggest that BAT visualisation could be associated with a lower HL tumour mass. These studies also emphasised the importance of influencing factors, such as the temperature in injection rooms in PET/CT laboratories, in terms of the connection between the season or outside temperature and BAT activation. Furthermore, the findings of the present studies also indicated that a correlation may be observed between BAT visualisation and age in paediatric patients with HL.

In the evaluation of the relation between FDG uptake by the four organs without tumour invasion and that by the HL lesions prior to treatment on bPET, a significant positive correlation was observed. Strong correlations were also observed between the FDG uptake of the four sites without tumour invasion on bPET and also on iPET. The greatest correlation coefficients were observed between the bone marrow and spleen, and before treatment between the liver and spleen that reduced after two cycles of treatment.

Two unfavourable criteria were derived from the evolution of diffuse uptake by organs between the FDG PET/CT acquisitions performed at the time of diagnosis (baseline) and after two cycles of treatment (interim) in the pilot study. Namely the lack of increase in the FDG uptake of the liver and increase of >5% in the FDG uptake of the spinal cord at Th12. Patients who satisfied these criteria seemed to be at high risk of developing refractory Hodgkin lymphoma and/or early relapse. The results of the validation study indicated that patients whose iPET is likely to correspond to an inadequate response can be delineated based on the FDG uptake by the lymphoma lesions on bPET (best with TLG, significant with TMTV, and borderline with maxSUVmax) and the FDG uptake of the spinal cord at Th12 or of the spleen

without tumour invasion on iPET after two cycles of chemotherapy.

6. Bibliography of the candidate's publications

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∑IF: 18,034