Integrating Early Rapid Post-Peptide Receptor Radionuclide Therapy Quality Assurance Scan into the Outpatient Setting

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Abstract

Objective: To understand value of early rapid, quality-assurance (QA), post-therapy whole-body scan (Tx-WBS) in patients receiving peptide receptor radionuclide therapy (PRRT) in outpatient setting.

Methods: Sixteen patients with metastatic neuroendocrine tumors received PRRT and underwent Tx-WBS after each cycle. Early imaging (3 hour post-injection) was favored. Planar-images obtained on dual-headed gamma camera (speed 30 cm/min) were visually assessed and qualitatively compared with pre-therapy diagnostic scans. Retention% and lesion/spleen (L/S) ratios were calculated.

Results: Fifty three Tx-WBS were analyzed. No cutaneous contamination, extravasation or unexpected tracer distribution was observed. 46/53 (87%) Tx-WBS in 14/16 (88%) patients demonstrated uptake in metastatic lesions. No significant correlation was seen between L/S ratios and response on follow-up imaging. Qualitative assessment of follow-up images during four-cycles of PRRT provided preliminary estimate of disease course in 11/16 patients; with unexpected findings in 2.

Conclusion: In daily practice, especially in outpatient setting, an early QA post-PRRT scan proved effective for validating successful treatment and allowing preliminary disease monitoring, at no additional cost.

Keywords

Neuroendocrine tumors; NET; PRRT; 177Lu-DOTATATE; Lutathera®; Post-therapy scan; Quality assurance; Radionuclide therapy

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Conflict of Interest

Dr. Lisa Bodei: Consultant for Advanced Accelerator Applications (Lutathera®) and Ipsen pharmaceutical companies. Dr. Wolfgang Weber: Research support by Ipsen pharmaceutical. Dr. Joseph O’Donoghue: Consultant to Janssen Research and Development, LLC. Dr. Sonia Mahajan reports no conflict of interest.
**Introduction**

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies that arise from the neuroendocrine cells, widely distributed throughout the body [1]. They may present as localized disease; however, they are frequently discovered when metastatic. They tend to be slow growing although some can be aggressive [1–4].

Only a minority of patients with localized NETs can be cured by surgery. Systemic therapies such as somatostatin analogs, everolimus, sunitinib, and chemotherapy are considered in inoperable cases, while specific locations can be treated by external beam radiation therapy or liver-directed therapies [5–8].

Somatostatin analogues are used for the treatment of well differentiated NETs that over-express somatostatin receptors, specifically the subtype 2, to control symptoms of hormone overproduction and, to a lesser extent, for cytostatic effect. However, most of the patients eventually develop disease progression and require further therapeutic options [9].

**Peptide receptor radionuclide therapy**

Peptide Receptor Radionuclide Therapy (PRRT) with radiolabeled somatostatin analogs has been in use since 1992 [10] and represents an innovative targeted treatment for inoperable or metastatic NETs. Its use has been established in the treatment of NETs, generally well/ moderately differentiated, in multiple phase I and II clinical trials employing 90Y labelled octreotide derivatives and more recently $^{177}$Lu-DOTATATE ($^{177}$Lu-DOTA0-Tyr3-Octreotate or Lutathera®) [11–13].

The efficacy and safety of $^{177}$Lu-DOTATATE was recently evaluated in a phase III, multicenter, stratified, open and randomized parallel group study (NETTER-1) in patients with inoperable, progressive, somatostatin receptor positive, mid-gut NETs that demonstrated a 79% reduction in risk of progression or death (median PFS not reached) over a follow-up period of 14 months, in patients receiving $^{177}$Lu-DOTATATE with standard octreotide dose compared with high-dose octreotide alone (median PFS 8.4 months) [11].

Evidence supports that PRRT significantly improves the quality of life [14]. Such favorable results constituted the basis for an FDA approved Expanded Access Protocol (https://clinicaltrials.gov trial identifier: NCT02705313) in patients with metastatic or inoperable somatostatin receptor positive GEP-NETs, activated in our Institution in December 2016, which includes the patient population for this analysis [15]. $^{177}$Lu-DOTATATE (Lutathera®) has been approved by US Food and Drug Administration for use in patients with somatostatin receptor positive gastro-entero-pancreatic NETs [16].

The treatment is performed as an outpatient procedure in the U.S.A. As for the original NETTER-1 trial, the Lutathera® EAP includes fractions of 7.4 ± 10% GBq each for a total of 4 cycles administered at an interval of 8 ± 1 weeks [17–19]. Therapeutic activity may be modified in case of toxicity, for example involving the hematologic or renal function [18,20].
Post-PRRT imaging

Lutetium-177 (\(^{177}\)Lu) is a beta-gamma emitting radionuclide that decays to hafnium (Hf-177) with a half-life of 6.7 days [21]. The simultaneous emission of imaging appropriate gamma photons [208 keV (11%) and 113 keV (6.4%)] along with particulate \(\beta\) (-) emission (\(\beta\) (max) 497 keV, maximum tissue penetration 2 mm), makes it a suitable isotope for radionuclide therapy, when chelated to a peptide by means of a covalently linked chelate (DOTA or 1,4,7,10-tetraazacyclododecane).

The gamma-emission of \(^{177}\)Lu can be utilized for post-therapy imaging to collect information pertaining to tumor localization and correct administration of treatment. Diagnostic imaging for image comparison and assessment of tumor response can be collected 18–24 hours after therapy [22,23].

Being performed as an outpatient procedure, early post-PRRT imaging is not included in the protocol recommendations. Considering the anticipated expansion of \(^{177}\)Lu-DOTATATE in the foreseeable future after the recent FDA marketing approval, the availability of imaging information appears crucial to enhance the standards and provide quality treatment.

The aim of this study was to understand the value of performing an early rapid quality assurance (QA) post-therapy whole-body scan in patients who received \(^{177}\)Lu-DOTATATE treatment as an outpatient procedure within the Lutathera® EAP.

Methods

This was a single-site retrospective analysis that included sixteen patients with metastatic NETs who underwent multiple \(^{177}\)Lu-DOTATATE treatments at Memorial Sloan Kettering Cancer Center between May 2017 and July 2018, under the Lutathera® EAP. All patients received early rapid post-therapy whole body scans for quality assurance after each treatment. The study was approved by institutional review board and ethics committee.

\(^{177}\)Lu-DOTATATE treatment protocol

The patients selected for treatment were thoroughly assessed for medical history, disease status, performance status and physical examination. Eligibility criteria for the Lutathera® EAP included age ≥ 18 years, presence of inoperable metastatic or locally advanced neuroendocrine tumor, progression of disease during or after somatostatin analogue therapy, and target lesions overexpressing somatostatin receptors on Octreoscan or \(^{68}\)Ga-DOTATATE imaging.

Baseline laboratory tests and pre-therapy imaging for disease receptor status were analyzed (\(^{68}\)Ga-DOTATATE for 14 patients and \(^{111}\)In-pentetreotide for 2 patients). All the patients signed a written informed consent prior to therapy, which included consent for the Tx-WBS.

On the day of treatment, the patients received anti-nausea premedications, followed by a 4-hour intravenous amino acid infusion. Aminosyn II 10% mixed-amino acid solution 2000 ml (500 ml/hour) was used in the first 5 patients, subsequently replaced by a 2.5% lysine and
2.5% arginine solution 1000 ml (250 ml/hour) due to nausea and/or emesis associated with former solution.

Amino acids were initiated 30 minutes before radiopharmaceutical infusion. $^{177}$Lu-DOTATATE was infused over 30 minutes utilizing a Graseby syringe pump, which allows for optimal infusion and environmental control. Amino acid infusion was continued for the remaining 2.5–3 hours. Patients were continuously monitored during the procedure for possible adverse events.

Radiation exposure rate was measured in each patient during and after radionuclide therapy using an ionization chamber survey meter, to ensure adequate delivery of radionuclide and compliance with the release rate mandated by the local regulatory agency.

**Post-therapy QA scan**

Approximately 3 hours from the completion of the radiopharmaceutical injection, a rapid planar whole-body scan was acquired for all patients on a dual-head Philips Bright view XCT-gamma camera equipped with medium energy general purpose collimators at a speed of 30 cm/min with 20% window around $^{177}$Lu peak energy of 208 keV, matrix 1024 × 512.

The scan duration was less than 10 minutes and considering quality assurance as the purpose of $^{177}$Lu-DOTATATE images, no complementary projections or tomographic images were acquired. Whole-body planar images were acquired and a standard with a known aliquot of the injected dose was also counted.

**Image evaluation**

Three nuclear medicine physicians (SM, LB, WW), familiar with the patient history and pre-treatment imaging findings, evaluated the planar whole-body images using a dedicated software (Hybrid Viewer; Hermes Medical Solutions). Qualitative and visual assessment was performed for each scan.

Circular regions of interest of 2.0 cm diameter were drawn on all planar $^{177}$Lu images, using dedicated Hermes workstation, over target lesion with maximum uptake (visualized best in anterior images) and spleen (visualized best in posterior images) to calculate the lesion/spleen (L/S) ratio.

The uptrend or downtrend in L/S ratios was correlated with imaging response in follow-up using independent T-test in SPSS v25.0 (IBM Corp., Armonk, 2017). Qualitative comparison of post-therapy whole body scans was performed with pre-therapeutic $^{68}$Ga-DOTATATE or $^{111}$In-pentetreotide scan.

**Whole-body retention (%) measurement**

Images were analyzed by an experienced medical physicist (JOD). Whole body regions of interest were drawn on anterior and posterior $^{177}$Lu planar images to obtain background-corrected geometric mean counts and inferred WB activity to yield relative retained activities (in %), 2.5–3 hours after treatment administration.
Results

A total of 53 post-therapy whole-body scans (Tx-WBS) were acquired for 16 patients. Patient characteristics are described in the Table 1. Post-therapy scans were performed approximately 3 hours after completion of the $^{177}$Lu-DOTATATE infusion and were successfully acquired in all our patients. Considering the fast acquisition technique (speed of 30 cm/min), the scan was tolerated well and no complaints or discomfort were reported by the patients.

Tumor imaging

All fifty-three scans showed physiological bio-distribution of $^{177}$Lu-DOTATATE in liver, spleen, kidneys, urinary bladder and blood pool. All the scans confirmed the successful administration of therapy with no evidence of cutaneous contamination, extravasation or unexpected tracer uptake.

More than one concordant lesions were demonstrated in 46 of 53 scans (87%) in 14/16 patients (88%), and predominantly included metastatic disease involving liver, pancreas, peritoneum, lymph nodes and bone. In two patients (2/16~12%) with consecutive 4 and 3 post-therapy scans respectively, metastatic lesions were not clearly demonstrated. These included small hepatic, nodal and peritoneal disease in one patient (Figure 1); and osseous and nodal disease in the other patient. Lesions not clearly visualized on post-therapy scans were either smaller-sized (range 0.8–1.1 cm) and/or metastases with low SUV values (<10) in baseline diagnostic $^{68}$Ga-DOTATATE scans. Similarly, in other patients with partly concordant lesions, smaller sized and/or low SUV disease was not optimally visualized on post-therapy scans.

Whole body retention percentage and lesion/spleen ratio

The estimated percentage of total activity retained in the whole-body, approximately 2.5–3 hours after radiopharmaceutical administration, was in the range of 51%–94% with a median value of 74%. The percentage of retained activity in the patients varied based on the overall disease burden and bladder activity. Lesion/spleen ratios (for the lesion with maximum visual uptake) were evaluated in follow-up planar images of eleven patients, 10 of whom had completed four cycles of treatment and 1 patient had received three cycles (Table 2).

Ratios were not calculated for two patients with no visually apparent lesion on post-therapy scans and three patients who had received only 1 cycle of treatment at the time of this analysis. L/S ratios of at least five patients showed down-trending values, which were associated with decreased symptomatology; however no significant correlation was seen between decrease in L/S ratios and response on follow-up imaging (Table 2).

Qualitative assessment of sequential follow-up post-therapy scans was also performed in these 11 patients. Four of 11 patients showed visually apparent decrease in size of liver metastases over the course of treatments, also seen on subsequent $^{68}$Ga-DOTATATE scan in two patients (Figure 2) and CT in 2 patients.
Six of 11 patients showed grossly stable disease on post-therapy scans, corresponding with only mildly decreased uptake on post-therapy \(^{68}\text{Ga-DOTATATE}\) scan in 3 patients; mild decrease in size of lesions on CT in 1 patient; mild increase in size of lesions on CT in 1 patient and mild increased uptake in metastases on post-therapy \(^{68}\text{Ga-DOTATATE}\) scan in 1 patient respectively (Table 2).

One patient with initial visually apparent decrease in metastatic tumor burden, showed increase in size of metastatic hepatic lesions on 4\(^{th}\) post-therapy scan in comparison to prior, and a new lesion in pelvis, that corroborated with findings on dedicated CT imaging and new avid osseous metastases on \(^{68}\text{Ga-DOTATATE}\) scan (Figure 3).

One of the two patients excluded from the calculation of L/S ratios due to no visually apparent disease on post-therapy scans (due to small lesion size), showed decreased uptake and number of hepatic metastases and peritoneal implants in post-treatment \(^{68}\text{Ga-DOTATATE}\) scan. Prominence of pelvicalyceal system was noted in the latter patient on 4\(^{th}\) Tx-WBS due to distal ureteric obstruction caused by pelvic implants that was later confirmed on dedicated imaging.

**Discussion**

In the present study, an early rapid planar whole-body post-therapy scan, acquired in less than 10 minutes, proved to be a simple and effective method to confirm the correct biodistribution of \(^{177}\text{Lu-DOTATATE}\), to provide a technical assessment of administered therapy and to obtain an approximate estimation of disease status. During the set-up and administration of the radiopharmaceutical, there is the possibility of accidental contamination or extravasation, in addition to the risk of contamination from bodily fluids such as urine, feces or vomit. This can be more common in patients with functional tumors (e.g. carcinoid syndrome), and in those with reduced mobility, who need assistance in the bathroom or use special medical equipment (colostomy bags, bedpan). The post-therapy scan confirms the absence of such events before the patient leaves the department.

The acquisition of post-treatment images immediately after the end of the amino acid infusion represents a favorable compromise between the need to assess treatment quality and to favor patient compliance, especially after at least 5 hours of treatment related procedures.

Despite its low resolution, early rapid post-therapy \(^{177}\text{Lu-DOTATATE}\) scan shows adequate concordance of metastatic lesions with baseline imaging, considering that it is acquired only approximately 3 hours after radioisotope injection [24]. The lower resolution of the gamma camera and the lower image contrast due to the early time point result in lower sensitivity for lesion detection when compared to pre-therapeutic \(^{68}\text{Ga-DOTATATE}\) scan, which is however sufficient for the quality assurance purpose. According to a study by Sainz-Esteban et al. highest concordance rate between pre-therapeutic \(^{68}\text{Ga-DOTATATE}\) and post-therapy \(^{177}\text{Lu-DOTATATE}\) imaging is observed at delayed time points i.e. 24, 48 and 72 hours post injection. This observation was attributed to progressive continuous accumulation of \(^{177}\text{Lu-DOTATATE}\) in NET metastases and decreasing background activity, resulting in better lesion to background ratio [25]. This is the basis for performing delayed post-therapy imaging in
many centers outside the US where patients are admitted for PRRT. We did not compare early and delayed imaging findings in the current study as this is not the purpose of the study.

Some of the lesions missed in early rapid post-therapy scans are probably related to small volume of disease, interference of background activity due to physiological uptake of radiotracer in the bowel and low density of somatostatin receptors in lesions characterized by low SUV value in the pre-therapeutic imaging.

None of our findings on first post-therapy scans were discordant with baseline imaging; except that the small sized lesions were not clearly visualized on $^{177}$Lu scan, which is probably related to early timing and rapid acquisition of scan. This is differing from the results of study by Sainz-Esteban et al. where $^{68}$Ga-DOTATATE negative/$^{177}$Lu-DOTATATE positive lesions were observed in liver in few patients, possibly explained by different concentration of somatostatin analog compound labeled to radioisotope [25]. Similar results were also seen in study by Mirzaei et al. where additional lesions were reported in post-therapy scan acquired 24 and 72 hours post injection compared to diagnostic scan performed with $^{99m}$Tc-EDDA/HYNIC-TOC, which could be related to differences in receptor affinity between diagnostic and therapeutic compounds [26].

As per the Lutathera® EAP, recommended follow-up during treatments of patients receiving $^{177}$Lu-DOTATATE includes, physical examination, pregnancy test in females and laboratory tests such as liver function tests (ALT, AST, albumin, bilirubin), kidney function tests (creatinine, creatinine clearance) and hematological tests (Hb, WBC count, and platelet count). Follow-up extent of disease assessment is done by CT or MRI imaging, every 12 weeks after last $^{177}$Lu-DOTATATE treatment until disease progresses. In this study, fourteen patients had received follow-up $^{68}$Ga-DOTATATE and/or conventional imaging after PRRT and it was reflected that post-therapy $^{177}$Lu-DOTATATE scans can give a gross estimate of disease, as seen in at least 11 of our patients. The possibility to use a QA scan to roughly estimate the course of disease during treatment is critical in disease management and can perhaps guide further imaging or decision in case of unexpected findings, such as increased extent and intensity of uptake or appearance of new lesions. Preliminary quantitative L/S ratios in at least 5 patients showed down-trending values, which were associated with decreased symptomatology in patients, although no significant correlation was seen with response on follow-up imaging.

An important limitation of this study is the small sample size; which limits our results on use of L/S ratios. Since the purpose of the Tx-WB scan was primarily qualitative, we did not use tomographic imaging/ SPECT for further characterizing the lesions seen on post-therapy scans and also, did not quantitatively compare the early and delayed post-therapy scans.

**Conclusion**

We suggest that an early rapid QA whole-body scan after $^{177}$Lu-DOTATATE treatment is a quick, effective and reliable method for assessment of radiotracer bio-distribution and successful treatment administration, at no added cost of imaging. In daily practice,
especially in outpatient setting, it can confirm absence of events such as contamination and extravasation. It also gives the possibility of performing a preliminary assessment of the course of disease during treatment and guiding further imaging, if required.

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Figure 1:
60-year-old male diagnosed with well differentiated intermediate grade NET of the ileum metastatic to the peritoneum s/p terminal ileum resection and right hemicolecotomy; Initial $^{68}$Ga-DOTATATE scan (A) showed somatostatin receptor positive disease involving liver surface implant, peritoneal and mesenteric nodules. Fused PET/CT and CT images (B, C) demonstrate a 1.1 × 1.0 cm small mesenteric nodule with SUV 25.6, however these lesions were not clearly seen in either of the $^{177}$Lu-DOTATATE scans as demonstrated in the anterior images of post-therapy scans performed after 1<sup>st</sup> (D), 2<sup>nd</sup> (E), 3<sup>rd</sup> (F), and 4<sup>th</sup> (G) treatments.
Figure 2: 
Post-treatment $^{177}$Lu-DOTATATE scans after 1$^{st}$ (A) and 4$^{th}$ (B) cycle of PRRT in a 73-year-old male diagnosed with well differentiated ileocecal neuroendocrine tumor, s/p terminal ileal resection and right hemicolecotomy, metastatic to liver, nodes, peritoneal implants and bone. The most prominent lesion in hepatic segment 3 has decreased in extent and avidity (arrows). This is confirmed at subsequent $^{68}$Ga-DOTATATE imaging (D-MIP image, E-transaxial fused image), which demonstrates decreased size and avidity compared to baseline enrolment scan (C-MIP image, E-transaxial fused image) (C-E). Note: Adjacent liver lesion in image (F) appears enlarged due to difference in transaxial sections.
Figure 3:
Post-treatment $^{177}$Lu-DOTATATE scans in a patient with pancreatic NET metastatic to liver shows initial decrease in uptake and size of hepatic metastases, visualized on scan 1$^{st}$ (A), 2$^{nd}$ (B) and 3$^{rd}$ (C, black arrows) post-therapy scans. The 4$^{th}$ post-treatment (D, orange arrow) scan shows increased size of few hepatic lesions, although the overall burden is decreased since 1$^{st}$ scan. This was confirmed on CT imaging, showing pre-therapy (E, orange arrows) and post-completion of PRRT (F) size comparison of hepatic lesions in segment 4. The posterior planar images after 4$^{th}$ cycle (G, arrow) showed focal uptake in left pelvis, corresponding to avid osseous lesion (H, fused axial) on $^{68}$Ga-DOTATATE scan (I, posterior MIP).
**Table 1:**
Patient Characteristics, demographic details and primary tumor description.

| Number of patients | 16 |
|--------------------|----|
| Mean age at presentation | 58.6 years (45–73) |
| Sex (%) M: F | 8:08 |

**Primary**

| Primary | |
|----------|-----------------|
| Small Bowel NET | 12 (75%) |
| Pancreatic NET | 2 (12.5%) |
| Atypical Carcinoid, Lung | 1 (6.3%) |
| Unknown | 1 (6.3%) |

**Grade, as per WHO classification 2017 [24]**

| Grade | Counts |
|-------|--------|
| G1 | 7 (43.8%) |
| G2 | 8 (50%) |
| G3 | 1 (6.3%) |

**Prior treatments**

| Prior treatments | Counts |
|------------------|--------|
| Sx†+Octreotide | 5 |
| Sx+Octreotide+Liver ¹Embo | 6 |
| Octreotide+Liver Embo+Everolimus | 3 |
| Octreotide+Everolimus | 1 |
| Octreotide+Liver Embo+ ²Chemo | 1 |

**Total number of scans performed per patient**

| Scans | Patients |
|-------|----------|
| 1 scan | 3 patients |
| 3 scans | 2 patients |
| 4 scans | 11 patients |

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†Sx: Surgery;

¹Embo: Embolization;

²Chemo: Chemotherapy
Table 2:
Lesion to spleen uptake ratio (L/S) measured on Tx-WBS (11 patients).

| S.No | L/S Scan 1 | L/S Scan 2 | L/S Scan 3 | L/S Scan 4 | Visual Tx-WBS imaging response (Yes/No) | Overall symptomatic response | Follow-up imaging (% change in highest SUV)/(% change in size per RECIST 1.1) |
|------|------------|------------|------------|------------|----------------------------------------|-----------------------------|--------------------------------------------------------------------------------|
| 1    | 7.5        | 2.6        | 2.5        | 2.2        | Yes                                    | Weight gain                 | Overall mildly decreased $^{68}$Ga-DOTATATE avidity in liver metastases with decreased size on CT (31.5%). |
| 2    | 0.8        | 0.6        | 0.7        | 0.6        | No                                     | Decreased diarrhea; Resolved abdominal pain; mild weight loss | Decreased $^{68}$Ga-DOTATATE avidity in peritoneal implants and bone lesions (44%); slightly decreased in capsular implants; however, size of few pelvic implants mildly increased on CT (18.5%). |
| 3    | 7.4        | 4.6        | 4          |            | No                                     | Decreased fatigue; Increased abdominal pain, decreased appetite; Mild weight loss | Mildly decreased size of liver and nodal metastases on CT (11.2%). |
| 4    | 2.6        | 2          | 1.9        | 2.2        | Yes                                    | Decreased diarrhea; Stable weight | Unchanged with mildly decreased size of few hepatic and peritoneal metastases on CT. |
| 5    | 1.6        | 1.7        | 2.1        | 2.1        | Yes                                    | Decreased flushing and diarrhea; gained weight | Nearly resolved peritoneal implants, unchanged hepatic and nodal metastases on CT. |
| 6    | 4.8        | 3.5        | 4.1        | 3.8        | Yes                                    | Decreased flushing and diarrhea; gained weight | Decreased size (6%) and avidity (47.6%) of metastases on CT and $^{68}$Ga-DOTATATE scan. |
| 7    | 1.1        | 0.9        | 1.1        | 1.2        | No                                     | Mildly increased fatigue; Stable weight | Mildly decreased avidity of metastases on $^{68}$Ga-DOTATATE scan (26%). |
| 8    | 5.1        | 5.5        | 4.6        | 3.4        | No                                     | Mildly decreased diabetes and unchanged flushing; Stable weight | Mildly decreased $^{68}$Ga-DOTATATE avidity in liver and peritoneal metastases (21.2%). Unchanged size on correlative MR abdomen/pelvis. |
| 9    | 3.1        | 2.6        | 2.6        | 2.8        | No                                     | Mild weight gain; Unchanged back pain | Mildly increased size of few metastatic lesions (21.4%) on interval CT (after 3 cycles); mildly increased SUV on $^{68}$Ga-DOTATATE (15.3%). |
| 10   | 5.6        | 3.1        | 3          | 2.9        | Yes (initial three scans)              | Increased appetite, weight gain | Mildly decreased size of pancreatic primary and few hepatic metastases on CT (7%). New avid nodes and osseous lesions on $^{68}$Ga-DOTATATE. |
| 11   | 2.6        | 2.8        | 2.3        | 2.6        | No                                     | Increased appetite, mildly decreased flushing and abdominal pain, stable weight | Mildly increased size on interval CT (after 2 cycles) (19.9%). |