Observational Study

Medicine

OPEN

Predicting subacute hematological toxicity of 177Lu-DOTATATE therapy using healthy organs' uptake on post-treatment quantitative SPECT

A pilot study

David Morland, MD, PhD[a,b,c,d,*], Elizabeth Katherine Anna Triumbari, MD[d], Christopher Hoog, MSc[e], Ghali Sézin, MD[a], Sébastien Dejust, MD[a], Guillaume Cadiot, MD, PhD[f], Pierre Paris, PharmD[g], Dimitri Papathanassiou, MD, PhD[a,b,c]

Abstract

The aim is to investigate the usefulness of ^{177}Lu-DOTA-0-Tyr3-Octreotate (DOTATATE) healthy organs' (spleen, kidneys, bone marrow) standard uptake value for the prediction of subacute hematological toxicity in patients undergoing ^{177}Lu-DOTATATE treatment. All patients referred from January 2021 to May 2022 for ^{177}Lu-DOTATATE treatment were retrospectively screened. For each treatment session, baseline clinical data including age, sex, weight, delay between ^{177}Lu-DOTATATE treatment and last cold somatostatin analogue intake were collected. Mean standardized uptake value (SUVmean) of healthy organs was measured and analyzed by generalized linear mixed effect models. Outcomes (significant decrease of platelets, hemoglobin levels and neutrophils) were assessed 1 month later, considering their within-subject biological coefficient of variation, published by the European Federation of Clinical Chemistry and Laboratory Medicine. A total of 9 patients (33 treatment sessions) were included. No predictive factors were identified for platelet and neutrophil decrease. Splenic SUVmean was found to be a significant predictor of hemoglobin levels decrease. Using an optimal threshold of ≥6.22, derived sensitivity and specificity to predict hemoglobin decrease were 85.7% [46.4; 99.0] and 76.9% [57.5; 89.2] respectively with an accuracy of 82.4%. Although not significantly predictive of hematological toxicity, bone marrow SUVmean and renal SUVmean were correlated with splenic SUVmean. Quantitative single photon emission computed tomography and healthy organs analysis might help to foresee hematological subacute toxicity in patients undergoing ^{177}Lu-DOTATATE treatment and improve patient management.

Abbreviations: DOTATATE = DOTA-0-Tyr3-Octreotate, GFR = glomerular filtration rate, NETTER = neuroendocrine tumors therapy trial, OR = odd ratios, RCV = reference change value, SA = somatostatin analogue, Se = sensitivity, Sp = specificity, SPECT = single photon emission computed tomography, SUVmean = mean standardized uptake value.

Keywords: neuroendocrine tumors, quantification, theranostics, toxicity

1. Introduction

Treatment with ^{177}Lu-DOTA-0-Tyr3-Octreotate (DOTATATE) has been shown to be superior to high-dose octreotide long-acting repeatable treatment, with a demonstrated 79% lower risk of progression or death with ^{177}Lu-DOTATATE in the neuroendocrine tumors therapy trial (NETTER)-1 study.[1] Among subacute adverse effects, hematological toxicity remains in the forefront, with varying frequencies depending on the cell type (25% thrombocytopenia, 14% anemia and 5% neutropenia).

The risk factors of subacute hematological toxicity reported by Bergsma et al[2] included poor renal function, low white blood cell count, age >70 years and extensive/high uptake tumor.

By contrast to external beam radiotherapy, molecular radiotherapy dosimetry, including peptide-receptor radionuclide therapy with ^{177}Lu-DOTATATE, is not routinely implemented, whether for the dose received by the tumor (hence the efficacy) or by the organs at risk (hence the toxicity). However, significant within-patient variability in uptake and radioactivity clearance

This research received no external funding.

GC: board member (Advanced Accelerator Applications, Ipsen, Keocyt). The other authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

[a] Service de Médecine Nucléaire, Institut Godinot, Reims, France, [b] Laboratoire de Biophysique, UFR de Médecine, Université de Reims Champagne-Ardenne, Reims, France, [c] CReSTIC (Centre de Recherche en Sciences et Technologies de l'Information et de la Communication), EA 3804, Université de Reims Champagne-Ardenne, Reims, France, [d] Unità di Medicina Nucleare, TracerGLab, Dipartimento di Radiologia, Radioterapia ed Ematologia, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma, Italia, [e] Service de Radiophysique et Radioprotection, Institut Godinot, Reims, France, [f] Hépatogastroentérologie, Université de Reims Champagne-Ardenne and Hôpital Robert Debré, CHU de Reims, Reims, France, [g] Radiopharmacie, Institut Godinot, Reims, France.

** Correspondence: David Morland, Service de Médecine Nucléaire, Institut Godinot, 1 rue du général Koenig, Reims 51100, France (e-mail: david.morland@reims.unicancer.fr).*

How to cite this article: Morland D, Triumbari EKA, Hoog C, Sézin G, Dejust S, Cadiot G, Paris P, Papathanassiou D. Predicting subacute hematological toxicity of 177Lu-DOTATATE therapy using healthy organs' uptake on post-treatment quantitative SPECT: A pilot study. Medicine 2022;101:49(e32212).

Received: 2 November 2022 / Received in final form: 16 November 2022 / Accepted: 16 November 2022

http://dx.doi.org/10.1097/MD.0000000000032212

can be observed.[3] In vivo dosimetry requires multiple steps, notably to estimate the residence time and the distribution of the tracer in the organs. In the context of treatment toxicity prediction, the arrival of new quantitative single photon emission computed tomography (SPECT) reconstructions[4] could offer a simpler alternative.

The objective of the study was to investigate the usefulness of healthy organs' standard uptake value, derived from post-treatment quantitative ^{177}Lu-DOTATATE SPECT, to predict subacute hematological toxicity.

2. Materials and Methods

2.1. Inclusion and exclusion criteria

All patients referred to our center from January 2021 to May 2022 for ^{177}Lu-DOTATATE treatment were retrospectively screened.

Each ^{177}Lu-DOTATATE cycle was considered separately and consisted of an initial biological assessment (including a complete blood count) performed the day before administration, an administration of 3.7 to 7.4 GBq of ^{177}Lu-DOTATATE, a post-treatment SPECT the day after, and a follow-up biological assessment 1 month after the administration (including a complete second blood count). For an administration to be included in the study, the following conditions had to be met: actual administration of the ^{177}Lu-DOTATATE dose, availability of biological results (baseline and follow-up). Exclusion criteria were: age <18 years, and lack of consent.

This retrospective study was conducted in accordance with the Declaration of Helsinki and was declared on the Health Data Hub (N°F20220613170159) in conformity with the reference methodology MR004 of the "Commission Nationale de l'Informatique et des Libertés," allowing the computerized management of medical data. The participants were informed of the possibility of using the information concerning them and had a right of opposition. No additional ethics committee approval was required.

2.2. Post-treatment imaging

The morning after each ^{177}Lu-DOTATATE administration, a post-treatment scintigraphy including a whole-body planar image (16 cm/min) and an abdominal SPECT/CT was performed on a Symbia Intevo Bold system (Siemens Healthineers, Erlangen, Germany). Two protocols were used successively in the department for the quantitative SPECT acquisition:

Protocol 1: acquisition of 32 × 2 projections of 30 seconds (matrix: 128²). xSPECT/Broadquant reconstruction (24 iterations, 2 subsets), gaussian post-filtering (full width half maximum: 16 mm)

Protocol 2: acquisition of 32 × 2 projections of 30 seconds (matrix: 256²). xSPECT/Broadquant reconstruction (25 iterations, 1 subset), gaussian post-filtering (full width half maximum: 8 mm).

2.3. Quantitative SPECT measurements

SPECT exams were reviewed on a dedicated console (AW Server, General Electrics, MKE). To measure spleen and kidneys uptake, an encompassing cubic region of interest was drawn around the targeted organ. Thresholding at 41% of maximum standardized uptake value (SUV) was then applied to delineate its outline. The contours were then manually corrected, if necessary (Fig. 1). Spleen mean standardized uptake value (SUVmean) and kidney SUVmean (averaged SUVmean of right and left kidneys) were measured. Bone SUVmean was measured using a spherical volume of interest positioned in the body of the L2 vertebra (adjacent vertebrae could be selected in case of presence of metastasis or artifacts).

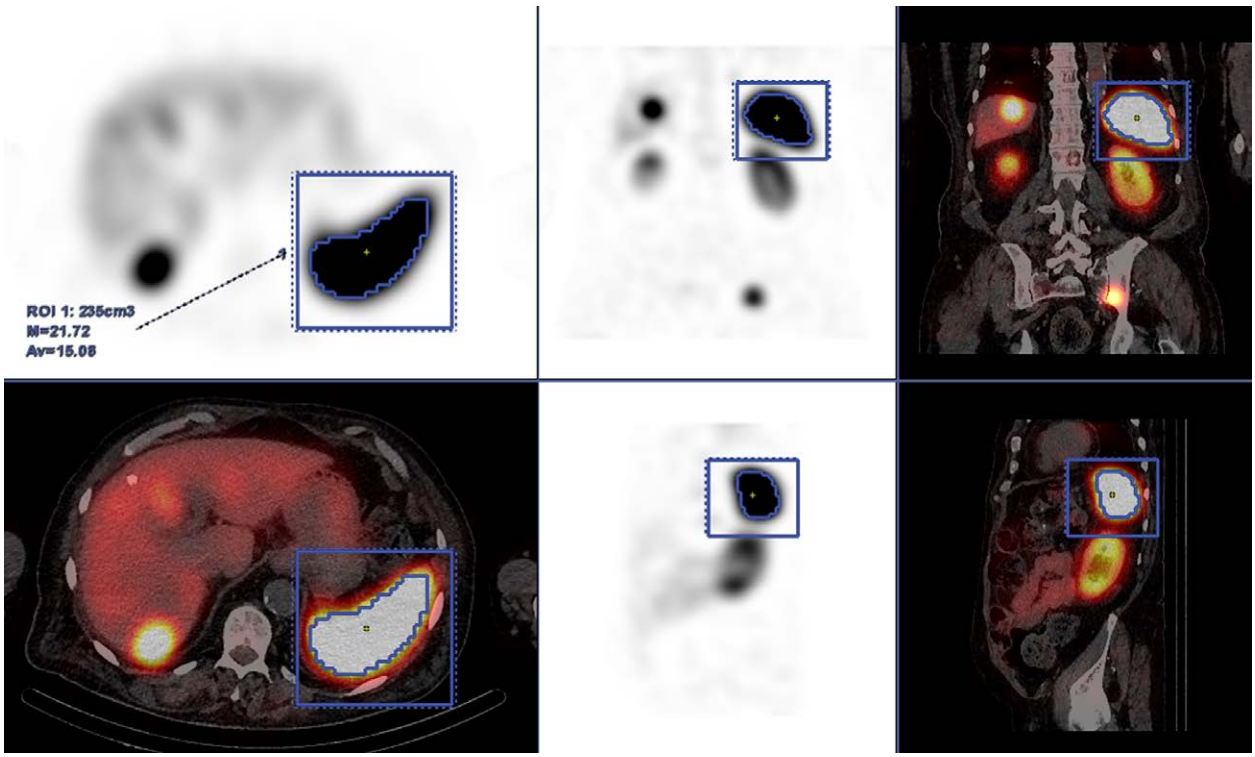

Figure 1. Example of the delineation of the spleen. An encompassing cubic ROI is drawn around the spleen. Thresholding at 41% of SUVmax is applied to delineate its outline. No manual correction is required in this case. Volume, SUVmax (M) and SUVmean (Av) are displayed. ROI = region of interest, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value.

In order to compensate for the 2 different acquisition and reconstruction protocols, a ComBat batch harmonization[5] was used to adjust the measured features. Reference was set to protocol 1, as it was the protocol used in most patients.

2.4. Collected clinical and biological data

Three binary outcomes were considered namely significant decrease of hemoglobinemia, significant decrease of thrombocytes and significant decrease of neutrophils. Hemoglobinemia, thrombocytes and neutrophils counts were collected at both baseline (i.e., the day before administration of the treatment) and at 1-month follow-up. The decrease percentages of those 3 parameters were computed and then binarized (significant vs non-significant) using reference change value (RCV).[6] RCV is defined as the change needed between 2 serial results from the same individual to be statistically significantly different and is calculated based on coefficient of variation due to the measurement system (variation due to the measurement system, set to 0 in our study) and within-subject biological coefficient of variation, whose values are regularly monitored by the European Federation of Clinical Chemistry and Laboratory Medicine.[7] As by May 20, 2022, the within-subject biological coefficient of variation values for thrombocytes, hemoglobinemia and neutrophils were 7.6%, 2.7% and 14%, respectively, resulting in RCV values of 21.07%, 7.48% and 38.81%.[6,7]

Age, sex, weight, delay between 177Lu-treatment and last cold somatostatin analogue (SA) intake, ^{177}Lu-DOTATATE activity received during current session, and cumulative activity received were collected for each treatment. In addition to the biological baseline parameters previously described, lymphocyte counts (baseline absolute count, follow-up absolute count, and decrease percentage) and baseline glomerular filtration rate (GFR) were collected.

2.5. Statistical analysis

Quantitative parameters were described using mean, standard deviation, median, first and third quartile. Binary parameters were described by their absolute number and percentage.

For the 3 outcomes, analyses were conducted using generalized linear mixed effect models to take into account the random effect linked to the repeated measures (2–4 treatment sessions per patient). Patient number was set as random effect factor and the other collected baseline parameters were tested as fixed effect factors.

Parameters with a P value < .05, if any, were included in a model selection procedure based on Akaike information criterion minimization. Results were presented using odd ratios (OR) and their 95% confidence intervals.

Calculations were performed a second time using non-harmonized data as harmonization quality control.

Identified parameters were then displayed using whiskers box plot and studied using receiver operating characteristic curves to characterize area under curve, and sensitivity (Se)/specificity (Sp) at optimal threshold (defined as the threshold giving the highest Se while having a Sp >50%). Correlation with the other measured parameters was computed using Pearson coefficient.

3. Results

A total of 33 treatment sessions were included, representing 9 patients: 6 (66.7%) females and 3 (33.3%) males. The characteristics associated with each treatment session are reported in Table 1.

A significant platelet decrease was noted after 17/33 treatments, followed by significant hemoglobin decrease (7/33) and neutrophil decrease (1/33).

Univariate analysis (Table 2) did not identify significant predictors of platelet or neutrophil decrease. Two parameters were predictors of hemoglobin decrease: spleen SUVmean (OR 1.53 [1.09; 2.14] P = .01) and baseline hemoglobin levels (OR 0.36 [0.15; 0.87]). Both parameters were considered for multivariate analysis. By testing the 3 possible models (spleen SUVmean alone, baseline hemoglobin levels alone and both parameters together), spleen SUVmean model alone was retained as the best, based on Akaike information criterion (Table 3).

Analyses were verified on non-harmonized data. Non-harmonized spleen SUVmean remained significant (OR 1.59 [1.08; 2.35] P = .02) and the model selection led to the same results.

Spleen SUVmean was then studied using receiver operating characteristic curve analysis: with an identified threshold of ≥6.22, derived Se and Sp to predict hemoglobin decrease were 85.7% (46.4; 99.0) and 76.9% (57.5; 89.2), respectively, with an area under curve of 0.82 (Fig. 2). Median and first quartile-third quartile intervals were 9.56 (7.5–12.9) for patients with significant hemoglobin decrease and 3.75 (2.4–5.3) for patients without hemoglobin decrease.

Considering each treatment independently, spleen SUVmean was significantly and positively correlated with bone SUVmean (0.56, P = .001) and kidney SUVmean (0.80, P < .001) and negatively correlated to baseline platelet counts (–0.41, P = .017), hemoglobin levels (–0.53, P = .001) and GFR (–0.60, P < .001). Spleen uptake was also positively correlated with the delay of last cold SA intake and to the lymphocytes' decrease percentage 1 month after treatment (Table 4).

4. Discussion

The advent of SPECT quantification techniques opens new perspectives for dosimetry and prediction of treatment toxicity. Among them, xSPECT with Broadquant[4] enables image quantification assessment such as SUV measurements. Clinical significance of such reconstructions remains uncertain, especially in the emerging field of theranostics, though some very recent experiences are beginning to find their light in the literature.[8] In our study, spleen SUVmean allowed us to predict a drop in hemoglobin level within 1 month, with an accuracy of 82.4%. High baseline hemoglobin levels were a protective factor at univariate analysis but spleen SUVmean was the only factor selected in the multivariate model selection procedure.

Table 1

Baseline characteristics of the 33 treatment sessions.

Characteristics	Mean (SD)	Median [Q1; Q3]
Age (yr)	73.85 (8.45)	72.0 [69.0; 78.0]
Weight (kg)	65.27 (18.15)	64.0 [46.0; 80.0]
Last intake of cold SA (d)	101.24 (72.63)	91.0 [32.0; 161.0]
Administered activity (GBq)	7.20 (1.02)	7.50 [7.40; 7.60]
Quantitative SPECT data (after ComBat)		
Tumor SUVmax	21.97 (8.94)	21.97 [14.39; 25.42]
Spleen SUVmean	5.43 (3.98)	4.13 [2.47; 8.08]
Kidneys SUVmean	4.77 (1.82)	5.00 [3.26; 5.93]
Bone SUVmean	0.30 (0.28)	0.21 [0.07; 0.48]
Biological results		
Baseline platelets count (x10^9/L)	178.09 (54.84)	177.0 [142.0; 204.0]
Baseline Hb levels (g/dL)	11.84 (1.44)	11.8 [11.0; 12.6]
Baseline neutrophils (/µL)	3340.97 (949.90)	3419 [2460; 4157]
Baseline lymphocytes (/µL)	1184.45 (419.67)	1129 [939; 1360]
Baseline GFR (mL/min/1.73m^2)	67.15 (14.65)	64.0 [55.0; 77.0]

GFR = glomerular filtration rate, Hb = hemoglobin, Q1 = first quartile, Q3 = third quartile, SA = somatostatin analogue, SD = standard deviation, SPECT = single-photon emission computed tomography, SUV = standard uptake value.

Table 2

Univariate analysis.

	Platelets significant decrease n = 17	Hemoglobin significant decrease n = 7	Neutrophils significant decrease n = 1
Age	0.314	0.199	0.479
Sex	0.555	0.099	0.989
Weight	0.209	0.158	0.475
Last intake of cold SA	0.625	0.150	0.621
Administered activity			
Current treatment	0.293	0.116	0.635
Cumulative activity	0.424	0.228	0.701
SPECT data (after ComBat)			
Tumor SUVmax	0.349	0.837	0.818
Bone SUVmean	0.946	0.454	0.517
Spleen SUVmean	0.481	**1.53 [1.09–2.14] *P* = .013***	0.403
Kidneys SUVmean	0.334	0.494	0.532
Biological results			
Baseline platelets count	0.307	0.642	0.266
Baseline Hb levels	0.498	**0.36 [0.15–0.87] *P* = .023***	0.427
Baseline neutrophils	0.123	0.418	0.242
Baseline lymphocytes	0.121	0.084	0.231
Baseline GFR	0.434	0.377	0.344

Significant predictors are presented as odd ratios, 95% confidence intervals, and *P* value. Only *P* value is reported for nonsignificant predictors.

GFR = glomerular filtration rate, Hb = hemoglobin, SA = somatostatin analogue, SPECT = single-photon emission computed tomography, SUV = standard uptake value.

* $P < .05$.

Table 3

Model selection for hemoglobin decrease prediction.

	Hemoglobin significant decrease	
	Model selection	
	AIC	Final model
Model 1: spleen SUVmean alone	29.0	1.53 [1.09–2.14] *P* = .013*
Model 2: hemoglobin levels alone	30.2	Rejected
Model 3: spleen and hemoglobin	32.2	Rejected

AIC = Akaike information criterion.

* $P < .05$.

Significant decreases were observed in the 3 blood lines with, in decreasing order of frequency: platelets (51.5%, 17/33), hemoglobin (21.2%, 7/33) and neutrophils (3.0%, 1/33). The same order was encountered in the NETTER-1 study,[1] but with lower percentages: the NETTER study focused on the detection of clinically significant decreases according to the common terminology criteria for adverse events classification,[9] whereas our study focused on lower, biologically significant thresholds. Almost no events were recorded when studying neutrophil levels, explaining the negativity of our analyses for neutrophil decrease prediction. The lack of predictive factors for platelet decrease may be related to their short life span with more fluctuating levels or indicate a multifactorial character to the thrombocytopenia, which our low number of patients did not allow to detect.

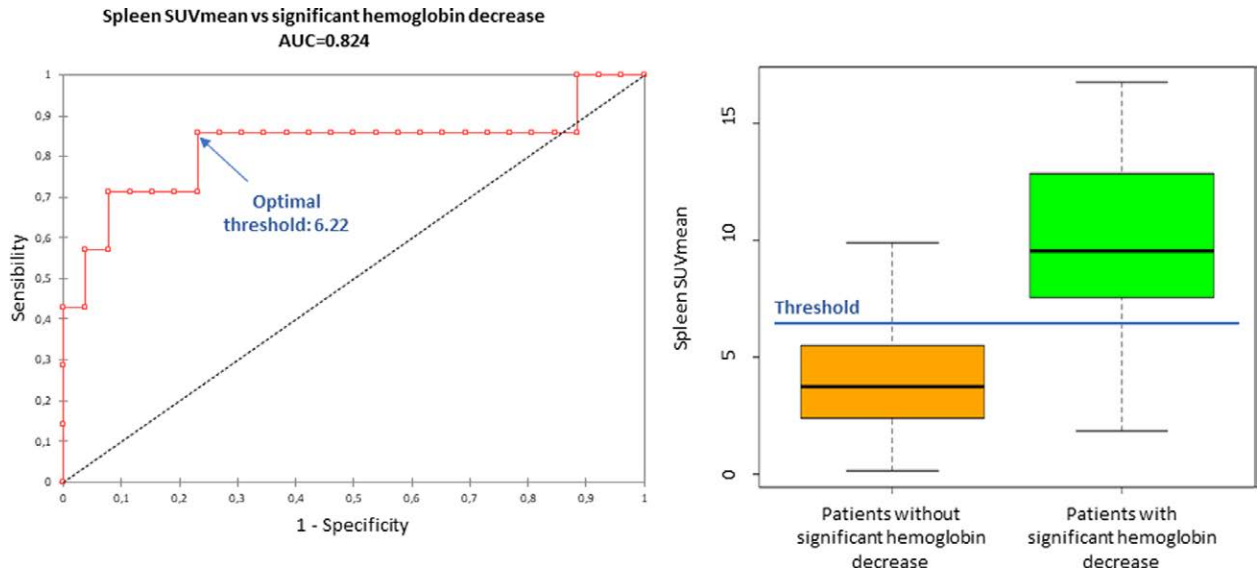

Figure 2. ROC curve analysis (spleen SUVmean vs hemoglobin decrease) and spleen SUVmean distribution. AUC = area under curve, ROC = receiver operating characteristic, SUVmean = mean standardized uptake value.

Table 4

Correlation of harmonized spleen SUVmean with the other factors.

	Correlations with spleen SUVmean
Age	$P = .656$
Weight	0.70 ($P < .001$)
Last intake of cold SA	0.44 ($P = .011$)
Administered activity	
Current treatment	−0.72 ($P < .001$)
Cumulative activity	$P = .342$
Quantitative SPECT data	
Tumor SUVmax	$P = .054$
Bone SUVmean	0.56 ($P = .001$)
Kidneys SUVmean	0.80 ($P < .001$)
Biological results	
Baseline platelets count	−0.41 ($P = .017$)
Baseline Hb levels	−0.53 ($P = .001$)
Baseline neutrophils	$P = .493$
Baseline GFR	−0.60 ($P < .001$)
Baseline lymphocytes	$P = .878$
Lymphocytes' decrease	0.40 ($P = .02$)

Correlation coefficients are reported only where P value < 0.05.

GFR = glomerular filtration rate, Hb = hemoglobin, SA = somatostatin analogue, SPECT = single-photon emission computed tomography, SUV = standard uptake value.

The SUVmean of the 3 healthy organs (bone marrow, spleen and kidneys) appeared to be positively correlated. However, only the SUVmean of the spleen was associated with hematological toxicity. The identification of the spleen and not the bone marrow may seem surprising. The hematotoxicity of peptide receptor radionuclide therapy is considered to be related to the destruction of hematopoietic cells[2] (i.e. a production impairment) and the radiosensitivity of platelets and red blood cells in the peripheric blood is reported as low.[10] One explanation could be that the SUVmean of the spleen actually reflects the irradiation of the bone marrow. The measurement of the SUV of the bone marrow is indeed complex (small structures, exposed to the partial volume effect) and the absolute value remains low (<1) and therefore remains vulnerable to noise related to the surrounding structures. Spleen SUVmean could be a more reliable surrogate in this setting.

While the correlation of splenic SUVmean to weight and activity are self-explanatory, as both parameters are included in the SUV formula,[11] a positive correlation was noted with the date of the last SA intake. Decreased healthy organ uptake under SA treatment is documented in 68Ga somatostatin receptors imaging.[12] The inverse correlation with GFR could be explained by a higher bioavailability of the tracer due to lower elimination. The inverse correlation with platelet and hemoglobin levels is less straightforward. Somatostatin receptors are located mainly in the red pulp of the spleen[13] and are thought to have a vasoconstrictive effect[13] reducing spleen filtering. The question of whether this regulation can partially explain the inverse correlation will require however further investigation. Splenic SUVmean is finally positively correlated to the decrease of lymphocytes (before vs after treatment). The explanation is probably 2-fold. The decrease in lymphocytes is often considered a reflection of the dose received by the bone marrow,[14] so this correlation could confirm the link between splenic uptake and bone marrow irradiation. Peripheral destruction can also be evoked, however, as shown in external radiotherapy settings.[15]

Age, white blood cell count and primary tumor uptake have been reported as predictive factors of hematotoxicity in previous works.[2] Our population does not cover a wide range of ages and is centered around 70 years (cutoff considered in previous studies), which probably explains the negativity of this parameter. The uptake of the primary tumor is at the limit of significance, probably due to a lack of power in the study. This phenomenon probably also explains the lack of predictive value of white blood lines levels. Extensiveness/total metabolic tumor volume, one of the last predictive factors reported in the literature,[2] was not assessed in our study: its measurement was not possible due to the absence of whole-body SPECT acquisitions. However, we may have indirectly captured part of this factor via the "Tumor sink effect,"[16,17] that refers to the phenomenon by which high burden tumors can lead to a decrease in the uptake of healthy organs by tracer sequestration.

Limitations of our study include the small number of patients and its retrospective monocentric design. The coexistence of 2 acquisition protocols may limit the reproducibility of measurements but this problem was addressed by using a validated harmonization method.[5,18] This harmonization corrected the SUV values of 10/33 patients (reconstruction protocol 2). However, the identified predictive factors were unchanged whether using harmonized or non-harmonized data. We did not consider prior treatments such as chemotherapy. Although the concomitant use of alkylating agent do not greatly affect the incidence of toxicity,[19] more recent studies suggest that heavily pretreated patients could increase this risk.[19] The heterogeneity of previous treatments and the small number of patients made it impossible to integrate this factor.

5. Conclusions

The study of splenic uptake, measured on quantitative post-treatment SPECT could predict and anticipate subacute anemic complications after Lutathera treatment. Larger studies are needed to confirm these results.

Acknowledgments

We would like to thank the whole team of the Godinot Institute, with a special thought for the very first persons who participated in the implementation of this new therapeutic activity: Caroline Cossus-Haye, Fabien Robinet, Justine Wateau, Aline Goulard, Nathalie Gaillot, and Marion Kolloch.

Author contributions

Conceptualization: David Morland.
Data curation: David Morland, Christopher Hoog, Ghali Sézin, Pierre Paris.
Formal analysis: David Morland.
Investigation: David Morland, Sébastien Dejust.
Methodology: David Morland, Elizabeth Katherine Anna Triumbari.
Software: David Morland.
Validation: David Morland.
Writing – original draft: David Morland.
Writing – review & editing: David Morland, Elizabeth Katherine Anna Triumbari, Christopher Hoog, Ghali Sézin, Sébastien Dejust, Guillaume Cadiot, Pierre Paris, Dimitri Papathanassiou.
All authors have read and agreed to the published version of the manuscript.

References

[1] Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of ^{177}Lu-Dotatate for midgut neuroendocrine tumors. N Engl J Med. 2017;376:125–35.
[2] Bergsma H, Konijnenberg MW, Kam BLR, et al. Subacute haematotoxicity after PRRT with 177Lu-DOTA-octreotate: prognostic factors, incidence and course. Eur J Nucl Med Mol Imaging. 2016;43:453–63.
[3] Kayal G, Clayton N, Vergara-Gil A, et al. Proof-of-concept of DosiTest: a virtual multicentric clinical trial for assessing uncertainties in molecular radiotherapy dosimetry. Phys Medica. 2022;97:25–35.

[4] Peters SMB, Meyer Viol SL, van der Werf NR, et al. Variability in lutetium-177 SPECT quantification between different state-of-the-art SPECT/CT systems. EJNMMI Phys. 2020;7:9.
[5] Orlhac F, Eertink JJ, Cottereau AS, et al. A guide to combat harmonization of imaging biomarkers in multicenter studies. J Nucl Med. 2022;63:172–9.
[6] Braga F, Panteghini M. Generation of data on within-subject biological variation in laboratory medicine: an update. Crit Rev Clin Lab Sci. 2016;53:313–25.
[7] European federation of clinical chemistry and laboratory medicine-biological variation database. Available at: https://biologicalvariation.eu/meta_calculations.
[8] Thuillier P, Maajem M, Schick U, et al. Clinical assessment of 177Lu-DOTATATE quantification by comparison of SUV-based parameters measured on both post-PRRT SPECT/CT and 68Ga-DOTATOC PET/CT in patients with neuroendocrine tumors: a feasibility study. Clin Nucl Med. 2021;46:111–8.
[9] CTCAE v5.0 quick reference 5x7. Published online November 27, 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. [access date July 18, 2022].
[10] Bober B, Saracyn M, Zaręba K, et al. Early complications of radioisotope therapy with Lutetium-177 and Yttrium-90 in patients with neuroendocrine neoplasms-a preliminary study. J Clin Med. 2022;11:919.
[11] Buvat I. Les limites du SUV. Médecine Nucléaire. 2007;31:165–72.
[12] Ayati N, Lee ST, Zakavi R, et al. Long-acting somatostatin analog therapy differentially alters ^{68}Ga-DOTATATE uptake in normal tissues compared with primary tumors and metastatic lesions. J Nucl Med. 2018;59:223–7.
[13] Sarikaya I, Sarikaya A, Alnafisi N, et al. Significance of splenic uptake on somatostatin receptor imaging studies. Nucl Med Rev Cent East Eur. 2018;21:66–70.
[14] Wang Q, Qiu Q, Zhang Z, et al. Bone marrow dosimetric analysis of lymphopenia in patients with esophageal squamous cell carcinoma treated with chemoradiotherapy. Cancer Med. 2021;10:5847–58.
[15] Liu J, Zhao Q, Deng W, et al. Radiation-related lymphopenia is associated with spleen irradiation dose during radiotherapy in patients with hepatocellular carcinoma. Radiat Oncol. 2017;12:90.
[16] Gafita A, Calais J, Fendler WP, et al. Tumor sink effect: myth or reality? J Nucl Med. Published online April 28, 2022;63:1124.
[17] Beauregard JM, Hofman MS, Kong G, et al. The tumour sink effect on the biodistribution of 68Ga-DOTA-octreotate: implications for peptide receptor radionuclide therapy. Eur J Nucl Med Mol Imag. 2012;39:50–6.
[18] Da-Ano R, Masson I, Lucia F, et al. Performance comparison of modified ComBat for harmonization of radiomic features for multicenter studies. Sci Rep. 2020;10:10248.
[19] Kesavan M, Turner JH. Myelotoxicity of peptide receptor radionuclide therapy of neuroendocrine tumors: a decade of experience. Cancer Biother Radiopharm. 2016;31:189–98.