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Imagerie des récepteurs de la somatostatine dans la sélection et l'évaluation de la réponse à la radiothérapie interne vectorisée par 177-Lu-DOTATATE chez les patients porteurs de tumeurs neuro-endocrines gastro-entéropancréatiques

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Abstract

Introduction

Peptide receptor radionuclide therapy (PRRT) with 177-Lu-DOTATATE has recently emerged as a treatment of reference for metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NET). Our retrospective study analyzed on the one hand the performances of somatostatin receptors PET/CT (SSTRs-PET/CT) in predicting tumor uptaking, and on the other hand the value of post-therapy scans and SSTRs-PET /CT in assessing tumor response to PRRT.

Material and methods

Patients with GEP-NET treated with 4 cycles of 177-Lu-DOTATATE between June 2016 and April 2019 underwent SSTRs PET/CT before and 1 year after the first PRRT cycle, as well as post-therapy scintigraphy (whole-body planar and SPECT/CT scans) performed 24 hours after each 177-Lu-DOTATATE injection. Clinical, biological, and imaging follow-up data were collected to determine the duration of tumor control (DTC). Head-to-head Pearson correlation analysis between SPECT/CT realized after PRRT 1st cycle and baseline SSTRs PET/CT was performed. Post-therapy scintigraphy and SSTRs PET/CT were analyzed visually and semi-quantitatively to assess tumor response.

Results

Twenty-nine patients (15M/14F, median age 62 years old, small intestine primitive in 26 of them) were included. Pearson correlation coefficients calculated between baseline STTRs PET/CT and cycle 1 SPECT/CT SUV values were 0.63 for lesion SUVmax, 0.72 for lesion/liver and 0.71 for lesion/spleen SUVmax ratios. Visual analysis performed on post-therapy scintigraphy predicted the 1-year PET visual response in 20 patients (69%), underestimated significant responses in 5 patients (17%) and failed to detect the 4 patients with progression (14%). DTC were significantly different between responder/stable patients and progressing patients based on the 1-year SSTRs PET/CT response. In contrast, DTC was not significantly different between responders and stable patients. SUVmax of the hottest lesion on baseline SSTRs PET/CT were overall higher in responder/stable patients than in patients with progression, based on the 1-year SSTRs PET/CT visual response. The PERCIST-like approach did not predict the 1-year SSTRs PET/CT response or the DTC.

Conclusion

Our preliminary results confirmed the performances of pre-therapy SSTRs PET/CT to predict uptake of targeted lesions. Value of post-therapy scintigraphy appears to be limited to predict therapeutic response. SSTRs PET/CT visual response at 1 year showed a prognostic value in terms of DTC in our small and selected population. Interestingly, DTC was not significantly different between responders and stable patients. However, studies with larger populations are needed to confirm these results.

Keywords*: Neuroendocrine tumors, 177-Lu-DOTATATE, 68-Ga-DOTATOC, 68-Ga-DOTANOC, SPECT-CT, PET-CT*

Somatostatin receptor imaging in the selection and assessment of tumor response to 177-Lu-DOTATATE peptide receptor radionuclide therapy in patients with gastroenteropancreatic neuroendocrine tumors.

Introduction

Neuroendocrine neoplasms (NENs) represent a particular family of solid tumors, which mostly develops into digestive organs. Current gastroenteropancreatic neuroendocrine neoplasms (GEP-NEN) age-adjusted incidence is estimated to be 6.98 per 100,000 persons, with a significant increase observed during the last decade, partly due to improvements in diagnosis techniques (1).

Clinical features of NENs are quite heterogeneous and vary a lot between patients. When present, secretary syndromes may allow for early diagnosis. Nevertheless, in most cases, NENs are asymptomatic or poorly symptomatic, and their diagnosis is usually made incidentally or at an advanced stage.

Following the 5th WHO classification of the digestive system (2), gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) are separated into two main groups, "well" or "poorly" differentiated tumors, called respectively neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs). NETs are subsequently classified in grade 1, 2 or 3 according to two histopathological features: Ki-67 index and mitotic rate.

GEP-NENs are of particular interest as they express in a vast majority of cases somatostatin surface cell receptors (SSTRs), with an over-representation of subtype 2 (3).

Somatostatin is an hormonal peptide which binds to SSTRs, leading in numerous inhibitory effects on endocrine and exocrine secretions as well as on cell proliferation (4). Natural somatostatin has a very short half-life but synthetic analogs of somatostatin (octreotide, lanreotide) are routinely used in management of GEP-NETs, particularly efficient on secretary syndromes and tumor control (5).

Considering the benefits from synthetic analogs therapies in GEP-NETs, subsequent therapeutic agents as peptide receptor radionuclide therapy (PRRT) emerged. In 2017, treatment with 177-Lu-DOTATATE (Lutathera®) demonstrated a significant longer progression-free survival compared to high dose somatostatin analogs in patients with advanced progressive midgut NETs (6), leading to an authorization delivered by the US Food and Drug Administration (FDA) and the European Medical Agency (EMA) in 2018.

In that respect, biomarkers are particularly of great interest for a long and costly therapy as PRRT in order to improve patient selection and tumor response evaluation in GEP-NEN.

Eligibility of patients for PRRT is based on a sufficient SSTRs expression assessed by

molecular imaging. Formerly determined visually on planar scintigraphy with (111In)-pentetreotide using Krenning scale (7), tumor uptake is now largely assessed with pre-therapy 68-Ga-DOTA-peptide PET/CT, as suggested by guidelines (8) despite a lack of standardized criteria.

Indeed, Krenning score at patient level are not always concordant between conventional scintigraphy and PET/CT with consequences in patient selection for PRRT. It is mainly explained by a lower sensitivity of planar scintigraphy and an underestimation of tracer uptake in infra-centimetric lesions (9). In 2018, Werner et al proposed a stantardized framework system "SSTR-RADS", a 5-point scale derived from the PSMA-RADS (10) considering PRRT for patients showing a score of 4 or 5 (respectively lesion uptake superior to physiological liver uptake in site typical for NETs without/with corresponding findings on conventional imaging), with a high interobserver agreement (11),(12).

Furthermore, SSTRs PET/CT is not yet validated in the evaluation of therapeutic response after PRRT. Few studies evaluated correlations between changes in semi-quantitative SSTRs PET/CT parameters and PFS according to RECIST 1.1 criteria, without consistent results (13), (14), (15). As a result, and despite acknowledged limitations (16), RECIST 1.1 criteria (17) remain the reference for therapeutic response assessment after PRRT.

Our retrospective monocentric study evaluated both visual and semi-quantitative parameters derived from pre and post-therapeutic SSTRs PET/CT and post-therapy scans in patients with progressive metastatic GEP-NETs treated with 177-Lu-DOTATATE. The main objectives were firstly to confirm the performances of pre-therapy SSTRs PET/CT to predict 177-Lu-DOTATATE uptake by targeted lesions; secondly to evaluate if visual or semi-quantitative parameters derived from 177-Lu-DOTATATE post-therapy scans and pre and post-therapeutic SSTRs PET/CT could predict PET tumor response at one year and duration of tumor control (DTC).

Methods

Patient selection

Patients with histologically proven metastatic or locally advanced NETs according to WHO 2019 criteria (2) treated with four cycles of 177-Lu-DOTATATE (Lutathera®) between June 2016 and April 2019 were retrospectively included.

Patients were selected for PRRT after validation by the regional multidisciplinary team committee of the ENDOCAN-RENATEN network (Réseau national de reference pour la prise en charge des Tumeurs Neuroendocrines Malignes), and based on SSTRs PET/CT and 18-FDG PET/CT. Selection criteria were the presence of lesion with SSTRs uptake above healthy liver and the absence of NETs lesions showing exclusive FDG uptake.

Radiopeptide therapy

All patients underwent PPRT using 177-Lu-DOTATATE (Lutathera®), as part of the transitional authorization for nominative use (ATU) prior to September 2017, and then as part of full market approval delivered by the EMA. Each patient was meant to receive 4 intravenous injections of approximately 7,4 GB of 177-Lu-DOTATATE (Lutathera®) administered every 8 weeks, with the 4th injection realized approximately 6 months after beginning of therapy. Amino-acid (15g of Arginin and Leucin in 1 liter of Na-Cl) were perfused during 4 hours and started 30 min before radiopeptide injection for renal protection. Cold somatostatin analogs were required to be stopped at least 28 days before each radiopeptide administration.

Follow-up

Patients were followed clinically during and after the last PRRT and all clinical, biological and imaging data were collected. A SSTRs PET/CT follow-up was performed one year after the first cycle of PRRT (1-year SSTRs PET/CT). Morphological tumor response was assessed by thoraco-abdomino-pelvic computed tomography at baseline, 3, 6 and 9 months after completion of the first cycle of PRRT, according to RECIST 1.1 criteria. After 9 months, morphological follow up was not standardized and left to physician's appreciation. Results were collected to determine the duration of tumor control (DTC).

DTC was defined as the duration between PRRT1 and either a morphological progressive disease according to RECIST 1.1 criteria, NEN-related deaths, changes/intensification of therapy owing to substantial clinical symptoms changes or progressive functional imaging based on multi-disciplinary decision.

Imaging Protocol

SSTRs PET/CT procedure

During the period between June 2016 and July 2017, patients were explored with 68-Ga-DOTANOC PET/CT as part of a transitional authorization for nominative use (ATU) obtained from the Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Labelling of DOTANOC was performed with the Modular-Lab Standard automaton (Eckert & Ziegler Eurotope, Berlin, Germany), as previously described by Decristoforo et al. 2007 (18). Patients included after July 2017 were explored with 68-Ga-DOTATOC PET/CT using SomaKIT TOC® (AAAlaboratory). Gallium chloride solution was obtained from the 68Ge/68Ga generator GalliaPharm 1.85 GBq (Eckert & Ziegler, Berlin, Germany).

SSTRs PET/CT was performed 60 minutes after the injection of 150 MBq of 68Ga-SMSa, using a dedicated PET/CT system: Biograph mCT or Biograph Vision 450 (Siemens Healthcare Molecular Imaging USA, Inc.). Time acquisition was 3 min per bed-position.

Low-dose CT 3D was acquired for attenuation and scatter correction, without intravenous contrast enhancement, from vertex to mid-thighs, automatic mA according to the patient weight (80-140 kV) with 3mm slice thickness. PET data were reconstructed using the ordinary Poisson OSEM (3 iterations, 21 subsets and 3mm-full-width-at-half-maximum gaussian post-filtering).

Post-therapy SPECT/CT imaging

Whole body planar scans (WB) and thoracic-abdominal-pelvic SPECT/CT were obtained 24-hours after 177-Lu-DOTATATE injections at cycle 1 (cycle 1 SPECT/CT) and 4 (cycle 4 SPECT/CT).

Images were acquired on a dual head Intevo system using medium-energy collimators. Planar whole body acquisition (256x1024, 10 cm/min) and SPECT ranging from skull base to mid-thigh (2 steps, 256x256, 60 projections per head, 16s per projection, energy windows: 15% centered at 208 and 113 keV) were performed.

Low dose CT (automatic mA according to the patient weight (110 kV) with 3mm slice thickness) was carried out subsequently after SPECT, allowing for attenuation correction.

Data were reconstructed with attenuation, scatter and point spread function corrections using a 64 MLEM-equivalent iterations (voxel size: 2.4x2.4x2.4 mm3).

Image Analysis

All scans were analyzed on a dedicated workstation equipped with Syngo.via ® (Siemens Healthineers; Erlangen, Germany).

Visual analysis

Tumor response was visually assessed both on post-therapy WB and SPEC/CT, between cycle 1 and 4 (WB-SPECT visual response), and on SSTRs PET/CT, between baseline and one year after beginning of PRRT (PET visual response).

Visual analysis was performed independently by two experienced nuclear medicine physicians,20 using a pre-established 5-point visual scoring system based on uptake intensity, size and number of lesions. In case of discordance, a 3rd nuclear medicine physician was consulted.

The 5-point visual scoring system was defined as followed:

- Complete response (CR) corresponded to the absence of residual lesion.

- Significant response (SR) corresponded to a strong global decrease in lesion uptake intensity and/or decrease in number associated or not with a decrease in the size of lesions.

- Stable disease (SD) was defined as no significant change in uptake intensity, size and number of lesions.

- Progressive disease (PD) was defined as a significant increase in uptake intensity and size of lesions and/or an increase of number of lesions.

Visual longitudinal comparison was allowed by adjusting the contrast on the a priori healthy organs (spleen, kidneys and overall background) between the two scans.

Semi-quantitative parameters analysis

SUVmax values extracted from SPECT/CT scans were calculated using a conversion factor, allowing to convert the number of counts recorded to activity concentration. This value was normalized by the injected activity and corrected for decay.

Cycle 1 SPECT/CT and baseline SSTRs PET/CT scans were simultaneously analyzed side by side. Up to 5 lesions per patient were selected by a single operator, targeting lesions with intense uptake well defined on both image modalities, measuring more than 2cm3 in volume. These lesions included liver, bone and lymph node metastases as well as primary tumor site. When possible, lesions of the hepatic dome were not chosen, to prevent from quantification errors due to respiratory movements. Confluent lesions were also avoided, as they may lead to non-representative measurements. SUVmax-based measurements were recorded for each lesion.

Physiological uptake of liver and spleen was assessed thanks to the "region of reference" tool from Syngo.via® software, automatically drawing a region of interest (ROI) in the choosen organ. The SUVmax was then extracted from this ROI. When necessary, liver region of reference was moved manually on healthy parenchyma in patient presenting with a metastatic liver.

In addition to the above, the highest lesion SUVmax value was extracted independently for each scan (cycle 1 and cycle 4 SPECT/CT, baseline and 1-year SSTRs PET/CT). Highest lesion SUVmax from cycle 1 SPECT/CT and baseline SSTRs PET/CT were reported separately ("initial hottest lesion SUVmax") to assess their potential predictive value. Lesions were not necessarily the same between SPECT/CT and SSTRs PET/CT. Variations in percentage were computed using a PERCIST-like approach ($\Delta SUVmax_{PERCIST}$) between cycle 1 and 4 for SPECT/CT and between baseline and 1-year SSTRs PET/CT.

All lesions SUVmax and $\Delta SUVmax_{PERCIST}$ were normalized to spleen and liver SUVmax.

Statistical analysis

Head-to-head Pearson correlation coefficients were calculated, assuming a linear relationship between SUV values extracted from cycle 1 SPECT/CT and baseline SSTRs PET/CT.

Population was divided into subgroups according to PET visual response (CR, PR, SD or PD) at one year and to the duration of tumor control (DTC) median value.

Distributions of initial hottest lesion SUVmax values as well as changes in semi-quantitative parameters using the PERCIST-like approach (ΔSUVmaxPERCIST) were compared between subgroups. Same procedure was repeated with SUV values and ΔSUVmaxPERCIST normalized to spleen and liver physiological uptakes.

A DTC analysis was performed, based on a survival analysis model using Kaplan-Meier estimates. Log-rank tests were subsequently derived between subgroups according to PET visual response at one year.

Results

1. Population

A total of 29 patients (15 Men /14 Females; median age: 62 y/o) with progressive metastatic GEP-NETs were included between June 2016 and April 2019. Twenty-six patients had a primary location in small intestine, two in pancreas and one in rectum. The median Ki67 was 5%. Among the 29 patients, 27 received 4 cycles of PRRT at full dose, one received a half-dose at cycle 2, 3 and 4 and one had a half-dose at cycle 4. All patients underwent prior different therapies including surgery, chemotherapy, targeted therapy or local therapies. Nineteen patients were on long-acting somatostatin analogs during and after PRRT. Detailed characteristics of patients and prior therapies are illustrated in Tables 1 and 2.

Morphological imaging follow-up at 9 months according to RECIST 1.1 criteria reported 25 stable diseases, two partial responses and one progressive disease. One patient (n°24) did not perform the follow-up thoraco-abdomino-pelvic CT at 9 months.

Median DTC was 24 months, with a minimum value of 10 months and a maximum limit not reached (51 months at last follow up). Seven patients were considered as non-progressive at their last follow-up. Two patients died from carcinoid heart disease. Among the 20 patients left who were considered as progressive, 7 showed a progressive disease on conventional imaging according to RECIST 1.1 criteria and 13 experienced changes or intensification in therapy after considering functional imaging and/or clinical and biological data.

2. Performance analysis of pre-therapy SSTRs PET/CT to predict 177-Lu-DOTATATE uptake of targeted lesions

Eleven patients underwent 68-Ga-DOTANOC PET/CT before beginning of PRRT. Among these patients, only two performed 68-Ga-DOTANOC PET/CT after completion of PRRT. Other PET/CT scans were acquired with 68-Ga-DOTATOC.

Median delay between baseline SSTRs PET/CT and first cycle of PRRT was 67 days (9-207).

In total, 129 initial lesions (3 to 5 per patient) were segmented on cycle 1 SPECT/CT and baseline SSTRs PET/CT. Median lesion/liver and lesion/spleen SUVmax ratios were 8,3 and 2,9 in cycle 1 SPECT/CT and 4,5 and 1,6 for baseline SSTRs PET/CT respectively.

Linear associations between the two image modalities showed a moderate correlation (Pearson correlation coefficients R ranging from 0.63 to 0.72). Lesion/liver SUVmax showed the strongest correlation with a coefficient of 0.72.

Table 1. Patient's characteristics.

Age at first cycle* (y/o)	62 (43-78)
Sex ratio, M/F (n)	15/14
Primary tumor site	
Small intestine (n, %)	26 (90)
Pancreas (n, %)	2 (7)
Rectum (n, %)	1 (3)
2019 WHO grade	
G1 (n, %)	7 (24)
G2 (n, %)	17 (59)
NA (n, %)	5 (17)
Proliferation index: Ki67 % (n=19)*	5 (1-15)
Secretory syndrome (n=18)	
Carcinoid syndrome (n, %)	17 (59)
Zollinger-Ellison syndrome (n, %)	1 (3)
Ongoing long-acting SMSa during PRRT (n, %)	19 (66)

**Median and range*

SMSa: somatostatin analogs

Table 2. Therapies prior to PRRT

	First line	Second line	Third line	Fourth line	Fifth line
Number of patients	29	28	22	6	1
Surgery	27	1			
SMSa*	2	25	2		
Targeted therapy			5	2	1
Chemotherapy		2	6	2	
Liver TACE*			8	1	
Liver SIRT*				1	
External radiotherapy			1		

**SMSa: Long-acting somatostatin analogs, TACE: Trans-arterial chemoembolization, SIRT: Selective internal radiation therapy*

Table 3. Pearson correlation coefficients, R, between cycle 1 SPECT and baseline SSTRs PET/CT SUV values.

	R
Lesion SUVmax	0,62
Lesion/liver SUVmax ratio	0,72
Lesion/spleen SUVmax ratio	0,71

3. Evaluation of SSTRs imaging to predict PET tumor response at one year and duration of tumor control (DTC)

3.a Visual analysis

Based on our pre-defined 5 points visual scale, 9 out of 29 (31%) patients showed a significant response (SR) on the 4th post-therapy scan compared to the first one (WB-SPECT visual response). Among these 9 patients, 8 patients showed a SR on the 1-year SSTRs PET/CT with 2 patients considered PR and 6 SD according to RECIST 1.1 criteria at 9 months. The last patient showed a CR on the 1-year SSTRs PET/CT but was still classified SD according to RECIST 1.1 criteria at 9 months.

The others 20 (69%) patients were considered stable (SD) on the 4th post-therapy compared to the first one. Among them, 15 remained SR and 4 showed a PD on 1-year SSTRs PET/CT. Eighteen were considered with SD and one with PD according to RECIST 1.1 criteria at 9 months. One (patient n°24) did not perform the follow-up thoraco-abdomino-pelvic CT at 9 months. All results are shown in Table 4.

No patients of our cohort showed PD on the 4th post-therapy scintigraphy.

In total, WB-SPECT visual response predicted correctly PET visual response at 1 year in 20/29 (69%) patients, showing a SD in 10 patients (34%), and a PR or a CR in 9 patients (31%). However, WB-SPECT visual response underestimated response in 5 patients (17%) and did not predict PET visual progression at 1 year in 4 patients (14%).

No significant difference of DTC was observed between responders (SR) or patients showing SD ($p=0.76$) after WB-SPECT visual response. In contrast, significant difference was observed ($p<0.05$) between the three subgroups of patients classified as CR/SR, SD and PD after PET visual response (Figure 3). More precisely, CR/SR and SD subgroups showed significantly higher DTC than PD subgroups ($p= 0.025$ and $p=0.025$ adjusted for multiple comparison, respectively for CR/SR and SD subgroups). On the other hand, there was no significant difference of DTC between CR/SR and SD subgroups ($p=0.083$ adjusted for multiple comparison).

3.b Semi-quantitative analysis

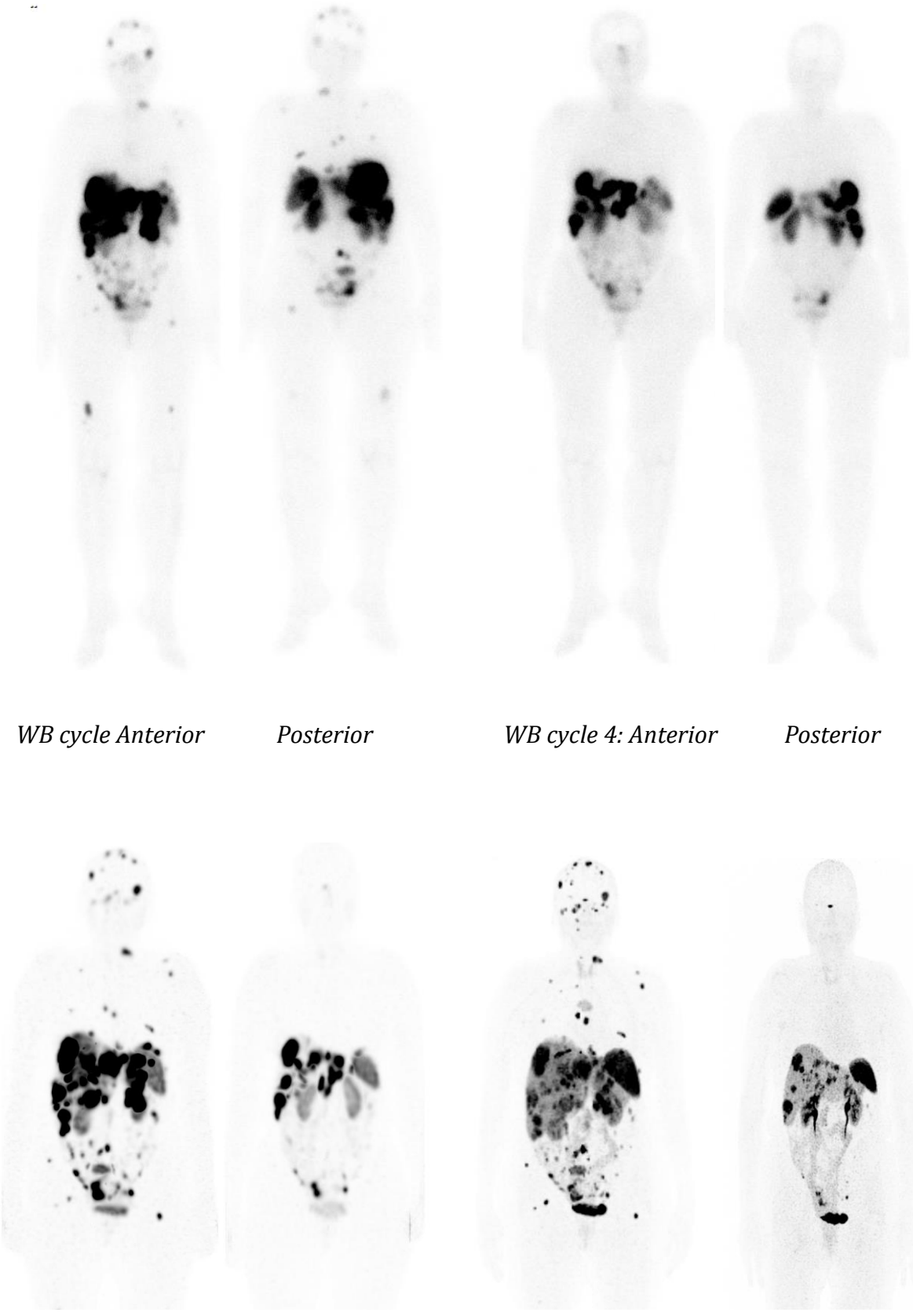
Patients from the CR/SR and SD PET visual response subgroups showed a significantly higher initial hottest lesion SUVmax on baseline SSTRs PET/CT than in the PD subgroups (respectively median values : 46 and 24), as shown in figure 4. There was no significant difference between CR/SR and SD subgroups.

No significant difference was observed between the PET visual response subgroups regarding the hottest lesion SUVmax measured on cycle 1 SPECT/CT.

Initial hottest lesion SUVmax values were not significantly different between the two subgroups divided according to the median value of DTC (<24 and ≥24) for both cycle 1 SPECT and baseline SSTRs PET/CT. Differences remained non-significant when adjusting with spleen and liver physiological uptakes.

Variations of semi-quantitative parameters between cycle 1 and 4 SPECT/CT following the PERCIST-like approach previously described failed to predict PET visual response (Figure 5). Indeed, $\Delta SUVmax_{PERCIST}$ obtained from post-therapy SPECT/CT were not significantly different between subgroups. In addition, there was no interest in adjusting for physiological liver and spleen backgrounds, as differences between subgroups remained non-significant.

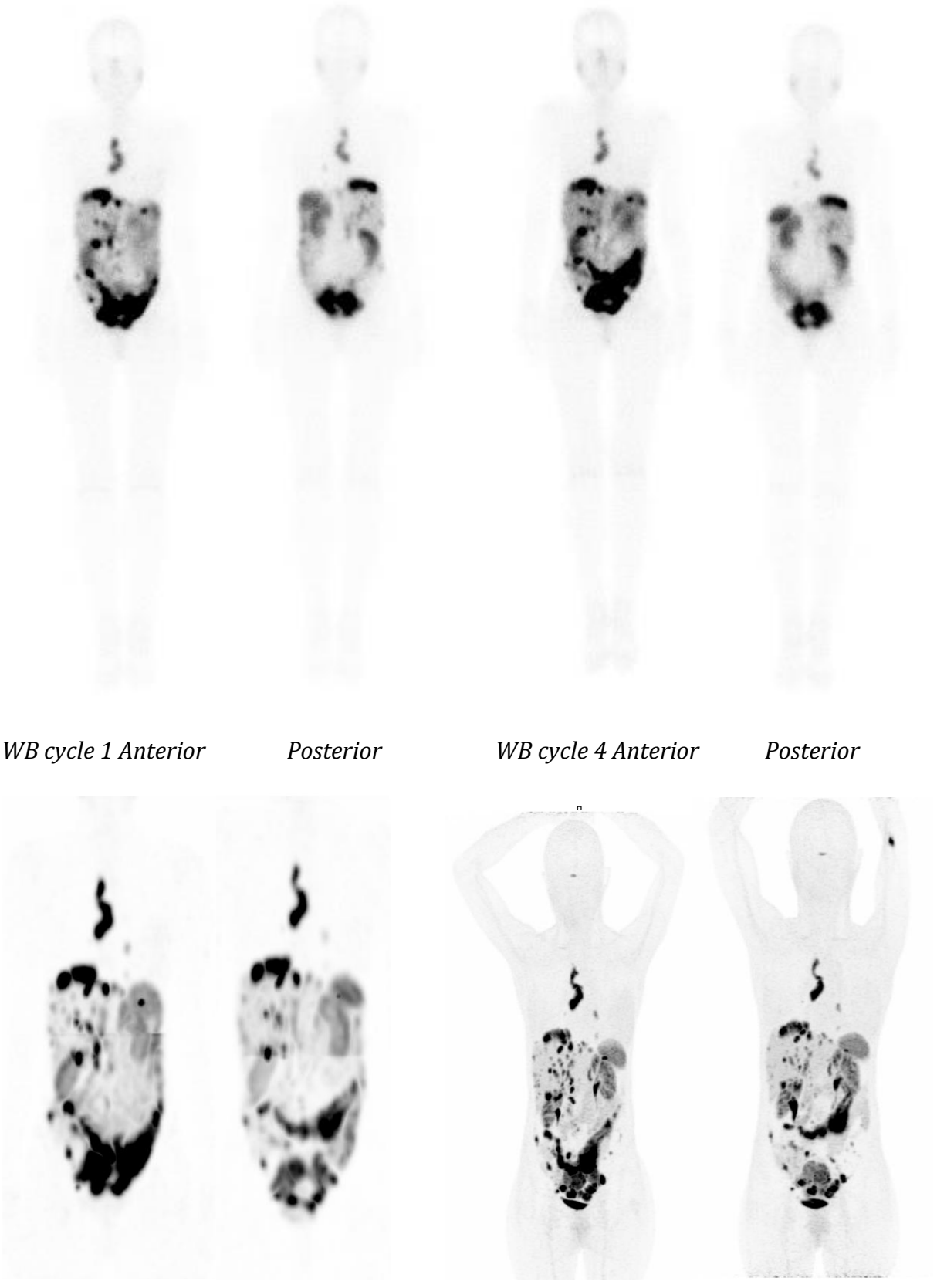
Similarly, there was no significant difference between $\Delta SUVmax_{PERCIST}$ derived from post-therapy SPECT/CT and SSTRs PET/CT regarding the DTC subgroups. Same observation was made after normalization of $\Delta SUVmax_{PERCIST}$ to liver and spleen uptakes.



WB cycle Anterior *Posterior* *WB cycle 4: Anterior* *Posterior*

SPECT cycle 1 SPECT cycle 4 Baseline SSTRs PET 1-year SSTRs PET

Figure 1: Patient n° 7 (DTC =27 months) showing a SR on cycle 4 post-therapy scintigraphy and on 1-year SSTRs PET/CT.



WB cycle 1 Anterior *Posterior* *WB cycle 4 Anterior* *Posterior*

SPECT cycle 1 *SPECT cycle 4* *Baseline SSTRs PET* *1-year SSTRs PET*

Figure 2: Patient n°16 (DTC=48 months) showing SD on cycle 4 post-therapy scintigraphy and on 1-year SSTRs PET/CT.

Table 4. Tumor response according to visual analysis 5-point scale of post-therapy scintigraphy, SSTRs PET/CT and RECIST 1.1 criteria at 9 months.

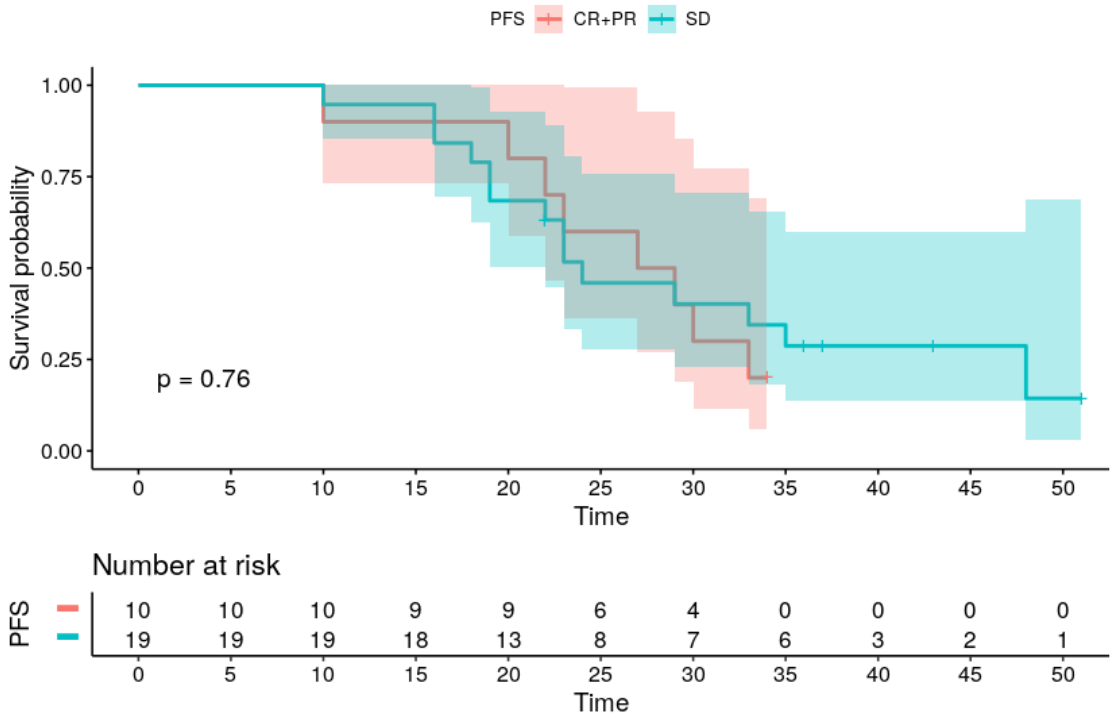
Patient	Cycle 4 PTS	RECIST 1.1 at 9 months	1-year SSTRs PET/CT	DTC
1	SR	SD	CR	30
2	SR	PR	SR	29
3	SR	PR	SR	20
4	SR	SD	SR	>34
5	SR	SD	SR	>34
6	SR	SD	SR	33
7	SR	SD	SR	27
8	SR	SD	SR	23
9	SR	SD	SR	22
10	SD	SD	SR	24
11	SD	SD	SR	23
12	SD	SD	SR	>22
13	SD	SD	SR	19
14	SD	SD	SR	16
15	SD	SD	SD	>51
16	SD	SD	SD	48
17	SD	SD	SD	33
18	SD	SD	SD	>43
19	SD	SD	SD	>37
20	SD	SD	SD	>36
21	SD	SD	SD	35
22	SD	SD	SD	29
23	SD	SD	SD	22
24	SD	-	SD	10
25	SD	PD	SD	10
26	SD	SD	PD	23
27	SD	SD	PD	19
28	SD	SD	PD	18
29	SD	SD	PD	16

PTS: Post-therapy scintigraphy

5-points scale visual analysis: CR: Complete Response, SR: Significant Response, SD: Stable Disease, PD: Progressive Disease.

PR: Partial Response, SD: Stable Disease according to RECIST 1.1 Criteria

3A



3B

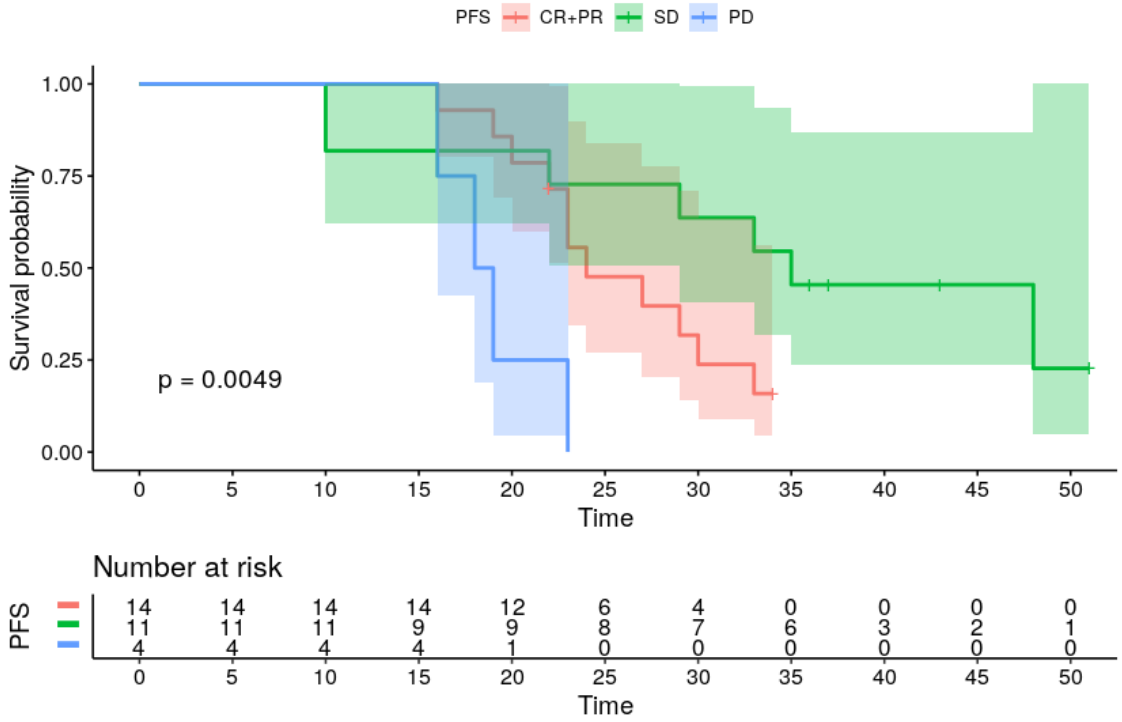


Figure 3. Kaplan-Meier estimates of survival probability (DTC) according to WB-SPECT (3A) and PET (3B) visual responses.

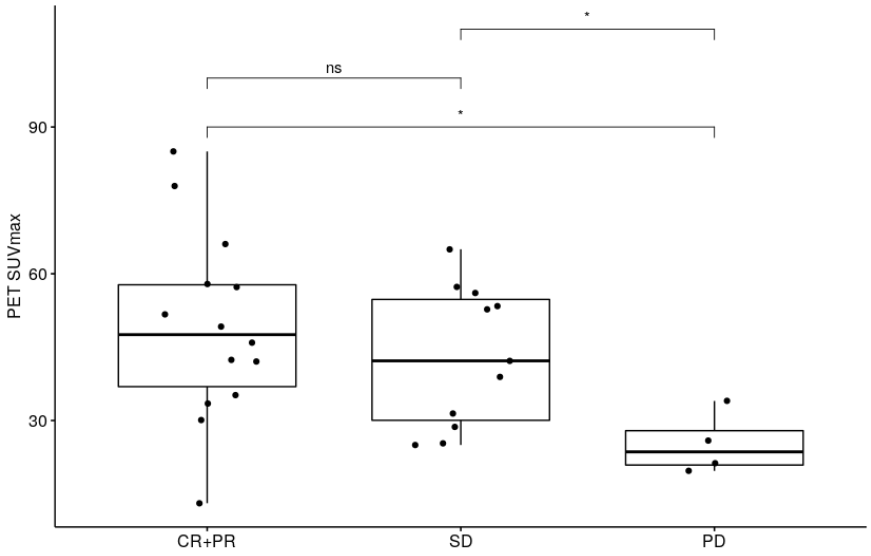


Figure 4. Distribution of baseline SSTRs PET/CT initial hottest lesion SUVmax regarding the PET visual response subgroups.

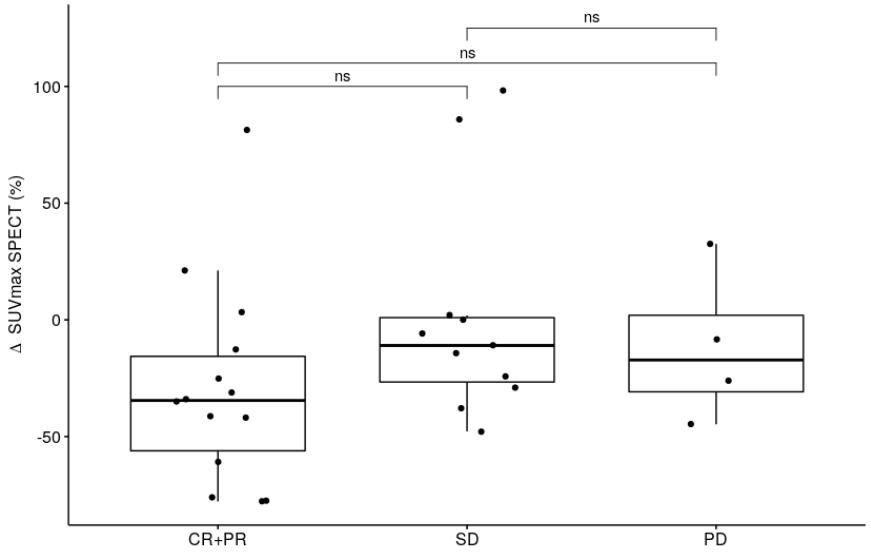


Figure 5. Distribution of $\Delta SUVmax_{PERCIST}$ from post-therapy SPECT/CT regarding the PET visual response subgroups.

Discussion

In a theranostic approach, pre-therapeutic SSTRs PET/CT is necessary before internal radiation therapy in order to ensure a sufficient tumor targeting.

Head-to-Head correlation: a moderate correlation

Our results showed that tumor SUV values from baseline SSTRs PET/CT and cycle 1 SPECT/CT were moderately correlated, with slightly higher correlations for normalized SUVmax to liver and spleen uptakes, bearing out that SSTRs PET/CT may predict uptake of targeted lesions. Our results confirm those recently published by Thuillier et al. (19), who observed a moderate to strong linear correlation between SUV values from SPECT/CT and TEP/CT (R = 0.80 for tumor SUVmax and R = 0.68 for tumor-to-spleen SUVmax ratio). Surprisingly, lesion SUVmax correlation became higher when adjusted for physiological uptake of liver in our work but decreased in Thuillier et al. study.

We only found a moderate correlation between cycle 1 SPECT/CT and baseline SSTRs PET/CT SUV values (at best R= 0.72 for lesion/liver SUVmax ratio), which is not surprising for multiple reasons. SSTRs PET/CT and post-scintigraphy were performed with different peptides (-NOC or –TOC or -TATE) and isotopes (68-Ga and 177-Lu), resulting in radioligands with different biological and chemical properties. DOTATOC and DOTATATE are two peptides which exhibit different in-vitro binding affinity profiles, with a nearly 10-fold higher affinity on SSTR2 subtype showed for DOTATATE than for DOTATOC (20). This difference has been verified with higher SUV values of 68-Ga-DOTATATE than 68-Ga-DOTATOC observed on SSTRs PET/CT (21). Similarly, choice of radiometal impacts the radioligand affinity binding profile (20) and may have been partly responsible for the correlations observed.

Another explanation to these modest correlations could be the differences in delays between injections and acquisitions (24 hours for post-therapy scintigraphy and 1 hour for SSTRs PET/CT). Indeed, biodistribution of radioligands changes over time, potentially modifying lesion and physiological organs SUV values. Of note, we observed approximately 2-fold higher lesion/liver and lesion/spleen SUVmax ratios in SPECT/CT than in SSTRs PET/CT. These results may be attributed to the decrease of the spleen and liver physiological uptakes of 177-Lu-DOTATATE over time, as proposed by Thuillier et al. who reported comparable values (19).

Finally, partial volume effect in SPECT (19), delay between baseline SSTRs PET/CT and cycle 1 SPECT/CT, as well as delay between last cold somatostatin injection and baseline SSTRs PET/CT were additional uncontrolled factors that could have led to a moderate correlation.

Visual analysis: interest of post-therapy scintigraphy visual response

Early prediction of treatment response is usually of great interest for patient management, but remains poorly documented with PRRT. In particular, value of post-therapy imaging and follow-up with SSTRs PET/CT scans remains to be evaluated.

In our population, WB-SPECT visual analysis was able to correctly predict PET visual response at 1 year in 20/29 (69%) patients, but underestimated response in 5 patients and did not predict progression in 4. It did neither discriminate population regarding the median DTC value, potentially owing to a too early evaluation compared with SSTRs PET/CT performed one year after the beginning of PRRT. As a matter of fact, because of the low-dose rate of irradiation delivered by PRRT, tumor response may not be consistent at an early stage and be delayed with best response observed in some cases several years after initiation of PRRT. The high rate of patients considered SD according to RECIST 1.1 criteria in our population (25 out of 28 patients,) at 9 months corroborates this hypothesis. Indeed, a delayed tumor response could partly explain our results regarding the 5 patients who were considered in SD on cycle 4 post-therapy scintigraphy and became in SR on 1-year SSTRs PET/CT. Post-therapy scans neither did predict progressive disease after PET visual response. Progressive diseases could have been underestimated at 6 months, as NETs usually are slow-growing tumors, and new small metastases could be occulted on SPECT, limited by the spatial resolution.

Visual analysis: interest of PET visual response

PET visual response performed at 1 year showed a pronostic value in terms of DTC in our population, with a longer DTC in CR/SR and SD subgroups of patients than in PD subgroup. Interestingly, no significant difference between CR/SR and PD subgroups was found. These results comfort the idea that despite a lack of tumour shrinkage, SD could be considered as a satisfactory response after PRRT. Indeed, in a study involving 310 patients, Kwekkeboom et al. (22) reported an improved survival of SD patients over PD patients according to CT using RECIST 1.1 criteria performed 3 months after the end of PRRT, which was of particular interest as SD was the most frequent response they observed, as well as in NETTER-1 study (6). However, SSTRs PET visual analysis failed to predict DTC for patients n°24 and 25. Patient n°24 showed a significant morphologic extent of a single liver lesion with low uptake on the one-year SSTRs PET/CT, suspect of de-differentiation later confirmed by a 18-FDG PET/CT. Still, he was considered PD by default in our PET visual analysis, as the whole disease burden remained stable. This outlined the limit of our tumor response assessment, as we only assess SSTRs positive lesions. This patient was considered PD according to RECIST 1.1 criteria on morphologic imaging performed shortly before the one-year SSTRs PET/CT, explaining the 10 months DTC. Patient n°25 showed a PD after appearance of small hypervascular liver lesions, possibly occulted in SSTRs PET/CT owing to the partial volume effect. For these reasons, morphological follow-up is complementary to functional imaging and remains recommended (23).

Semi-quantitative analysis: Initial hottest lesion SUVmax

When considering our semi-quantitative analysis, baseline SSTRs PET/CT hottest lesion SUVmax showed different value levels with significantly higher values in CR/SR and SD subgroups than PD subgroups according to PET visual response (Median values 46 and 24, respectively for CR/SR/SD and PD subgroups). Four patients out of 12 (33%) with an initial hottest lesion SUVmax ≤ 34 showed a PD according to the PET visual response at

one year. Previous studies already outlined the impact of a high baseline SUVmax as a prognostic factor of PRRT outcome and even PFS, based on a morphologic imaging follow-up (14,24,25). Interestingly, progressive patients according to PET visual response showed relatively high SUVmax values compared to prognostic cut-off-values of PRRT outcome proposed in the litterature, superior to 13 and to 17,9 respectively for Sharma et al. (14) and Öksüz et al. (24). Nevertheless, all these patients had a G2 disease, with two of them showing a Ki67≥10% and one who received mostly half-doses of 177-Lu-DOTATATE, which may have explained differences in terms of PET visual response at one year. If our data suggest a predictive value of hottest lesion SUVmax on the baseline SSTRs PET/CT towards PRRT outcome at one year, it did not seem to predict DTC in our population with indolent tumors, mainly of small intestine origin. Indeed, no significant difference was observed between DTC subgroups for the two images modalities. One explanation may be the use of a different endpoint, the DTC, based on the true live, substituting the PFS classically defined as time to progressive disease according to RECIST 1.1 criteria on morphologic imaging. Among the 22 patients who were considered progressive in our population, 15 experienced whether intensification or a change in treatment modalities, without progression formerly determined by morphologic imaging. This result suggests discordance between the clinical situation and conventional imaging. Indeed, in the settle of slow-growing tumors such as NETs, RECIST 1.1 criteria can be limited, especially for the assessment of small lesions such in bone or peritoneum and progression. Despite potential biases owing to the retrospective follow-up, DTC probably reflects in a more accurate way the global tumor response, taking in account clinical symptoms or functional imaging data that sometimes precede progression a few months before conventional imaging according to RECIST 1.1 criteria (15,26).

Semi-quantitative analysis: PERCIST-like approach

The semi-quantitative analysis performed based on a PERCIST-like approach, for both post-therapy SPECT/CT and STTRs PET/CT, did not bring relevant information in comparison to visual analysis regarding prediction of PET visual response or DTC.

PERCIST criteria have been initially developed for 18-FDG PET/CT, which makes their use for SSTRs PET/CT questionable. Indeed, with radiopeptides, decrease in SUV values could be related to tumor response, but also may reflect a reduction of SSTRs expression of various natures such as a competition with cold somatostatin analogs or a de-differentiation of the tumor likely to end in a progression. In 2019, Sharma et al. realized a PERCIST-type approach on a subgroup of 25 patients who underwent one to three cycles of PRRT, with a follow-up SSTRs PET/CT 3 months after completion of therapy, showing no prediction of PFS according to RECIST 1.1 criteria (14). These results were in line with those recently published by Huizing et al. on a retrospective study involving 44 patients (15). Moreover, question arose about standard uptake value as the most appropriate tool to assess SSTRs density. As a matter of fact, different studies pointed out the non-linearity between SUV and kinetic parameters, such as net influx rate, with probably non-reliable values of SUV observed beyond a threshold (27,28). If they might be useful for patient selection, kinetic parameters have not been tested for response evaluation in the settle of

SSTRs imaging and need to be evaluated in further studies.

To our knowledge, no robust relation has been established to date between SUV variations and PFS. One study suggested the potential role of tumor-to-spleen ratio after one cycle of PRRT for early prediction of tumor response, using 68-Ga-DOTATATE, as it tended to predict PFS more accurately than ΔSUVmax (13). However, authors observed an increase in spleen and physiological uptake along PRRT cycles, which may have influenced their results. Indeed, radiotracer biodistribution and then SUV values may fluctuate owing to PRRT side effects on renal clearance, possibly altering measurements and adding difficulties when interpreting SUV decrease.

Limitations

Besides limitations due to the retrospective nature of the study, the main limitation probably was our small but selected population who showed homogeneous features in terms of morphologic tumor response. Indeed, we reported 25 stable disease (89%) and only one progressive disease (3%) was observed according to RECIST criteria at 9 months, as opposed to approximately 66% and 15% respectively in the NETTER-1 study (6). This could be related to our monocentric-design study, leading to potential selection bias. In addition, population shared similar baseline characteristics, as 26 out of the 29 patients had a small intestine origin and had relatively low Ki67 (only 5 patients showed a Ki67 index equal or superior to ten). As a consequence, results should be taken with caution and need to be confirmed on a larger cohort of patients.

Finally, we limited our analysis to SSTRs positive lesions, which appears to be insufficient to fully assess the tumor response. Indeed, complementary imaging modalities such as 18-FDG-PET/CT or CT may bring important information regarding the tumor burden, such as dedifferentiation in tumors or appearance of metastases without SSTRs expression, likely to classify the disease as progressive.

Conclusion:

Our preliminary results confirmed the performances of pre-therapeutic STTRs PET/CT to predict uptake of targeted lesions with 177-Lu-DOTATATE. Post-therapy scans value seemed limited as it underestimated PET response at 1-year in some patients and did not allow to detect early progressions. PET visual analysis at 1-year showed a prognostic value regarding the DTC in our small and selected population, with a significant worst prognosis of patients showing PD on imaging compared to SD or CR/SR responders. Interestingly, CR/SR and SD DTC were not significantly different. However, these results need to be confirmed on a larger cohort of patients.

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Titre de Thèse: Imagerie des récepteurs de la somatostatine dans la sélection et l'évaluation de la réponse à la radiothérapie interne vectorisée par 177-Lu-DOTATATE chez les patients porteurs de tumeurs neuro-endocrines gastro-entéropancréatiques

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Introduction

La radiothérapie interne vectorisée (RIV) par 177-Lu-DOTATATE s'est récemment imposée comme un traitement de référence des tumeurs neuro-endocrines gastro-entéro-pancréatiques (TNE-GEP) métastatiques. Notre étude rétrospective a analysé d'une part les performances de la TEP aux analogues de somatostatine (TEP-SMSa) pour prédire la captation tumorale, et d'autre part l'intérêt des balayages post-thérapeutiques et de la TEP-SMSa dans l'évaluation de la réponse à la RIV.

Matériel et méthodes

Les patients porteurs d'une TNE-GEP traités par 4 cycles de RIV au 177-Lu-DOTATATE entre Juin 2016 et Avril 2019 ont bénéficié d'une TEP-SMSa avant et 1 an après la RIV1, ainsi que d'une scintigraphie post-thérapeutique SPT (balayage corps entier et SPECT/CT) à 24 heures de chaque injection de 177-Lu-DOTATATE. Les données du suivi clinique, biologique et d'imagerie ont été receuillies pour determiner la durée de contrôle tumoral (DCT). Une analyse de corrélation de Pearson lésion à lésion a été réalisée entre la SPECT du cycle 1 et la TEP pré-thérapeutique. Les SPT et les TEP ont été analysées visuellement et semi-quantitativement pour évaluer la réponse tumorale.

Résultats

29 patients (15H/14F, âge median 62 ans, 26 primitifs grêliques) ont été inclus. Les coefficients de corrélation de Pearson calculés entre les valeurs TEP et SPECT dans le cadre de l'analyse lésion à lésion étaient de 0,63 pour la SUVmax tumorale, 0,72 pour le ratio SUVmax tumeur/foie et 0,71 pour le ratio SUVmax tumeur/rate. L'analyse visuelle des SPT a prédit de manière imparfaite la réponse visuelle TEP a un an (69%), sous-estimant certaines réponses significatives (17%) et ne décelant pas les 4 (14%) patients en progression. Les DCT étaient significativement différentes entre les patients stables ou en réponse comparativement aux patients en progression d'après la réponse visuelle en TEP à 1 an. En revanche, les DCT n'étaient pas significativement différentes entre les patients répondeurs et stables. La SUVmax de la lésion la plus fixante en TEP pré-thérapeutique était globalement plus élevée chez les patients répondeurs et stables que chez les patients en progression d'après la réponse visuelle TEP à un an. L'approche PERCIST-like n'a pas permis de prédire la réponse TEP à 1 an ni la DCT.

Conclusion

Nos résultats préliminaires ont confirmé les performances de la TEP-SMSa pré-thérapeutique afin de prédire la captatation tumorale des lésions d'intérêt. La valeur des SPT dans la prédiction de la réponse tumorale semble limitée. La réponse TEP à 1 an a montré une valeur pronostique en termes de DCT au sein de notre faible population sélectionnée. Il est intéressant de noter que les patients répondeurs et stables n'ont pas montré de DCT significativement différentes. Des études portant sur de plus grands effectifs sont néanmoins nécessaires afin de confirmer ces résultats.

Mots-clés: Tumeurs neuro-endocrines, 177-Lu-DOTATATE, 68-Ga-DOTATOC, 68-GA-DOTANOC, SPECT-CT, PET-CT