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Prognostic value of bone marrow tracer uptake pattern in baseline PET scans in hodgkin lymphoma: Results from an international collaborative study / Zwarthoed, C., El-Galaly, T.C., Canepari, M., Ouvrier, M.J., Viotti, J., Ettaiche, M., Viviani, S., Rigacci, L., Trentin, L., Rusconi, C., Luminari, S., Cantonetti, M., Bolis, S., Borra, A., Darcourt, J., Salvi, F., Subocz, E., Tajer, J., Kulikowski, W., Malkowski, B., et al.. - In: THE JOURNAL OF NUCLEAR MEDICINE. - ISSN 0161-5505. - 58:8(2017), pp. 1249-1254. [10.2967/jnumed.116.184218]

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Journal of Nuclear Medicine, published on January 26, 2017 as doi:10.2967/jnumed.116.184218

Prognostic value of bone marrow tracer uptake pattern in baseline PET scan in Hodgkin Lymphoma: results from an International Collaborative Study

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Word count Abstract: 325
Text: 4982
Number of Tables: 2 (+ 3 Supplemental Tables)
Number of Figures: 3 (+ 1 Supplemental Figure)

Running title: Bone marrow uptake in Hodgkin Lymphoma

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ABSTRACT

Rationale: Positron Emission Tomography/Computed Tomography (PET/CT)-ascertained bone marrow involvement (BMI) constitutes the single most important reason for upstaging by PET/CT in Hodgkin lymphoma (HL). However, BMI assessment in PET/CT can be challenging. This study analysed the clinico-pathological correlations and prognostic meaning of different patterns of bone marrow (BM)-Fluorodeoxyglucose (FDG)-uptake in HL.

Patients and methods: 180 newly diagnosed early unfavourable and advanced stage HL patients, all scanned at baseline and after 2 Adriamycin-Bleomycin-Vinblastine-Dacarbazine (ABVD) courses with FDG-PET, enrolled in two International studies aimed at assessing the role of interim PET scan in HL, were retrospectively included. Patients were treated with ABVD x 4-6 cycles and involved-field radiation when needed, and no treatment adaptation on interim PET scan was allowed. Two blinded reviewers independently reported the scans.

Results: Thirty-eight patients (21.1%) had focal lesions ($fPET^+$), 10 of them with a single (unifocal) and 28 with multiple (multifocal) BM lesions. Fifty-three (29.4%) had pure strong (> liver) diffuse uptake ($dPET^+$) and 89 (48.4%) showed no or faint (≤ liver) BM uptake ($nPET^+$). BM biopsy (BMB) was positive in 6/38 (15.7%) of $fPET^+$, in 1/53 (1.9%) of $dPET^+$ and in 5/89 (5.6%) of $nPET^+$. $dPET^+$ was correlated with younger age, higher frequency of bulky disease, lower hemoglobin levels, higher leucocyte counts and similar diffuse uptake in the spleen. Patients with pure $dPET^+$ had an identical 3-year Progression Free Survival (3Y-PFS) to patients without any FDG uptake (82.9% and 82.2%, respectively *p=0.918*). However patients with fPET+ (either unifocal or multifocal) had a 3-Y-PFS significantly inferior to patients with dPET+ and nPET+ (66.7% and 82.5%, respectively, *p=0.03)*. The kappa-values for inter-observer agreement were 0.84 for focal uptake and 0.78 for diffuse uptake.

Conclusions: We confirmed that FDG-PET scan is a reliable tool for BMI assessment in HL and BMB is no longer needed for routine staging. Moreover, the inter-observer agreement for BMI in this study proved excellent and only focal FDG BM uptake should be considered as a harbinger of HL.

Keywords: PET/CT, Hodgkin, bone marrow involvement, inflammation

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INTRODUCTION

HL has been for long considered as a disease of the lymphatic system, with a less frequent extranodal spread compared to B-cell aggressive non-Hodgkin lymphoma. However, this concept has been challenged in recent years upon introduction, in HL staging, of FDG-PET/CT *(1-4)*. The latter proved also valuable for lymphoma restaging, to discriminate active tumor lesions from structural abnormalities and non-viable residual masses with high accuracy *(5-7).* Compared to CT, PET/CT proved more sensitive at baseline for extranodal site detection, which can be recognized as an increased FDG-uptake in otherwise normally structured organs *(1,4)*. As a result, PET/CT upstages 15-29% of HL patients, and modifies treatment plans in a clinically relevant fraction of them *(8).* The most frequent reason for stage IV migration in HL is the detection of single or multiple sites of focally increased FDG-uptake in BM without histological evidence of HL in the iliac crest BMB *(2,4)*. Many studies have shown a superior diagnostic sensitivity of PET/CT for BMI assessment over BMB, as the latter often fails to detect patchy BMI *(4, 9-11)* . It is generally accepted that focally increased FDG-uptake in the BM with or without the presence of CT abnormalities is a sign of BMI, but the prognostic relevance of this finding is controversial *(8,12)*. However, some patients display a diffuse baseline BM FDG-uptake with a superior intensity compared to that of liver. In expert opinion, diffuse BM uptake represents inflammatory changes, although sporadic positive BMB in the setting of a diffuse BM FDG-uptake have been reported *(13,14)*.

In the present study, we analyzed the prognostic meaning of different patterns of FDG-uptake in the BM of newly diagnosed adult HL patients and their association with clinico-pathological features.

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MATERIALS AND METHODS

Patients

Patients included in the present report were previously enrolled in two international studies aimed at assessing the prognostic role of interim PET in ABVD-treated HL: the International Validation Study (IVS) and the Polish observational study. The IVS cohort has been described in detail elsewhere *(7,15)*. In short, patients diagnosed with classical HL in the period 2002-2009 were enrolled if they had stage IIB–IVB disease or stage IIA disease with adverse prognostic factors (bulky disease, ≥ 3 nodal lesions, erythrocyte sedimentation rate > 40 mm/h or sub-diaphragmatic presentation). Other IVS inclusion criteria were first-line therapy of ABVD, and PET/CT at baseline and after two cycles of chemotherapy. No treatment change was allowed based solely on a positive PET scan. Additional patients, fulfilling the same inclusion criteria of IVS were included from the Polish observational study on the predictive role of early and very early interim PET on ABVD treatment outcome in HL *(16)*. The results of blinded independent central review of interim PET scan in both studies have been published elsewhere *(7,15,16)*.

PET/CT Equipment and Image Acquisition

Baseline and interim PET/CT studies were performed according to standard protocol in use at each PET site. Scans were performed from the skull base to the mid-thigh level and attenuation-correction was done using iterative reconstructions. All baseline and interim PET/CT studies were anonymized and uploaded to a central server located in the study core lab (Medical physics department, Cuneo

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Hospital, Italy). The image quality of each individual PET/CT study was critically assessed before inclusion in the study.

PET/CT Review

Two reviewers blinded to treatment outcome and other clinical information, independently reported baseline and interim PET/CT studies. Review results were presented in a joint session and consensus decisions were made in case of disagreement. Disease stage was determined according to the Ann Arbor Classification for staging of lymphoma *(17)* with Cotswolds modifications *(18),* and to the Lugano classification *(19)*. Focal BM lesions ($fPET^+$) were visually defined as focally increased FDG-uptake with an intensity > liver FDG-uptake with or without corresponding CT abnormalities in at least two slices of fused images. The number of focal BM lesions (0, 1 or ≥2) and their anatomic localization were recorded. Diffusely increased FDG-uptake in the BM ($dPET^+$) was visually categorized as diffuse uptake with an intensity > liver ($dPET^+$). No uptake ($nPET^+$) was defined as complete absence of FDG uptake or a faint diffuse uptake ≤ than that of liver. Finally, CT images were reviewed for structural abnormalities corresponding to areas of focally increased FDG-uptake (osteolytic, osteosclerotic lesion, mixt lesions or no CT abnormalities). FDG-uptake in the spleen was categorized as focal FDG-uptake or diffuse FDG-uptake > liver, and CT-ascertained structural abnormalities were recorded.

Statistical Analysis and Ethics

Differences between categorical values were tested with Fishers exact test and Chi-square test, whereas differences between continue variables were tested with Wilcoxon test. Overall survival was defined as the time from diagnosis until death from any cause or censoring in patients still alive at the

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time of last follow-up. PFS was defined as the time from diagnosis until progression, death, or censoring at the time of last follow-up. The prognostic significance of the FDG-uptake patterns in the BM was examined using univariate and multivariate Cox regression models and Log-rank tests. Statistical analyses were performed using R.3.2.2 Software for windows. Double-sided p-values <0.05 were considered statistically significant. The Ethical Committee of the coordinating center in Cuneo approved the IVS study and data collection was compliant with national regulations. The Ethical Committee of the coordinating center in Gdańsk approved the Polish observational study.

RESULTS

Baseline Characteristics and Treatment

Overall, 180 patients with stage IIA and adverse risk factors (bulky disease, 3 or more nodal localizations, erythrocyte sedimentation rate > 40mm/h, or subdiaphragmatic disease) or stage IIB-IV were included in the present study. The patient breakdown according to Ann Arbor stage was: stage II *n=62* (34.4%), stage III *n=58* (32.2%), and stage IV *n=60* (33.3%). Detailed baseline characteristics and treatment information are provided in Table 1. Median age was 38.6 (19-82) years and male: female ratio was 0.8. First-line chemotherapy regimen was ABVD x 4 courses (early stage unfavorable) or ABVD x 6 courses (advanced stage). Involved-field radiotherapy was given as standard treatment of early stage disease in 62/180 (35%) of patients; 6 patients with advanced stage-disease had consolidation RT for residual mass at the end of treatment.

PET/CT Bone marrow Findings

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At baseline, 89 patients (49.4%) had normal FDG-uptake (nPET$^+$). Thirty-eight (21.1%) had focal BM lesions (fPET$^+$, 10 patients with unifocal, 28 with multifocal lesions, 9 with lytic, 8 with sclerotic, 2 with mixt CT lesions and 19 without any CT corresponding abnormality). In 21 out of 38 fPET$^+$ patients (55%), a diffuse FDG uptake was simultaneously present (f/dPET$^+$). Pure dPET$^+$ without evidence of focal uptake was recorded in 53 patients (30.1%)(Fig. 1; Table 2). Out of 60 patients with stage IV disease, 38 (63.3%) had focal BM lesions, 27 (40%) of them had focal BM lesions only (this was the only criterion that upstaged them to stage IV), while 11 had focal BM and other extranodal lesions. Twenty-two patients had stage IV disease based on extra osseous extranodal lesions. In contrast, only 17/142 patients (11.6%) with dPET$^+$ or nPET$^+$ had extranodal disease outside BM. The relationship between the pattern of FDG uptake and BMB-detected BMI is shown in Table 2. Routine BMB was performed as part of the routine staging work-up in all but two patients (98.9%). BMB was positive for BMI in 6/38 patients with fPET$^+$ and in 1/53 patients with pure dPET$^+$ (15.7%, *p=0.022* and 1.9%, *p=0.185*, respectively). However, BMB-ascertained BMI was found in 5 patients without focal BM uptake on staging PET/CT, which led to upstaging of five patients from stage III to IV, thereby increasing their International Prognostic Score value of one point (Supplemental Table 1). However, none of them would have had his treatment upgraded by BMB as stage III and IV patients were treated the same according to standard treatment guidelines. When considering only positive BMB as reference standard, PET/CT had a sensitivity, specificity, positive predictive value and negative predictive value of 50% (CI. 21;79), 81% (CI. 74;86), 16% (CI. 6;31), and 96% (CI. 91;98), respectively. When considering both fPET$^+$ and positive BMB as reference standards, the sensitivity and negative predictive value for BMB and PET/CT were 27% (CI. 15; 43) and 81% (CI. 74; 86) vs. 84% (CI. 70; 93)

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and 95% (CI. 90; 98), respectively. PET/CT had a higher overall accuracy (95%: CI. 91; 98) than BMB (82%: CI. 76; 87).

Clinical-imaging Correlations and Prognosis

Compared to non-fPET$^+$ patients (i.e. nPET$^+$ or pure dPET$^+$ patients), fPET$^+$ patients (either pure fPET$^+$ or f/dPET$^+$) had lower levels of albumin (*p=0.002*) and hemoglobin (*p=0.013*), and higher frequency of B symptoms (*p=0.002*). Overall, compared to the entire patient population of 180-patients, dPET$^+$ was associated with younger age (*p=0.002*), bulky disease (*p=0.004*), lower hemoglobin levels (*p<0.001*), and higher leucocyte counts (*p<0.001*). Of note, dPET$^+$ patients also more often displayed diffuse uptake >liver in the spleen (*p=0.049*) (Supplemental Table 2). After a median follow-up of 33.8 (range 16.6-108.6) months, 38 patients (21.2%) progressed or relapsed, and 9 (5%) died (all deaths preceded by disease progression). The resulting 3-year overall survival and PFS estimates were 96.1% (CI. 0.93-0.99) and 79.2 % (CI. 0.73-0.86), respectively. In univariate analyses, bulky disease, with a Hazard Ratio (HR) 2.5 (*p=0.007)*, International Prognostic Score (HR 3.2, *p=0.0003*), multifocal BM fPET$^+$ lesions (HR 1.9, *p=0.011*) and positive interim PET/CT (HR 11.0, *p<0.0001*) were the only factors significantly associated with poor 3Y-PFS. In multivariate analysis including the covariates significant at individual level, only positive interim PET/CT retained an independent statistical significance (*p<0.0001*)(Supplemental Table 3). PET ascertained BMI was not prognostic for outcome (*p=0.072*) in the present patient cohort. Figure 2 shows the PFS Kaplan Meier Curves according to the pattern of FDG uptake in the baseline PET/CT of (0) patients without any FDG uptake, (1) patients with diffuse uptake only, (2) patients with single focal uptake (with or without dPET$^+$) (3) patients with more than 1 focal lesion (with or without dPET$^+$). With no-uptake as reference group, the 53 patients with a pure

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dPET$^+$ had an identical 3Y-PFS to the 89 patients with nPET$^+$: 82.9% and 82.2%, respectively; *p=0.918;* HR=0.95 CI. 0.42-2.2). Patients with a single focal lesion (N= 10) or multiple focal lesions (N=28) had very similar 3Y-PFS: 68.6% (HR: 2.4, CI. 0.8-7.1) and 66.1% (HR: 1.9, CI. 0.86-4.4), respectively. Importantly, patients with fPET$^+$, either uni- or multifocal had a significantly inferior long-term disease control compared to patients with dPET$^+$ and nPET$^+$ (66.7% and 82.5%, respectively, *p=0.03*) (Fig. 3). The presence of CT morphological changes in areas of abnormal focal uptake in the bone marrow was not prognostic for PFS (HR 1.8, CI. 0.43-7.7). In 33 out of 38 fPET$^+$ patients (86.8%), all the focal FDG lesion disappeared in the interim PET, and in 3 of them a photopenic aspect of the scan was recorded in the areas of a previous hot focal lesion, consistent with a classical "mirror" effect (uptake less to other skeletal areas). Five out of 38 (13.2%) fPET$^+$ patients had persisting BM uptake in the same focal areas recorded at baseline (Deauville score 4 or 5), and 4 of them relapsed, with a significantly worse PFS compared to patients with focal uptake who became PET negative on interim assessment *(p = 0,007)*(Supplemental Fig. 1). The kappa-values for inter-observer agreement for BM uptake were 0.83 for focal uptake (focal vs. non-focal and number of focal lesions) and of 0.78 for diffuse uptake, both consistent with a high degree of reviewer agreement. In 3 out of 38 fPET$^+$ cases a disagreement between reviewers was recorded concerning the number of focal BM lesions (uni vs. multifocal). In 15 out 53 dPET$^+$ cases (28%) the disagreement between reviewers concerned the intensity of visually assessed BM uptake.

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DISCUSSION

An accurate HL staging, including detection of BMI, is clinically relevant, as disease stage remains a major determinant of outcome and treatment strategy *(9,20,21).* In the present detailed analysis of 180 patients with treatment-naïve HL, we first gave a detailed description of BM FDG-uptake patterns to provide helpful key points for BMI assessment in PET/CT staged patients. The significance of pure strong diffuse BM uptake is still unknown, but probably not related to BMI by neoplastic tissue, as recently stressed *(8,12).* Moreover, we confirmed that BMB is not a clinically relevant diagnostic tool, due to its scarce sensitivity and low likelihood to upstage PET/CT-staged patients (no patient upstaged from limited to advanced stage by BMB), thus far confirming that in PET era BMB can be safely omitted for HL staging *(8,19,20)*. Interestingly, a strong diffuse BM FDG-uptake, a common finding at baseline in HL, was reported in 53/180 patients (29.4%) in the present study, with a higher rate than previously described (9.3% in a recent cohort of 75 patients *(22)*, 5.2% in El Galaly et al. cohort of 454 patients) *(9).* This discrepancy is probably accounted by the thorough imaging review in our study, while in other studies data were based on nuclear medicine reports only. Consistent with previous literature *(9,12,14,23)*, the results of this study confirm a clear correlation between strong diffuse BM uptake and some clinical parameters, as lower hemoglobin level, and higher leucocyte count. In this patient group, we also frequently noticed a strong diffuse uptake in the spleen, younger age, bulky disease and lower levels of albumin compared to patients with no FDG uptake in BM. The homogeneous and diffuse FDG uptake in BM probably reflects an unspecific metabolic activation, or simply an hyperplasia of haemopoietic cell compartment at the time of HL diagnosis *(24)*, with a morphological aspect similar to that recorded in patients treated with hematopoietic growth factors

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to prevent chemotherapy-induced neutropenia *(8)*. More importantly, only one positive BMB was observed in our study in patients showing dPET$^+$, in full agreement with previous studies (0/24 patients according to El Galaly et al *(9)*, 0/7 patients according to Adams et al. cohort *(22)*, 2/11 according to Muzahir et al. *(11)*). However, in the latter study no hint was provided on the coexistence of focal areas of FDG uptake in the context of a dPET$^+$. Finally, in our knowledge, this is the first study reporting an identical PFS of patients with pure strong diffuse and no significant FDG-uptake in BM. Taken together, all the above observations suggest that a pure strong diffuse FDG-uptake recorded in BM of HL at baseline is a nonspecific finding and should not be considered as a harbinger of BMI by lymphoma. In the present cohort, a focal BM FDG-uptake (fPET$^+$: visually defined as focally increased FDG-uptake > liver FDG-uptake visible on at least two PET slices with or without corresponding CT abnormalities) was reported in 38 patients (21.1%), with a frequency in keeping with the existing literature, showing a prevalence of BMI ranging between 12.9 and 26.8% *(9,12,25).* Notably, 5 of 89 patients (5.6%) with a totally absent FDG uptake in BM (nPET$^+$) were upstaged from stage III to IV after BMB (false negative results); nonetheless, none of them had his treatment changed by BMB, as reported by El Galaly et al. (5/27 patients with positive BM biopsy upstaged from stage III to IV)*(9)*. Moreover, in the Danish and in our study, no patient staged II by PET/CT had a positive BMB. In conclusion, when considering fPET$^+$ and/or positive BMB as diagnostic for BMI, the sensitivity and negative predictive value of BMB and PET/CT were 27% and 81% vs. 84% and 95%, respectively. In previous studies, the same high diagnostic performance of FDG-PET/CT was observed, as described in a meta-analysis of 955 patients with sensitivity ranging from 87.5% to 100% *(10).* The sensitivity of PET for BMI was indeed suboptimal in our study (84%) and, this finding, though non-influent on

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treatment decision should be taken in to account during patient restaging in case of resistant or relapsing lymphoma. Considering either a positive BMB or focal BM lesions on PET/CT that disappear during treatment in the following scans or both, as standard reference for BMI by HL, as previously suggested *(10,12)*, is more accurate than BMB alone, due to the inability of BMB to detect BMI for the patchy nature of BM infiltration by HL. As a matter of fact, in our study only 12/180 patients (6.6%) had a positive BMB, while, predictably, most focal lesions recorded at baseline (86.8%) disappeared in the interim PET, in keeping with the negativization rate of interim PET in ABVD-treated HL (80-85%) *(26).* Overall, these data stress the likelihood of the suggestion that focal FDG-avid lesions are indeed true bone marrow invasion by lymphoma. Interestingly, El Galaly et al. found a similar proportion of negativization of BM lesions in the interim PET in 72/82 patients (87.8%) *(9)*. Importantly, $fPET^+$ patients had a worse prognosis and a higher proportion of ENS disease (62.5%) compared to non-$fPET^+$ patients (11.6%). Moreover, 24 of 38 $fPET^+$ patients (63%) in stage IV by PET had extranodal site in BM only and patients with unifocal lesions were classified as stage IV, according to the Lugano classification *(19).* The fact that patients with $fPET^+$ patients had a significant worse treatment outcome (*p=0.03)* compared to those with $dPET^+$ and $nPET^+$ could depend on a possible "protective" effect of patients with a $dPET^+$, as witnessed by the younger age (36.5 vs. 41.8, *p= 0.002*), and on the adverse prognostic meaning of a stage IV disease *(27).* However, when all the known clinical, biological and imaging variables were taken into account, the only strong significant predictive factor associated with a poor PFS in multivariate analysis was positive interim PET/CT (*p<0.0001*), in agreement with the large literature data *(27,28).* The very good inter-observer agreement in PET reporting points toward feasibility in clinical practice of these simple rules for BMI detection.

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CONCLUSION

In conclusion the present study suggests that (1) FDG-PET scan is a reliable tool for the assessment of BM invasion by HL; (2) BMB is no longer needed for HL staging and could be safely omitted; (3) only focal FDG uptake at BM level should be considered as an harbinger of HL; (4) focal BMI could be detected with high accuracy and inter-observed agreement in routine HL staging with PET/CT.

Disclosure

The authors have no conflict of interest to declare.

ACKNOWLEDGMENTS

We thank Dr Fabrizio Bergesio for imaging quality check, collecting, and distribution to reviewers.

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Figure 1:

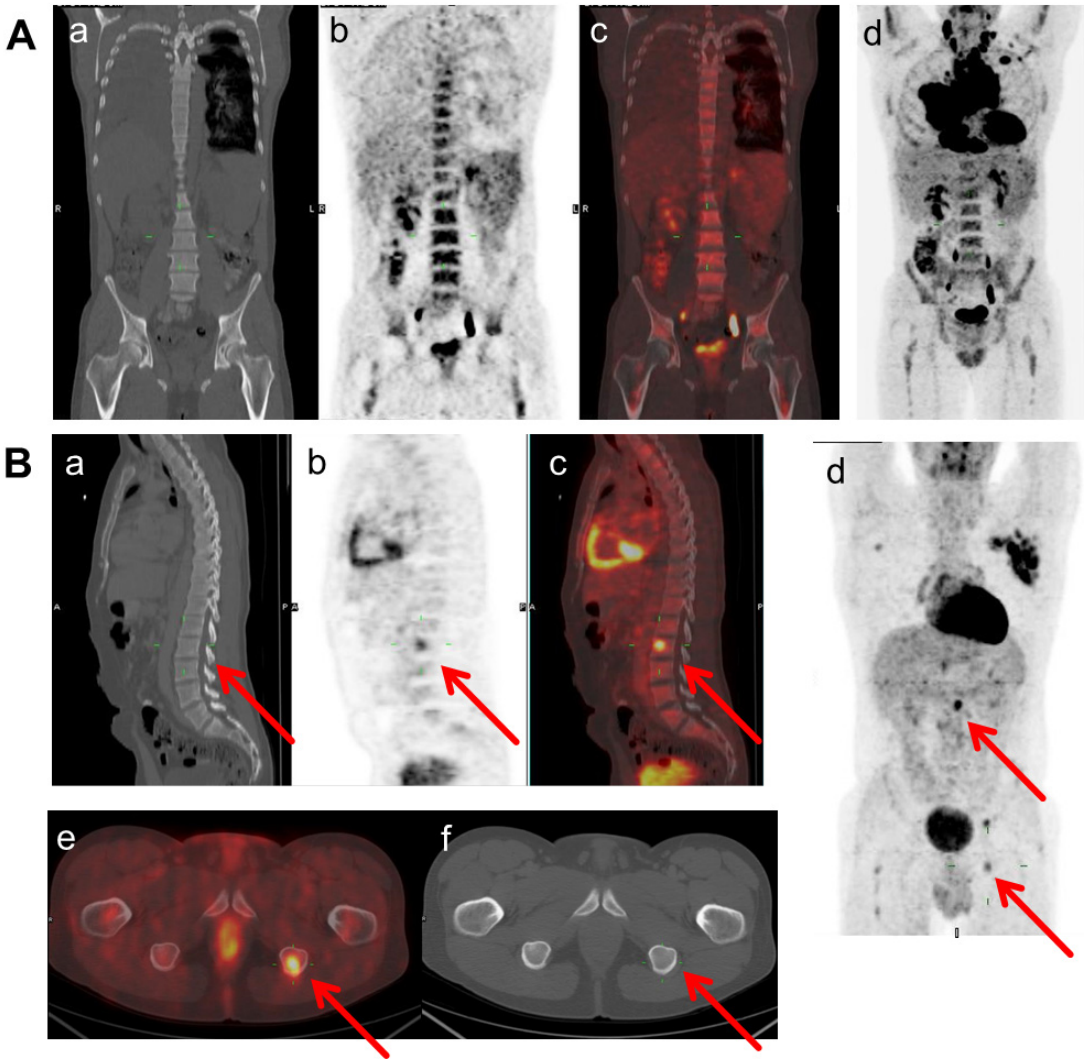


Figure 1: A: Example of a pure diffuse BM uptake > liver uptake in baseline FDG-PET (coronal CT slices(a), PET(b) and fused PET/CT(c) and MIP(d)). BMB was negative, and the patient was in complete remission (follow-up: +81 months). B: Example of a multifocal BMI, with three focal BM lesions (L2, left ischium and right scapula) in baseline FDG-PET, without corresponding CT abnormalities (sagittal slices of CT (a), PET (b) and fused PET/CT (c), MIP (d), axial fused PET/CT (e) and CT slices (f)).BMB was negative and the patient relapsed 6 months after the end of ABVD treatment.

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Figure 2:

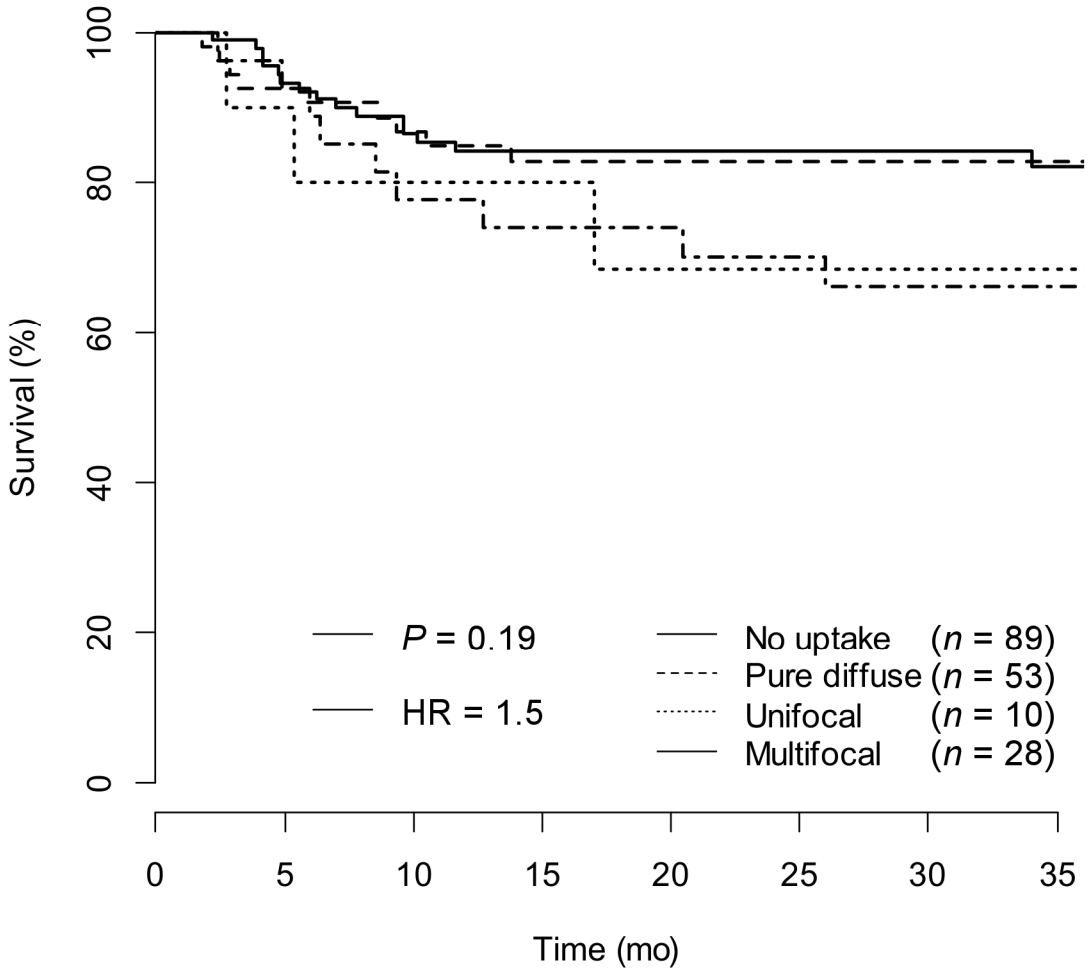


Figure 2: Kaplan Meier PFS curves of different BM-FDG uptake patterns: no FDG uptake, pure diffuse FDG uptae > liver, unifocal FDG uptake and multifocal FDG uptake. Log rank p-value = 0.19.

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Figure 3:

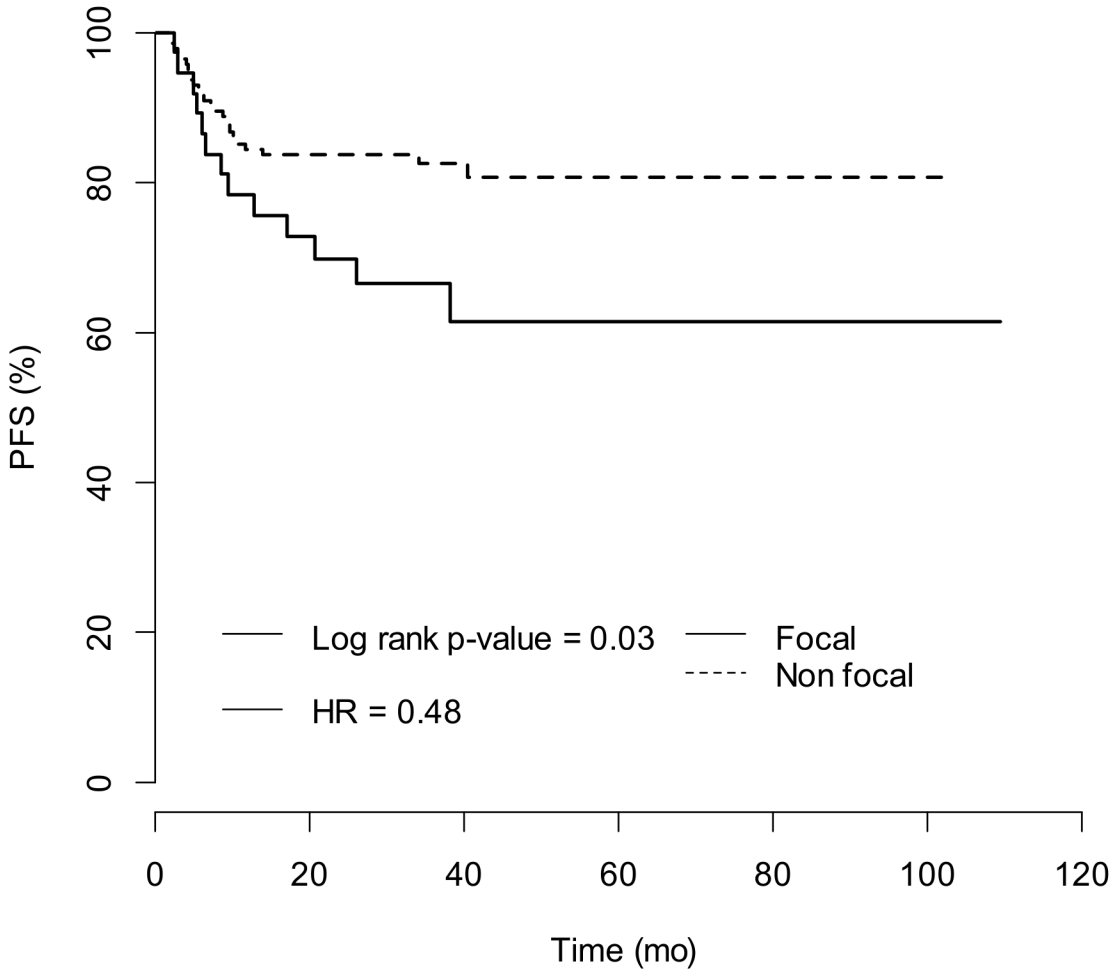


Figure 3: Kaplan Meier PFS curves of focal PET lesions and non-focal BM uptake groups (pure dPET⁺ and nPET⁺). Log rank p-value = 0.03.

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Table 1: Clinico-pathological characteristics and treatment of the 180 patients

	Total (n=180)	IVS (*n=133*)	Polish study (*n=47*)	*p-value*
Median age, years (range)	38.6 (19 – 82.5)	39 (32.6 – 48.3)	37.7 (26-49.8)	*0.101*
Male:female ratio (%)	0.8	0.9	0.6	*0.515*
B-symptoms, n (%)	123 (68.3)	88 (66.2)	35 (74.5)	*0.385*
Histology: Scleronodular Lymphocyte rich Mixed cellularity Lymph depletion Lymph predominance Undetermined	 142 (78.8 16 (8.8) 3 (1.6) 13 (7.2) 2 (1.1) 4 (2.2)	 101 (75.9) 15 (11.3) 2 (1.5) 9 (6.8) 2 (1.5) 4 (3)	 41 (87.2) 1 (2.1) 1 (2.1) 4 (8.5) 0 (0) 0 (0)	*0.275*
Ann Arbor stage, n (%) • II • III • IV	 62 (34.4) 58 (32.2) 60 (33.3)	 52 (39.1) 46 (34.6) 35 (26.3)	 10 (21.3) 12 (25.5) 25 (53.2)	*0.003*
Mediastinal bulk tumor, n (%)	78 (43.3)	54 (40.6)	23 (48.9)	*0.412*
International prognostic score >2, n (%)	55 (30.5)	33 (24.8)	22 (48.9)	*0.005*
Extranodal involvement, n (%)	61 (33.9)	40 (30.1)	21 (44.7)	*0.101*
Radiotherapy, n (%)*	68 (37.7)	53 (43.8)	15 (33.3)	*0.432*

*Missing data in 15 patients

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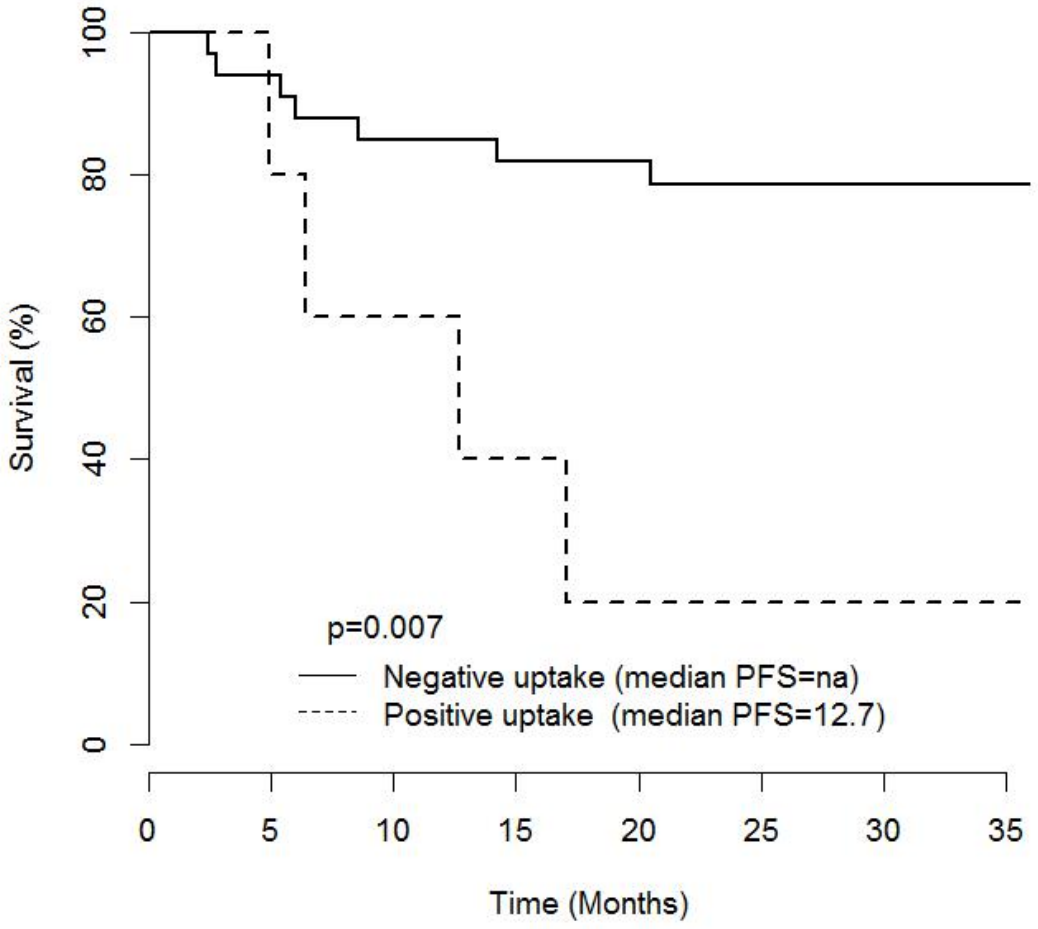
Table 2: BM FDG-uptake patterns of the 180 patients

BM FDG-uptake characteristics		N (%)	Positive BM biopsy N (%)
BM FDG-uptake < liver (nPET)*		89 (49.4)	5 (2.8)
Focal BM uptake Unifocal (N = 10) Multifocal (N = 28)	without diffuse BM uptake (pure fPET$^+$)	17 (9.4)	4 (2.2)
	with diffuse BM uptake (f/dPET$^+$)	21 (11.7)	2 (1.1)
Pure diffuse BM uptake (pure dPET$^+$)		53 (29.4)	1 (0.6)
Total		180 (100)	12 (6.6)

*missing data of BMB for 2 patients in this group

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Supplemental Figure 1:



Supplemental Figure 1: PFS Kaplan Meier curves according to interim BM uptake in the 38 patients with focal BM FDG lesions (5 patients with persistence of FDG BM uptake (Positive uptake), 33 patients without any significant BM uptake at interim (Negative uptake)). Log rank test: p = 0,007.

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Supplemental Table 1: Correlations between BM biopsy and PET/CT (among the 178 patients with BM biopsy)

BM biopsy	**Negative**	**Positive**	***P value***
Total	166	12	
fPET			
Positive	32 (19.3%)	6 (50.0%)	*0.022*
Negative	134 (80.7%)	6 (50.0%)	
dPET			
Positive	51 (30.7%)	1 (8.3%)	*0.185*
Negative	115 (69.3%)	11(91.7%)	
Stage according to CT/PET			
Stage II	60 (36.1%)	0 (0.0%)	
Stage III	52 (31.3%)	6 (50.0%)	*0.021*
Stage IV	54 (32.5%)	6 (50.0%)	

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Supplemental Table 2: Clinical correlations according to BM uptake on PET/CT: fPET$^+$ and dPET$^+$ groups compared to the overall population.

	fPET			dPET		
	+ (*n=38*) (Pure fPET$^+$ and f/dPET$^+$)	**- (*n=142*)**	***p***	**+ (*n=53*) (Pure dPET$^+$)**	**- (*n=127*)**	***p***
Positive bone marrow biopsy (%)	6 (15.0)	6 (4.3)	*0.022*	1 (1.9)[2]	11 (8.7)	*0.185*
Bulky (%)	13 (34.2)	64 (45.1)	*0.309*	32 (60.4)	45 (35.4)	*0.004*
B Symptoms (%)	34 (89.5)	89 (62.7)	*0.003*	38 (71.7)	85 (66.9)	*0.652*
Age median (IQR)	41.8 (30.9,49.8)	38.1 (30.1,48.3)	*0.468*	35.6 (28.4,40)	42.4 (33.1,53.7)	*<0.001*
Sex, M (%)	21 (55.3)	61 (43)	*0.242*	17 (32.1)	51 (98.1)	*0.185*
Stage IV (%)	--	--	--	11 (20.8)	50 (39.4)	*0.026*
Hb (g/dL) mean (SD)	11.5 (1.9)	12.5 (2.0)	*0.013*	11.7 (1.9)	12.5 (2.1)	*0.024*
WBC (cell/µL) median (IQR)	11855 (8475,17037.5)	10600 (8200,12700)	*0.056*	12310 (10982.5,16452.5)	9680 (7100,12000)	*<0.001*
Lymphocyte (cell/µL) median (IQR)	1437.8 (1096,1983.1)	1605 (1138.5,1932.1)	*0.609*	1575 (1160.4,1917.1)	1571 (1099,1948.7)	*0.759*
LDH elevated[1] (%)	15 (42.9)	35 (28.5)	*0.158*	17 (34.7)	33 (30.3)	*0.713*
Albumin, (g/dL) median (IQR)	3.7 (3.3,4.1)	4.1 (3.6,4.4)	*0.002*	4 (3.5,4.2)	4 (3.5,4.4)	*0.347*
Positive Interim PET (%)	12 (34.3)	38 (27.3)	*0.547*	14 (26.4)	36 (29.8)	*0.79*
Progression or relapse (%)	12 (32.4)	26 (18.3)	*0.1*	9 (17)	29 (23)	*0.483*
Alive (%)	35 (92.1)	136 (95.8)	*0.401*	52 (98.1)	119 (93.7)	*0.286*
Splenic uptake > liver (%)	3 (7.9)	16 (11.6)	*0.768*	11 (20.8)	8 (6.3)	*0.009*

Hb: hemoglobin; WB: white blood cells; IQR: InterQuartile Range; [1]over the limits referred by the local laboratory; [2]all of those 3 patients had both dPET$^+$ and fPET$^+$.

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Supplemental Table 3: Prognostic factors (progression-free survival)

Univariate analysis	**HR**	**IC 95%**	***p-Cox***
Age > 45	1.9	0.860 – 3.600	*0.053*
B Symptoms	1.9	0.860 – 4.100	*0.114*
Bulky	2.5	1.300 – 4.800	*0.007*
Stage IV	1.6	0.860 – 3.100	*0.133*
IPS	3.2	1.700 – 6.100	*0.0003*
BM biopsy^{+}	1.1	0.350 – 3.700	*0.820*
fPET^{+}	1.9	0.940 – 3.700	*0.073*
dPET^{+}	0.9	0.470 – 1.700	*0.728*
Multifocal PET^{+}	1.9	0.860 – 4.400	*0.011*
Unifocal PET^{+}	2.4	0.800 – 7.100	*0.119*
Interim PET^{+}	11.0	4.900 – 24.000	*<0.0001*

Multivariate analysis	**RR**	**IC 95%**	***p-Cox***
Interim PET^{+}	10.924	4.850 – 24.606	*<0.0001*

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Prognostic value of bone marrow tracer uptake pattern in baseline PET scan in Hodgkin Lymphoma: results from an International Collaborative Study

Colette Zwarthoed, Tarec Cristoffer El-Galaly, Maria Canepari, Matthieu John Ouvrier, Julien Viotti, Marc Ettaiche, Simonetta Viviani, Luigi Rigacci, Livio Trentin, Chiara Rusconi, Stefano Luminari, Maria Cantonetti, Silvia Bolis, Anna Borra, Jacques Darcourt, Flavia Salvi, Edyta Subocz, Joanna Tajer, Waldemar Kulikowski, Bogdan Malkowski, Jan Maciej Zaucha and Andrea Gallamini

J Nucl Med.
Published online: January 26, 2017.
Doi: 10.2967/jnumed.116.184218

This article and updated information are available at:
http://jnm.snmjournals.org/content/early/2017/01/25/jnumed.116.184218

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The Journal of Nuclear Medicine is published monthly.
SNMMI | Society of Nuclear Medicine and Molecular Imaging
1850 Samuel Morse Drive, Reston, VA 20190.
(Print ISSN: 0161-5505, Online ISSN: 2159-662X)

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