



Comprehensive analysis of the influence of G-CSF on the biodistribution of FDG in lymphoma patients: insights for PET scheduling

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par

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Né le 02/01/1991 à OLIVEIRA DE AZEMEIS (*Portugal*)

TITRE DE LA THÈSE :

Analyse de l'influence des facteurs de croissance granulocytaires sur la biodistribution du FDG chez les patients atteints de lymphome

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Abréviations

PET/CT: Positron emission tomography / computed tomography

FDG: 18F-Fluorodeoxyglucose

DLBCL: Diffuse large-B-cell lymphoma

G-CSF: Granulocytes colony stimulating factors

DS: Deauville Scoring

MATV: Metabolic active tumour volume

i-PET: Interim PET

Eot-PET: End-of-treatment PET

VOI: Volume of interest

HU: Hounsfield unit

BMI: Body Mass Index

%Variation__{BONE} : percentage variation between baseline and interim PETs for bone marrow

%Variation__{LIVER} : percentage variation between baseline and interim PETs for liver

%Variation__{SPLEEN} : percentage variation between baseline and interim PETs for spleen

%Variation__{BMI}: percentage variation between baseline and interim PETs for BMI

%Variation__{Glycaemia}: percentage variation between baseline and interim PETs for glycaemia

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Préambule

Dans la pratique quotidienne nous avons constaté, au cours de leurs suivi par Tomographie par émission de positons (TEP), que certains patients atteints de lymphome B diffus à grandes cellules, présentaient une hyperfixation splénique avec une inversion du rapport hépato/splénique, non présent sur les TEP initiales. Ces constatations avaient également déjà été remarquées dans d'autres études et dans d'autres pathologies sur la rate et sur l'os notamment. Nous nous sommes alors intéressés aux facteurs supposés altérer la biodistribution du FDG chez les patients cancéreux recevant une chimiothérapie. Parmi ces facteurs il y a les facteurs stimulant la formation de colonies de granulocytes (G-CSF), qui sont utilisés pour réduire l'incidence de la neutropénie en stimulant l'hématopoïèse. Cette hématopoïèse a lieu essentiellement dans la moelle osseuse mais certaines études évoquent également la présence d'une hématopoïèse résiduelle dans la rate.

La proportion de patients atteints de lymphome de Hodgkin et de lymphome non hodgkinien recevant du G-CSF est élevée, car les schémas de chimiothérapie utilisés tendent à induire une leucopénie. Plusieurs médicaments sont disponibles (pegfilgrastim, filgrastim et lénograstim), nécessitant en moyenne 1 à 5 injections sous-cutanées quotidiennes, commençant 2 jours après la fin de la chimiothérapie.

Les G-CSF agissent sur la lignée cellulaire hématopoïétique monocyte – macrophage pour stimuler la prolifération des progéniteurs, la différenciation et l'activation fonctionnelle des cellules hématopoïétiques matures. En raison de leur clairance rénale, le Filgrastim et le Lénogastrim sont des G-CSF à courte durée d'action qui nécessitent des injections quotidiennes. Le pegfilgrastim a le même mécanisme d'action que le filgrastim, mais il est pégylé et présente donc une clairance rénale réduite par rapport à celle du filgrastim, prolongeant la demi-vie sérique du médicament *in vivo* et nécessitant une seule injection.

Les directives 2014 de l'EANM pour l'imagerie des tumeurs par la TEP et les recommandations de l'ASCO pour l'imagerie TEP dans les lymphomes recommandent un intervalle de temps de 10 jours

entre la chimiothérapie et l'imagerie TEP. Par conséquent, il est de pratique courante de programmer un PET intermédiaire (i-PET) et en fin de traitement (EoT-PET) pas trop près de la dernière injection de G-CSF. Cela n'est toutefois pas toujours réalisable en pratique quotidienne parce qu'un traitement de chimiothérapie peut être différé pour diverses raisons, notamment une récupération insuffisante de la numération sanguine. Par conséquent, certains patients peuvent réaliser une imagerie peu de temps après leur dernière chimiothérapie et les dernières injections de G-CSF, entraînant une augmentation de l'absorption de la moelle osseuse et de la rate. Il en résulte une inversion du rapport foie / rate qui pourrait altérer l'évaluation post-traitement à l'aide du score de Deauville (DS). La séquestration de traceurs dans la moelle osseuse, appelée « sink effect » (ou vol métabolique), affecte également la biodistribution du FDG et potentiellement le DS. Il a été signalé que ce phénomène réduisait la disponibilité du traceur dans les tissus sains chez les patients atteints de tumeurs neuroendocrines volumineuses. Dans le cas des patients atteints de lymphome, cela pourrait affecter l'absorption hépatique et/ou l'absorption tumorale résiduelle.

Les objectifs de la présente étude, qui portait sur une population homogène de patients atteints de lymphome B diffus à grandes cellules et soumis à une analyse intermédiaire après immunochemiothérapie, consistaient : premièrement à effectuer une analyse complète du délai entre la dernière injection de G-CSF et la TEP sur la biodistribution du FDG, en mettant l'accent sur l'absorption du foie, de la rate et de la moelle osseuse; deuxièmement examiner si une inversion du rapport foie / rate affecte le score de Deauville.

Background

Amongst the factors thought to alter the FDG biodistribution in cancer patients receiving chemotherapy are granulocytes colony stimulating factors (G-CSF), which are used to reduce the incidence of neutropenia [1, 2]. The use of G-CSF close to the FDG PET examination affects the FDG biodistribution, by significantly increasing the FDG uptake in bone marrow and in the spleen [3, 4]. The proportion of Hodgkin lymphoma and non-Hodgkin lymphoma patients receiving G-CSF is high, as the chemotherapy regimens used tend to induce leucopenia. Several drugs are available (Pegfilgrastim, Filgrastim and Lenograstim), requiring 1 to 5 daily subcutaneous injections on average, starting 2 days after the end of chemotherapy.

G-CSFs act on the monocyte–macrophage hematopoietic cell lineage to stimulate progenitor proliferation, differentiation, and functional activation of the mature hematopoietic cells. Due to their renal clearance, Filgrastim and Lenograstim are short-acting G-CSF and require daily injections. Pegfilgrastim has the same mechanism of action as filgrastim, but is pegylated and therefore has a reduced renal clearance, compared with that of filgrastim, prolonging the serum half-life of the drug *in vivo* and requiring a single injection.

The 2014 EANM guidelines for PET tumour imaging [5, 6] and the ASCO recommendations for PET imaging in lymphoma [7] recommend a time-lapse of 10 days between chemotherapy and PET imaging. It is therefore common practice to schedule interim PET (i-PET) and end-of-treatment PET (EoT-PET) not too close to the last G-CSF injection. This is however not always feasible in busy PET centres and also because a chemotherapy regimen may be postponed for various reasons including insufficient blood count recovery. Consequently, some patients may be imaged shortly after their last chemotherapy and G-CSF injections, harbouring an increased bone marrow and spleen uptake. This results in an inversion of the liver to spleen ratio that could alter the post-treatment evaluation using the Deauville score (DS) [8]. Also affecting FDG biodistribution and potentially the DS is tracer sequestration in bone marrow, known as the sink effect. This phenomenon has been reported to reduce tracer availability in healthy tissues in patients with bulky

neuroendocrine tumours [9]. In the case of lymphoma patients, this could affect the liver uptake and/or the residual tumour uptake.

The aims of the present study that focused on a homogeneous population of diffuse large B cell lymphoma patients scanned for interim evaluation after immune-chemotherapy were (1) to perform a comprehensive analysis of the time elapsed between the last G-CSF injection and the PET examination on the biodistribution of FDG, with emphasis on liver, spleen and bone marrow uptake; (2) to investigate whether an inversion of the liver to spleen ratio affects Deauville Scoring.

Materials and methods

Patients' recruitment

This study retrospectively included consecutive patients referred to our PET unit for baseline and interim examinations (after 4 cycles of chemotherapy), diagnosed with DLBCL between December 2014 and December 2017. EoT-PET were not included, as these scans are usually performed several weeks after completion of treatment, when effects of G-CSF tend to be negligible. All selected patients had received (R)-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or (R)-ACVBP (Rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone) and G-CSF. For each patient, age, gender, Ann Arbor staging, baseline bone, spleen or liver involvement, Deauville scoring at interim PET, the number of injections of G-CSF and date of the last one, the type of G-CSF, and the date of the last injection of chemotherapy were recorded from the patients' medical files. Criteria of exclusion were chemotherapy other than R-CHOP or R-ACVBP, history of splenectomy, interim examinations not performed after 4 cycles and no use of G-CSF.

Approval to collect data for our study was validated by the national committee for data privacy, the National Commission on Information technology and Liberty (*CNIL*), with registration n° 2204611

v 0 and patients' consent to use anonymised data for research purposes was sought on an opt-out basis.

PET-CT acquisition and reconstruction parameters

PET examinations were performed as per the EANM guidelines for PET tumour imaging [5, 6].

Quantitative data presented in this study are EARL-compliant. Patients fasted at least 6 hours before intravenous injection of ^{18}F -FDG and were scanned on a Biograph TrueV system (Siemens Heathineers) from the skull base to the mid-thighs. A free-breathing CT acquisition (60 mAs, 130 kVp, pitch 1, and 6×2 mm collimation) was followed by a PET acquisition with time per bed position of 160 and 220 s for normal weight ($\text{BMI} \leq 25 \text{ kg/m}^2$) and overweight patients ($\text{BMI} > 25 \text{ kg/m}^2$), respectively.

PET studies were planned to be performed 60 ± 5 min post injection. Extraction of data from the PET DICOM headers showed the following information: mean injected dose $\pm$ SD was $4 \pm 0.1 \text{ MBq/Kg}$. Mean delay between injection and acquisition $\pm$ SD was 59.3 ± 5.2 min on baseline and $4 \pm 0.2 \text{ MBq/Kg}$ and 60.3 ± 5.0 min on interim TEP, respectively.

Raw data were reconstructed with point spread function (PSF) modeling (HD; TrueX, Siemens Heathineers), with 3 iterations and 21 subsets and no filtering. Matrix size was 168×168 resulting in voxels of $4.07 \times 4.07 \times 4$ mm.

PET-CT analysis

All PET-CT examinations were reviewed on Syngo.via Software (Siemens Medical Solution). A 6,3 mm Gaussian filter, determined as per the EARL accreditation program, was applied using the EQ.PET software [10, 11]. For each PET-CT examination, maximum standardized uptake values (SUV_{max}) were measured as follows:

- For liver and spleen, an automatic 3cm diameter volume of interest (VOI) was placed in the right liver lobe, avoiding liver or spleen lesions in the case of tumour involvement. A manually-set VOI fitting the size of the spleen was used in cases where spleen was smaller than the 3 cm VOI.
- For bone marrow assessment, a VOI of 2 cm was placed on the sacral promontory, avoiding sacral foramens.

Liver mean Hounsfield units (HU) were measured to seek hepatic steatosis [12]. Baseline metabolic active tumour volume (MATV) was measured for each patient using a 41% isocontour method as per the EANM guidelines. In the case of multiple lesions MATV of all lesions were summed.

Statistical analysis

Quantitative data are presented as mean $\pm$ standard deviation (SD). Baseline and interim PET technical PET characteristics (injected dose, glycaemia, delay), as well as patient's BMI and liver densities were compared using the non- parametric Wilcoxon test for paired samples. To seek a difference between %Variation_BONE, %Variation_LIVER or %Variation_SPLEEN among the three types of G-CSF, Kruskal-Wallis test was used. Spearman correlations were performed to seek a link between %Variation_BONE, %Variation_LIVER or %Variation_SPLEEN and BMI percentage variation (%Variation_BMI), glycaemia percentage variation (%Variation_Glycaemia), baseline MATV as well as the time elapsed between the end of chemotherapy or the last G-CSF injection and interim PET acquisition. Spearman correlation was also used to search for a correlation linking the time-lapse between chemotherapy or G-CSF last injection and interim PET. To seek a difference between SUV_{max}_{EARL} among different groups of patients, non-parametric Mann-Whitney or Kruskal-Wallis tests were used as appropriate. When needed, complementary multivariate analysis was performed using ANCOVA. With regards to the inversion of the liver to spleen ratio, differences in the time-lapse between the end of chemotherapy or the last G-CSF injection and interim PET in patients with this pattern versus those without were tested using Mann-Whitney test. Moreover, difference in the repartition of G-CSF type used between these 2 groups of patients was tested using Fischer's exact test.

Results

Population and PET characteristics:

Population characteristics can be seen in Table 1 and PET characteristics in Table 2. On paired comparison, the injected doses for baseline and interim PETs were not significantly different; neither was the time-lapse between injection and acquisition and liver densities. Mean BMI and glycaemia were significantly different between baseline and interim PET acquisition (Table 2, $p<0.0001$ and $p=0.044$, respectively). The mean bone uptake %variation between baseline and interim PETs (%Variation_BONE) was equal to 32.0 ± 46.9 % ($n=57$), the mean liver uptake %variation (%Variation_LIVER) was equal to 16.1 ± 42.8 % ($n=73$) and the spleen uptake %variation (%Variation_SPLEEN) was equal to 10.6 ± 51.1 % ($n=66$). None of them were influenced by the %variation_BMI: $\rho=0.210$ ($p=0.117$) for %Variation_BONE, $\rho=-0.071$ ($p=0.548$) for %Variation_LIVER and $\rho=0.151$ ($p=0.227$) for %Variation_SPLEEN. None of them were influenced by the %variation_Glycaemia: $\rho=-0.039$ ($p=0.772$) for %Variation_BONE, $\rho=0.138$ ($p=0.244$) for %Variation_LIVER and $\rho=0.012$ ($p=0.921$) for %Variation_SPLEEN. The mean time-lapse between the end of chemotherapy and i-PET for the whole series of patients ($n=74$) was equal to 16 ± 5 days (median=17 days) and the mean time-lapse between G-CSF injection and i- PET was equal to 8 ± 5 days (median=8 days). There was a significant correlation between these two variables ($\rho=0.629$, $p<0.0001$).

Characteristics	
Age (yr), mean $\pm$ SD [min-max]	60 $\pm$ 14 [21;80]
Sex n (%)	
Female	35 (47.3) %
Male	39 (52.7) %
Age-adjusted IPI, n (%)	
0	8 (10.8) %
1	28 (37.8) %
2	24 (32.4) %
3	14 (19.0) %
Deauville score at i-PET, n (%)	
1	23 (31.1) %
2	13 (17.6) %
3	11 (14.9) %
4	13 (17.6) %
5	14 (18.9) %
Growth factor type (G-CSF), n (%)	
Filgrastim	52 (70.3) %
Lenograstim	10 (13.5) %
Pegfilgrastim	12 (16.2) %
First line of chemotherapy, n (%)	
(R)CHOP	68 (91.9) %
(R)ACVBP	6 (8.1) %
Bone involvement*, n (%)	17 (23.0) %
Spleen involvement*, n (%)	8 (10.8) %
Liver involvement*, n (%)	1 (1.3) %
Baseline MATV (cc), mean $\pm$ SD	449.4 (732.0) %

IPI: International Prognostic Index, i-PET: interim PET,
MATV: metabolic active tumor volume, * based on PET analysis

Table 1: Patients' characteristics (n=74).

Characteristics (mean $\pm$ SD)	Baseline PET	Interim PET	P value
Injected dose (MBq/Kg)	4.0 $\pm$ 0.2	3.9 $\pm$ 0.4	0.132
Post-injection time (min)	59.2 $\pm$ 5.1	59.7 $\pm$ 4.9	0.602
BMI (Kg/m ²)	26.6 $\pm$ 5.6	25.7 $\pm$ 5.5	<0.0001
Glycaemia (g/L)	1.00 $\pm$ 0.15	1.05 $\pm$ 0.19	0.044
Liver density (HU)	49.4 $\pm$ 10.1	48.8 $\pm$ 12.5	0.721

Table 2: PET characteristics.

Bone %variations between baseline and interim PETs:

This analysis was performed on the 57 patients with no bone involvement at baseline and interim PET examinations.

%Variation_{BONE} between baseline and interim was not correlated to the baseline MATV ($p=0.199$, Fig. 1a). Moreover, there was no statistically significant difference in bone %variations between progressive disease patients ($n=5$) and non-progressive patients: 45.2 ± 74.8 % versus 30.8 ± 44.3 %, $p=0.924$. %Variation_{BONE} was not significantly different depending on which type of G-CSF was used ($p=0.512$, Fig. 1b). %Variation_{BONE} was negatively correlated to the time elapsed between the end of chemotherapy and i-PET acquisition but not correlated to the mean delay between G-CSF injection and interim PET acquisition: $\rho=-0.342$ ($p=0.010$) and $\rho=-0.208$ ($p=0.12$) (Fig. 1c). At interim PET, patients with a time-lapse between the end of chemotherapy and i-PET acquisition < 17 days (representing the median value of the data) displayed higher bone SUV_{maxEARL} than the other patients ($p<0.0001$). Of note, there were no significant differences in bone SUV_{maxEARL} at baseline between these two groups of patients ($p=0.087$).

Representative images of patients with a short (< 17 days) or long time-lapse (≥ 17 days) between the end of chemotherapy and i-PET acquisition scan be seen on Fig. 2 and 3, respectively.

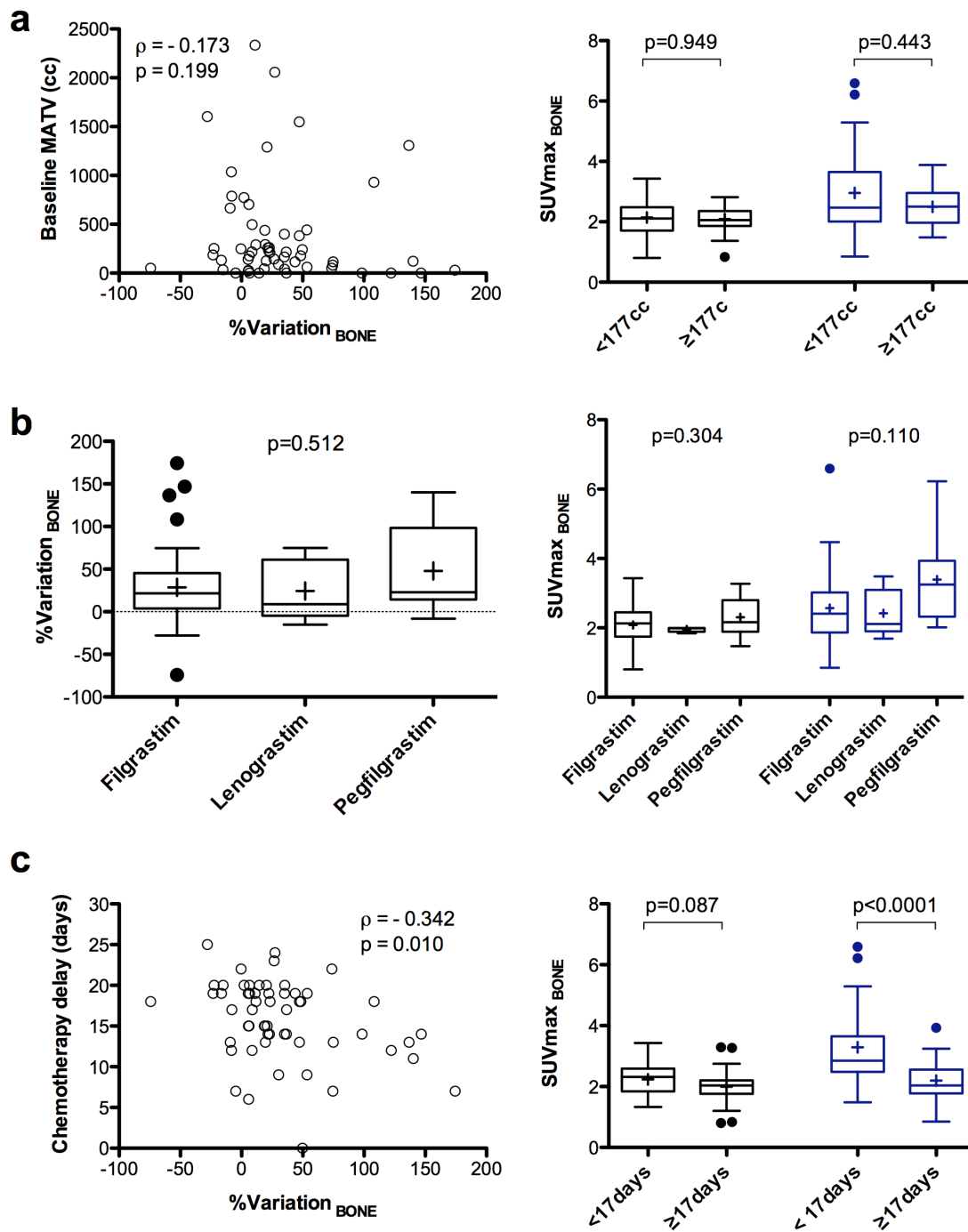
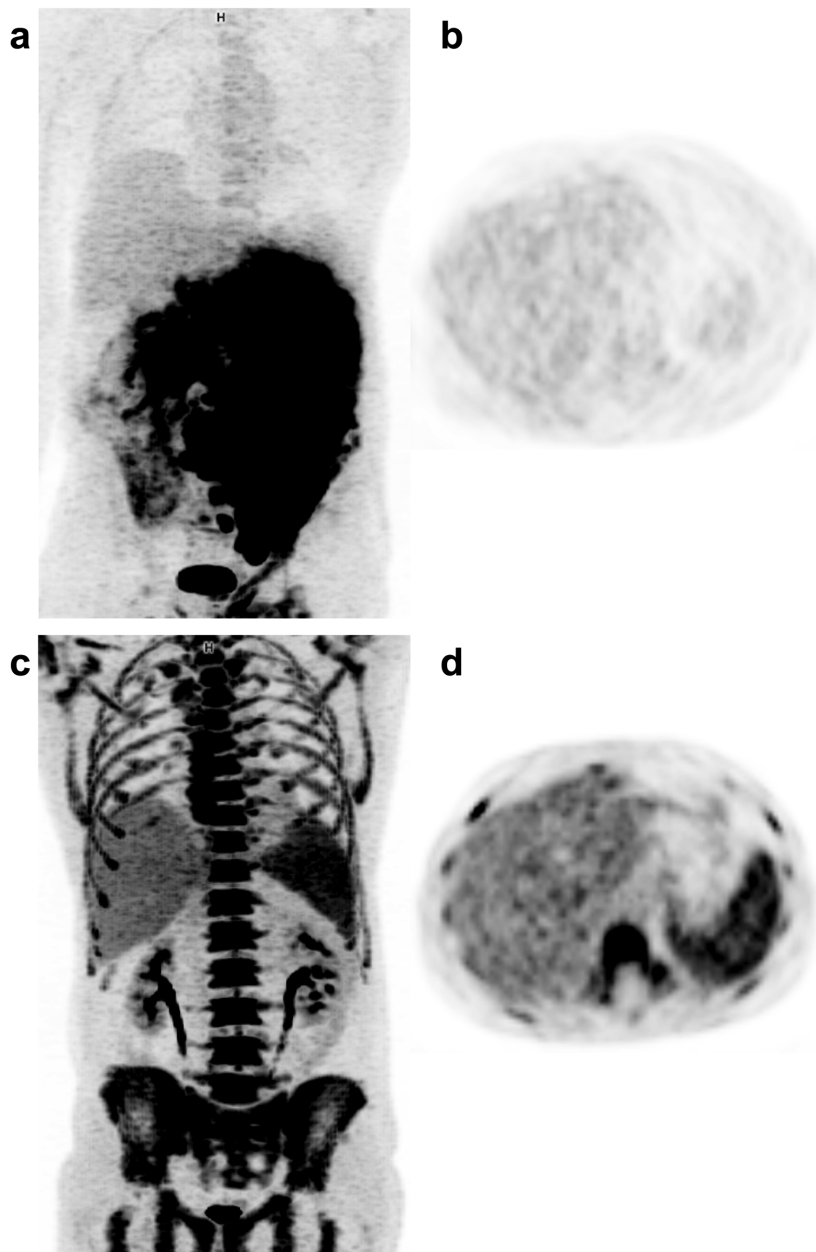


Figure 1: Percentage variation (right panels) or absolute value (left panels) for bone marrow uptake between baseline and interim PET, depending on the metabolic active tumour volume (MATV) on baseline scan (a), the type of G-CSF (b) and the time-lapse between the last injection of chemotherapy and the PET examination (c).



	<i>SUV_{max} Liver</i>	<i>SUV_{max} Bone</i>	<i>SUV_{max} Spleen</i>
<i>Baseline PET</i>	1.17	4.14	1.34
<i>Interim PET</i>	3.63	7.37	5.97
<i>% variation</i>	+210%	+78%	+345%

Figure 2: 52-year-old male patients imaged at baseline (**a and b**) and after 4 cycles of R-ACVBP (**c and d**). Interim PET was performed 7 days and 6 days following the last injection of chemotherapy and G-CSF, respectively. The injected G-CSF was Lenograstim, at a dosage of 34MUI daily for a 4-day period. In this case, low hepatic FDG uptake can be observed at baseline because of a tracer sequestration in the bulky mass. This pattern resolves after the tumour at shrunk on interim PET but because of a short time-lapse between the last chemotherapy injection and interim PET, an increased bone marrow and splenic uptakes are observed.

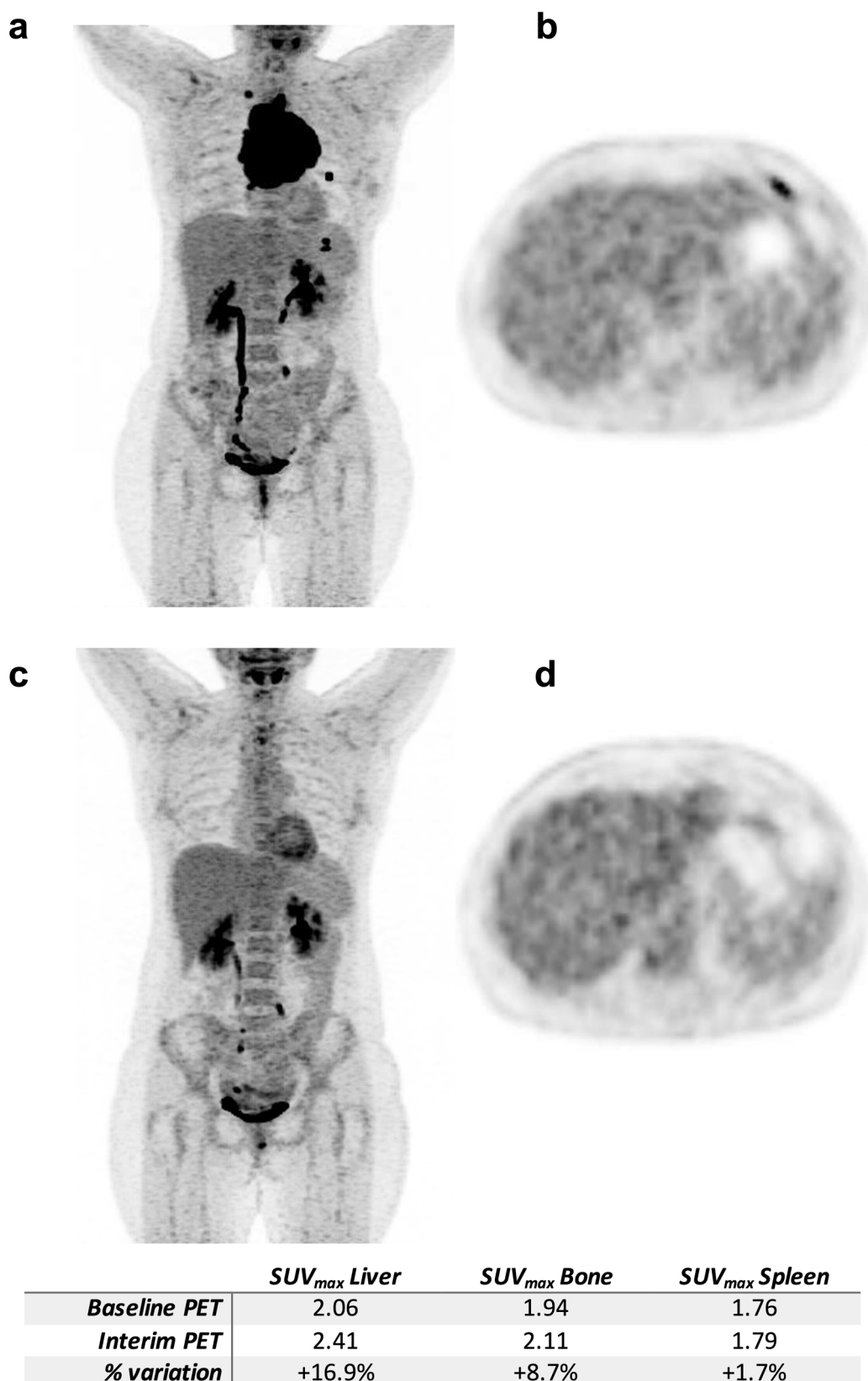


Figure 3: A 47-year-old female patient imaged at baseline (a, b) and after 4 cycles of R-ACVP (c, d). Interim PET/CT was performed 17 days and 12 days following the last injection of chemotherapy and G-CSF, respectively. The injected G-CSF was lenograstim, at a dosage of 34MUI daily for a 5-day period. Thanks to a time-lapse between the last chemotherapy injection and interim PET/CT, no significant increased bone marrow or splenic uptake are observed.

Liver %variations between baseline and interim PETs:

This analysis was performed on the 73 patients with no liver involvement at baseline and interim PET examinations.

%Variation_{LIVER} between baseline and interim was positively correlated to the baseline MATV ($p=0.243$, $p=0.039$, Fig. 4a). Moreover, %Variation_{LIVER} was lower in progressive disease patients ($n=5$): $-8.7 \pm 11.1\%$ versus $17.9 \pm 43.7\%$, $p=0.013$. Patients displaying a high baseline MATV $\geq 177\text{cc}$ (representing the median of the data) had significantly lower liver SUV_{maxEARL} at baseline ($p=0.0002$). This difference was no longer observed at interim PET ($p=0.305$). %Variation_{LIVER} was significantly different depending on which type of G-CSF was used ($p=0.026$). %Variation_{LIVER} was higher when using Lenograstim as compared to Filgrastim or Pegfilgrastim, with a mean %variation of $42.6 \pm 62.0\%$, $14.6 \pm 41.4\%$ and $0.2 \pm 10.8\%$, respectively. Baseline liver SUV_{maxEARL} were significantly lower for patients who received Lenograstim, whereas there was no significant difference at interim PET (Fig. 4b) %Variation_{LIVER} was not correlated to the time elapsed between the end of chemotherapy and i-PET acquisition ($p=0.946$, Fig. 4c) nor to the mean delay between G-CSF injection and interim PET acquisition ($p=0.870$).

On multivariate analysis accounting for baseline MATV and the type of G-CSF used, baseline MATV was the only independent explanatory variable for %Variation_{LIVER} ($p<0.0001$, Fig. 2).

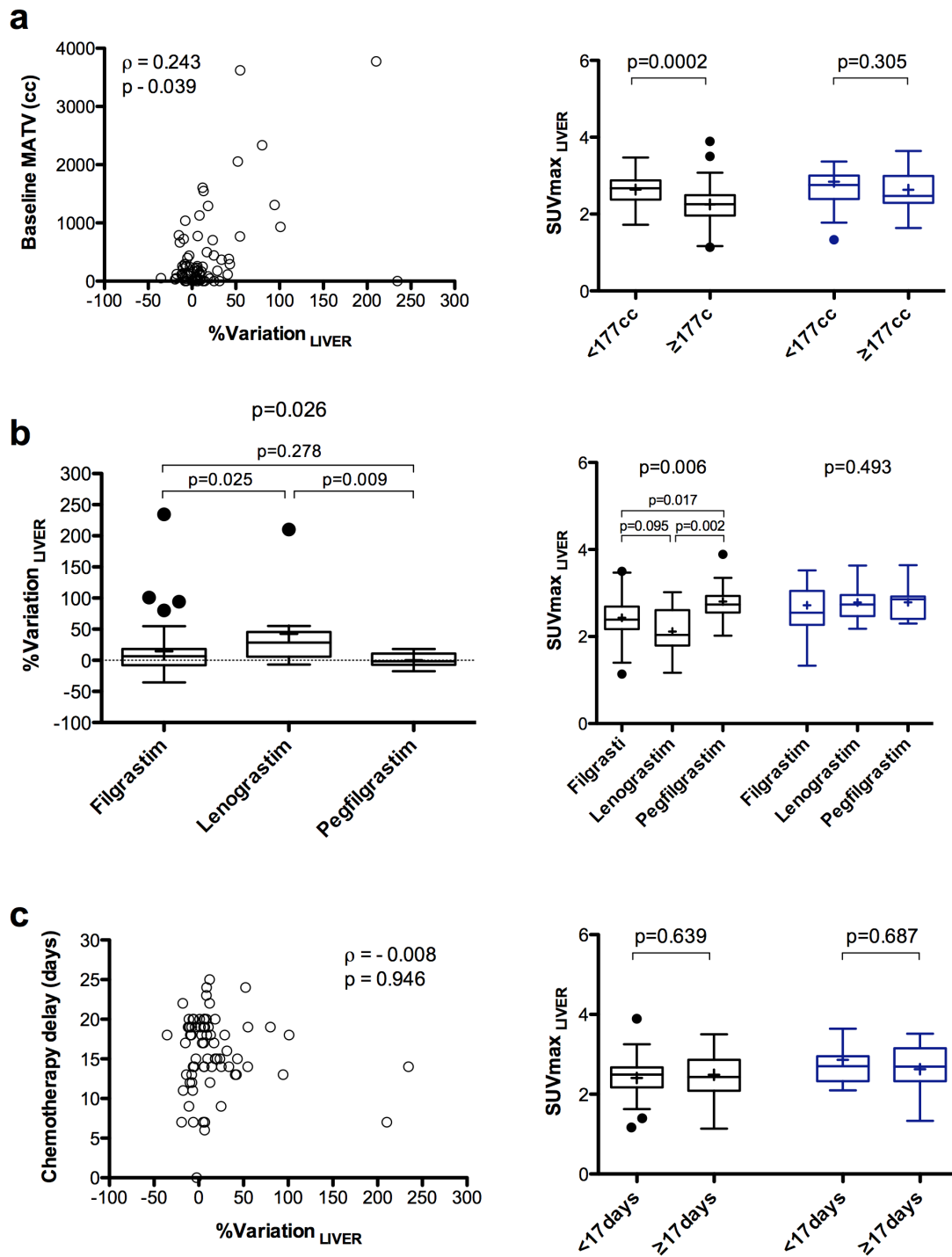


Figure 4: Percentage variation (right panels) or absolute value (left panels) for liver uptake between baseline and interim PET, depending on the metabolic active tumour volume (MATV) on baseline scan (**a**), the type of G-CSF (**b**) and the time-lapse between the last injection of chemotherapy and the PET examination (**c**).

Spleen %variations between baseline and interim PETs:

This analysis was performed on the 66 patients with no spleen involvement at baseline at baseline and interim PET examinations. %Variation_SPLEEN between baseline and interim was not correlated to the baseline MATV ($\rho=0.085$, $p=0.497$, Fig. 5a). There was no statistically significant difference in %Variation_SPLEEN between progressive disease patients ($n=5$) and non-progressive patients: -5.6 ± 17.6 % versus 11.9 ± 52.8 %, $p=0.45$. %Variation_SPLEEN was significantly different depending on which type of G-CSF was used ($p=0.034$). %Variation_SPLEEN was higher when using Lenograstim as compared to Filgrastim or Pegfilgrastim, with a mean %variation of 58.9 ± 110.3 %, 1.0 ± 24.1 % and 10.3 ± 44.8 %, respectively (Fig. 5b). Baseline spleen SUV_{maxEARL} were significantly lower for patients who received Lenograstim, whereas there was no significant difference at interim PET. %Variation_SPLEEN was negatively correlated to the time elapsed between the end of chemotherapy and i-PET acquisition ($\rho=-0.529$, $p<0.0001$, Fig. 5c) as well as to the mean time-lapse between G-CSF injection and interim PET acquisition ($\rho=-0.343$, $p=0.005$). At interim PET, patients with a time-lapse between the end of chemotherapy and i-PET acquisition < 17 days (representing the median value of the data) displayed higher spleen SUV_{maxEARL} than the other patients ($p=0.0002$). Of note, there were no significant differences in spleen SUV_{maxEARL} at baseline between these two groups of patients ($p = 0.199$). Representative images of patients with a short (< 17 days) or long time-lapse (≥ 17 days) between the end of chemotherapy and i-PET acquisition scan be seen on Fig. 2 and 3, respectively.

On multivariate analysis accounting the type of GCSF used, the time elapsed between the end of chemotherapy and i-PET acquisition and the mean time-lapse between G-CSF injection and interim PET acquisition, the use of Lenograstim and the time-lapse between the end of chemotherapy and i-PET acquisition were independent explanatory variables for %Variation_SPLEEN with p value 0.007 and 0.033, respectively.

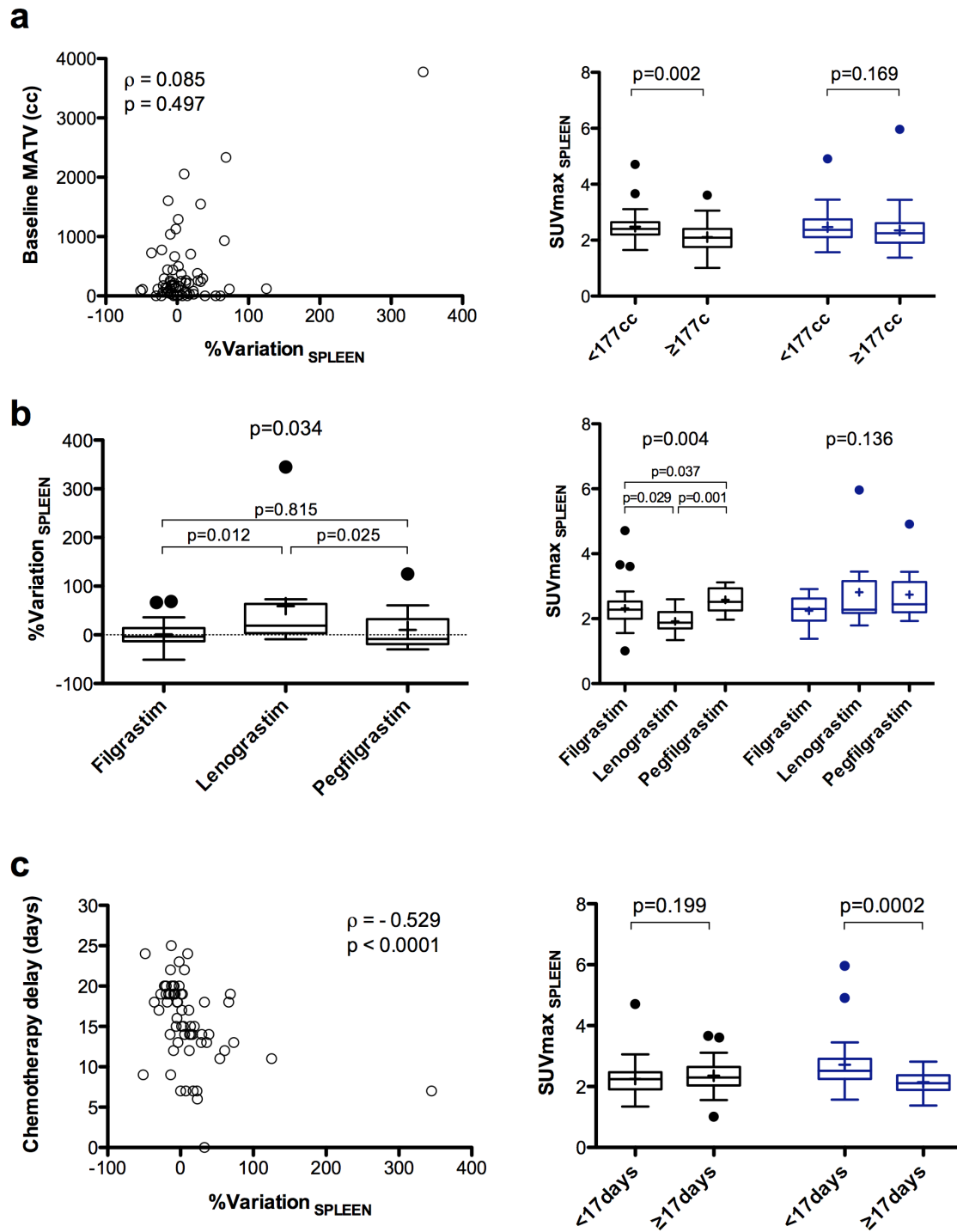


Figure 5: Percentage variation (right panels) or absolute value (left panels) for spleen uptake between baseline and interim PET, depending on the metabolic active tumour volume (MATV) on baseline scan (a), the type of G-CSF (b) and the time-lapse between the last injection of chemotherapy and the PET examination (c).

Occurrence of inversion of the hepatosplenic ratio:

This analysis was performed on the 65 patients with no spleen or liver involvement at baseline and interim PET examinations.

Inversion of the hepatosplenic ratio occurred in 17 patients (26.1%). Patients with an inversion of the liver-to-spleen ratio had lower time-lapse between the end of chemotherapy and i-PET acquisition as compared to others: 11 ± 5 days versus 18 ± 4 days, respectively ($p < 0.0001$). There was no significant difference in type of G-CSF used between patients displaying an inversion of the liver-to-spleen ratio and those who did not ($p = 0.218$).

Discussion

G-CSF are recommended after the two main chemotherapy regimens used to treat DLBCL, namely R-CHOP and R-ACVB, and have been reported to induce increased uptake in the spleen and in the bone marrow [3], the latter also being affected by normal regeneration following chemotherapy. Previous studies reported effects of G-CSF on the biodistribution of FDG at a time when only one type of G-CSF was available (Pegfilgrastim [3]), and did not account for the time elapsed between both the chemotherapy and the last injection of G-CSF and that PET scan. Indeed, while the physiopathological basis of G-CSF makes obvious the link between this treatment and the observed increased uptake in the spleen [13], increased bone marrow uptake could be due to either G-CSF and/or bone marrow regeneration. Sequestration of FDG within the skeleton could alter residual tumour uptake and therefore Deauville scoring. Given the observed variability in the type and duration of G-CSF treatment, a better knowledge of the phenomenon responsible for an altered bone marrow and spleen biodistribution and the duration of these patterns would be useful for a better scheduling of patients' scans in the busy PET unit. It would also help in deciding whether a PET scan has to be postponed when a patient shows up early after the last injection of G-CSF.

In our study, Lenograstim was associated with a higher percentage of variation in liver and spleen between baseline and interim PET. However, the variation in the liver and spleen was linked to a

lower uptake in the two organs at baseline, likely due to tumour sequestration in bulky tumour masses, and was therefore not due to the G-CSF itself. This hypothesis is supported by the fact that we found that %Variation_LIVER was lower in progressing patients compared to the non-progressing patients.

The time elapsed between the last injection of G-CSF and the interim PET examination appeared less decisive than the time-lapse between the end of chemotherapy and the i-PET examination, even if a strong correlation was observed. Indeed, no association between the variation in bone marrow, liver and spleen and the time-lapse between the last injection of G-CSF and the interim PET examination was found on multivariate analysis. On the other hand, a delay inferior to 17 days between the end of chemotherapy and the i-PET examination led to increased bone and spleen uptakes on interim PET images. These findings have practical consequences when planning PET examinations: as an *a priori* knowledge of the type and dose of G-CSF, as well as patients' compliance to injections is difficult to apprehend, scheduling PET scans at least 15 days after the last injection of chemotherapy may be recommended. Of note, guidelines for PET imaging in lymphoma patients recommend a 10 days delay after chemotherapy [7], which appears insufficient based on our data. Indeed, our results show that a time-lapse of 15 days could allow to eliminate the majority (9/12, 75%, Fig 2c and 3c) of patients displaying a percentage of variation in the bone uptake greater than 50%, while taking the 10-day time-lapse would identify only a few of these patients (3/12, 25%, Fig 2c and 3C).

Of note, despite its longer half-life compared to Filgrastim and Lenograstim due to its PEGylated nature, we did not observe larger variations in bone marrow and spleen uptake in the group of patients having received Pegfilgrastim. In the study from Jacene et al [3] involving breast cancer patients receiving Docetaxel plus Pegfilgrastim, the time-lapse between the last injection of chemotherapy and PET scan was 7 ± 0.7 days, and the time-lapse between the last injection of G-CSF and PET scan was 6 ± 0.7 days, compared to 16 ± 5 and 8 ± 5 days in our study, respectively. We feel likely that the greater increase in bone marrow and spleen they observed compared to our

data { $\%$ variation-BONE and $\%$ variation-SPLEEN equal to $244.6 \pm 127.3 \%$ and $171.3 \pm 60.6 \%$ versus $32.0 \pm 46.9 \%$ and 10.6 ± 51.1 , respectively}, is related to a shorter time-lapse post chemotherapy. On multivariable analysis percentage variation in the liver was only influenced by the baseline MATV via the well-known sink effect that led to low liver uptake at baseline, this phenomenon being reversible after chemotherapy, when bulky tumour masses had shrunk, as shown in Figure 4. Interestingly, hepato-splenic ratio inversion, which is only associated with a shorter time-lapse between the end of chemotherapy and the i-PET acquisition, is therefore only due to an increase in spleen uptake. Lower FDG hepatic uptake in lymphoma patients due to a tumour sink effect has already been suspected by Wu et al [14]. Another confounding factor potentially decreasing liver metabolism is liver steatosis [12]. However, in the present series, steatotic liver was only observed in 14 patients (18.9%) and liver densities were not different between baseline and interim PET examinations, meaning that $\%$ Variation_LIVER is certainly not biased by steatosis. Therefore, overall, inversion of the hepato-splenic ratio is unlikely to have any influence on Deauville score determination. However, Deauville scoring could still be influenced by a sink effect [9] due to tracer sequestration in the bone marrow: Teoh et al predicted the tumour uptake to be reduced by a maximum of 11.5 % in the case of G-CSF-induced hypermetabolism in the bone marrow [15]. Based on all these findings together, maintaining the time-lapse between the chemotherapy and the PET examination greater than 15 days appears to be a simple way of avoiding disturbance in FDG biodistribution and detrimental effect on Deauville scoring in interim PET.

Conclusion

Neither the type of G-CSF used nor the time elapsed between its last injection and interim PET examination independently influences bone, hepatic or splenic uptakes. The liver uptake is not influenced by any of these factors and therefore the occurrence of a hepato-splenic ratio inversion is only due to spleen hypermetabolism, making unlikely an impact on Deauville scoring. The major determinant for the occurrence of a bone or spleen hypermetabolism on interim PET is the time-lapse between the chemotherapy and the PET examination, which should be maintained greater than 15 days.

Conclusion finale

Ni le type de G-CSF utilisé ni le temps écoulé entre sa dernière injection et l'examen TEP intermédiaire n'influencent de manière indépendante l'absorption osseuse, hépatique ou splénique. L'absorption par le foie n'est influencée par aucun de ces facteurs et, par conséquent, la survenue d'une inversion du rapport hépato / splénique n'est due qu'à un hypermétabolisme de la rate, ce qui rend peu probable l'impact sur le score de Deauville. Le principal déterminant de la survenue d'un hypermétabolisme osseux ou splénique sur une TEP intermédiaire est l'intervalle de temps entre la chimiothérapie et l'examen TEP, qui devrait être supérieur à 15 jours.

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Annexes

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Comprehensive analysis of the influence of G-CSF on the biodistribution of ^{18}F -FDG in lymphoma patients: insights for PET/CT scheduling

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Abstract

Aims

(1) To perform a comprehensive analysis of the time elapsed between the last G-CSF injection and the PET/CT examination on the biodistribution of ^{18}F -FDG, with emphasis on liver, spleen, and bone marrow uptake, and (2) to investigate whether an inversion of the liver to spleen ratio affects the Deauville scoring.

Materials and methods

Retrospectively included were 74 consecutive diffuse large B cell lymphoma (DLBCL) patients referred for baseline and interim examinations and receiving immunochemotherapy with various G-CSF regimens. A comprehensive evaluation considering baseline metabolic active tumour volume (MATV), factors affecting liver uptake, the type of G-CSF, and the time elapsed between chemotherapy/G-CSF and interim PET/CTs was performed.

Results



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VU, le Président de Thèse

VU, le Doyen de la Faculté

VU et permis d'imprimer
en référence à la délibération
du Conseil d'Université
en date du 14 Décembre 1973

Pour le Président
de l'Université de CAEN et P.O

Le Doyen

ANNEE DE SOUTENANCE : 2019

NOM ET PRENOM DE L'AUTEUR : PEREIRE DE OLIVEIRA Magno

TITRE DE LA THESE : Analyse de l'influence des facteurs de croissance granulocytaires sur la biodistribution du FDG chez les patients atteints de lymphome

RESUME DE LA THESE EN FRANÇAIS :

Objectifs: (1) Effectuer une analyse complète du délai entre la dernière injection de G-CSF et l'examen PET sur la biodistribution du FDG, en mettant l'accent sur l'absorption du foie, de la rate et de la moelle osseuse; (2) Déterminer si une inversion du rapport foie / rate affecte le score de Deauville.

Matériels et méthodes: 74 patients consécutifs atteints de lymphome B diffus à grandes cellules (DLBCL) adressés pour des examens initiaux et intermédiaires, ainsi qu'une immunochimiothérapie sous divers schémas de G-CSF ont été inclus rétrospectivement. Une évaluation complète prenant en compte le MATV de base, les facteurs affectant l'absorption hépatique, le type de G-CSF et le temps écoulé entre la chimiothérapie / G-CSF et les PET intermédiaires a été réalisée.

Résultats: Le pourcentage de variation moyen ($\pm$ DS) entre les TEP initiales et intermédiaires (i-TEP) pour la moelle osseuse (% Variation_{OS}), le foie (% Variation_{FOIE}) et la rate (% Variation_{RATE}) était égale à 32.0 ($\pm$ 46.9)%, 16.1 ($\pm$ 42.8)% et 10.6 ($\pm$ 51.1)%, respectivement. Le % Variation_{FOIE} et le % Variation_{RATE} étaient plus élevés chez les patients traités par le lenograstim, mais ceci était lié à des absorptions plus faibles au départ et n'était donc probablement pas dû au G-CSF lui-même. Le délai moyen entre l'injection de G-CSF et l'acquisition d'i-PET n'était pas une variable explicative indépendante pour le % Variation_{OS}, % Variation_{FOIE} et le % Variation_{RATE}. Au contraire, le % Variation_{OS} et le % Variation_{RATE} étaient corrélés négativement au laps de temps entre la fin de la chimiothérapie et l'i-PET: $p = -0,342$ ($p = 0,010$) et $p = -0,529$ ($p < 0,0001$), respectivement. Les patients présentant un délai depuis la dernière injection de chimiothérapie < 17 jours présentaient un SUV_{max}EARL plus élevé au niveau des os et de la rate. Le % Variation_{FOIE} était positivement corrélé au MATV de base: $p = 0,243$ ($p = 0,039$). Les patients présentant un MATV ≥ 177 cc au début du traitement avaient un taux de SUV_{max}EARL au foie significativement plus bas au départ. Cette différence n'a plus été observée au i-PET après la réduction des tumeurs.

Conclusions: Ni le type de G-CSF utilisé, ni le temps écoulé entre sa dernière injection et l'examen i-PET n'influencent de manière indépendante l'absorption osseuse, hépatique ou splénique sur le i-PET. Le principal déterminant de la survenue d'un hypermétabolisme osseux ou splénique sur un i-PET est le temps écoulé entre la chimiothérapie et l'examen, qui doit être maintenu au-dessus de 15 jours. L'inversion du rapport foie / rate semble être due à une augmentation de l'hypermétabolisme de la rate sur i-PET, rendant peu probable un impact sur le score de Deauville.

MOTS CLES : Lymphome ; TEP ; FDG ; G-CSF ; Lenograstim; Filgrastim; Pegfilgrastim; vol métabolique ; Score de Deauville

TITRE DE LA THESE EN ANGLAIS : Comprehensive analysis of the influence of G-CSF on the biodistribution of FDG in lymphoma patients: insights for PET scheduling.

RESUME DE LA THESE EN ANGLAIS :

Aims:(1) To perform a comprehensive analysis of the time elapsed between the last G-CSF injection and the PET examination on the biodistribution of FDG, with emphasis on liver, spleen and bone marrow uptake; (2) To investigate whether an inversion of the liver to spleen ratio affects Deauville Scoring.

Materials and methods: Retrospectively included were 74 consecutive diffuse large-B-cell lymphoma (DLBCL) patients referred for baseline and interim examinations and receiving immunochemotherapy with various G-CSF regimens. A comprehensive evaluation considering baseline MATV, factors affecting liver uptake, the type of G-CSF and the time elapsed between chemotherapy/G-CSF and interim PETs was performed.

Results: Mean ($\pm$ SD) percentage variation between baseline and interim pets (i-PET) for bone marrow (%Variation_{BONE}), liver (%Variation_{LIVER}) and spleen (%Variation_{SPLEEN}) were equal to 32.0($\pm$ 46.9) %, 16.1($\pm$ 42.8) % and 10.6($\pm$ 51.1) %, respectively. %Variation_{LIVER} and %Variation_{SPLEEN} were higher in patients using lenograstim but this was linked to lower uptakes at baseline and was therefore likely not due to G-CSF itself. The mean delay between G-CSF injection and i-PET acquisition was not an independent explanatory variable for %Variation_{BONE}, %Variation_{LIVER} and %Variation_{SPLEEN}. On the contrary, %Variation_{BONE} and %Variation_{SPLEEN} were negatively correlated to the time-lapse between the end of chemotherapy and i-PET: $p = -0.342$ ($p = 0.010$) and $p = -0.529$ ($p < 0.0001$), respectively. Patients with a time-lapse since the last injection of chemotherapy < 17 days displayed higher bone and spleen SUV_{max}EARL. %Variation_{LIVER} was positively correlated to baseline MATV: $p = 0.243$ ($p = 0.039$). Patients displaying a high baseline MATV ≥ 177 cc had significantly lower liver SUV_{max}EARL at baseline. This difference was no longer observed at i-PET, after tumours had shrunk.

Conclusions: Neither the type of G-CSF used nor the time elapsed between its last injection and i-PET examination independently influences bone, hepatic or splenic uptakes at i-PET. The major determinant for the occurrence of a bone or spleen hypermetabolism on i-PET is the time elapsed between the chemotherapy and the examination, which should be maintained above 15 days. Inversion of the liver to spleen ratio appeared to be due to increased spleen hypermetabolism on i-PET, making unlikely an impact on Deauville scoring.

KEY WORDS : Lymphoma; PET; FDG; G-CSF; Lenograstim; Filgrastim; Pegfilgrastim; sink effect; Deauville score