

**Title:** SSTR-RADS Version 1.0 as a Reporting System for SSTR-PET Imaging and Selection of Potential PRRT Candidates: A Proposed Standardization Framework

**Running Title:** SSTR-RADS 1.0 for SSTR-PET

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## **ABSTRACT**

Reliable standards and criteria for somatostatin receptor (SSTR) positron emission tomography (PET) are still lacking. We herein propose a structured reporting system on a 5-point scale for SSTR-PET imaging, titled SSTR-RADS version 1.0, which might serve as a standardized assessment for both diagnosis and treatment planning in neuroendocrine tumors (NET). SSTR-RADS could guide the imaging specialist in interpreting SSTR-PET scans, facilitate communication with the referring clinician so that appropriate work-up for equivocal findings is pursued, and serve as a reliable tool for patient selection for planned Peptide Receptor Radionuclide Therapy.

## INTRODUCTION

Due to the promising results of recent randomized clinical trials, Peptide Receptor Radionuclide Therapy (PRRT) of inoperable, metastasized neuroendocrine tumors (NETs) is increasingly being utilized (1,2). As a prerequisite for endoradiotherapy using "hot" somatostatin analogues (SSA), somatostatin receptor (SSTR) positron emission tomography (PET) using agonists including 68Ga-labelled 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-d-Phe(1)-Tyr(3)-octreotide/-octreotate (68Ga-DOTA-TOC/-TATE), 68Ga-DOTA,1-Nal3-octreotide (68Ga-DOTA-NOC) or antagonists like 68Ga-NODAGA-JR11 (68Ga-OPS202) must demonstrate sufficient radiotracer uptake in suspicious NET lesions (3-5). Hence, from a long-term perspective, increased utilization of SSTR-PET can be envisaged. However, in contrast to the clinically well-established 4-point Krenning scale in terms of SSTR scintigraphy (111In-Pentetreotide, OctreoScan), which is mainly based on liver-versus-tumor uptake (6), reliable standards and criteria for SSTR-PET are still lacking (7). Of note, numerous studies have reported on pitfalls in interpreting SSTR-PET scans: 1.) the physiological distribution includes tissues that potentially exhibit SSTR, such as the pituitary gland, tonsils, thyroid, adrenal glands, liver, spleen, or the head of the pancreas (8,9), 2.) macrophages also express SSTR on the cell surface and increased inflammatory activity might lead to potential false-positive radiotracer uptake (10,11), 3.) individual tumors can have heterogeneous levels of SSTR expression related to their degree of differentiation (G1-G3) (7), and 4.) short- and long-acting SSA and chemotherapeutic agents could influence PET imaging due to receptor saturation and fluctuations of SSTR expression on the tumor cell surface (3,11,12).

Hence, in analogy to reporting and data systems that have been described for multiple different organs (13-16) as well as for molecular imaging of prostate cancer (prostate-specific membrane antigen (PSMA)-reporting and data systems, RADS) (17), we herein propose a structured reporting system on a 5-point scale for SSTR-PET imaging, titled SSTR-RADS version 1.0, which might serve as a standardized assessment for both diagnosis and treatment planning in NET. SSTR-RADS could guide the imaging specialist in interpreting SSTR-PET scans, aid communication with the referring clinician so that appropriate work-up for equivocal findings is pursued, and serve as a reliable tool for patient selection for planned PRRT.

## Patient Population

Since the herein presented data comprises a retrospective analysis of routinely acquired data, the local ethic committee waived the need for further approval. All patients gave written and informed consent to the procedures as well as all patients provided written informed consent for scientific analysis of the obtained data.

## Overview of SSTR-RADS and Description of Different Categories

Table 1 gives an overview of the SSTR-RADS reporting system in its current form, version 1.0. The reporting system is mainly based on the format of the recently published PSMA-RADS version 1.0 (17), consensus findings from the clinical experience of the two involved centers (Johns Hopkins University School of Medicine and European Neuroendocrine Tumor Society - Center of Excellence Würzburg University), as well as an extensive search in electronic databases including PubMed ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)), Science Direct ([www.sciencedirect.com](http://www.sciencedirect.com)), MEDLINE (<https://www.nlm.nih.gov/bsd/pmresources.html>) and Library of Congress (<https://www.loc.gov>). The search strategy included the following keywords: “SSTR-PET” and/or “PRRT” and/or “DOTATATE” and/or “DOTATOC” and “Standardization”, without restrictions to language or publication date. Using the SSTR-RADS reporting system, multiple different goals might be achieved: 1.) reflect the level of confidence of an imaging reader on the presence of a NET tumor lesion, 2.) provide guidance as to which lesions should be considered physiologic rather than pathologic, 3.) which test might be appropriate as a next step in the diagnostic algorithm (based on the SSTR-PET findings), and 4.) the establishment of which patients might be suitable candidates for subsequent PRRT. Table 2 summarizes the uptake level on SSTR-PET using a 3-point scale, which goes from score 1 (focal uptake, but lower than/equal to bloodpool) through score 2 (higher than bloodpool, but lower than/equal to physiological liver uptake) to score 3 (higher than physiological liver uptake). These categories will subsequently be referred to as “level 1,” “level 2,” or “level 3” uptake, respectively.

## SSTR-RADS-1

SSTR-RADS-1 signifies definitively benign lesions, as known by previous biopsy or pathognomonic anatomic imaging. These lesions are further divided into SSTR-RADS-1A and SSTR-RADS-1B (Table 1). SSTR-RADS-1A indicates definitively benign findings *without* any abnormal uptake (normal physiological biodistribution of a SSTR imaging agent, Fig. 1) (18,19). On the other hand, SSTR-RADS-1B includes those lesions, which although benign, demonstrate discernable radiotracer uptake, e.g. prostatitis, benign prostatic hyperplasia (Fig. 2)

or intense uptake in the thyroid (e.g. due to a known thyroid adenoma, Suppl. Fig. 1, level 2-3) which has been previously confirmed by biopsy or definitive diagnostic imaging (20). Of note, it has to be emphasized that SSTR-RADS scores can be dynamic based on the work-up that the patient has had done: If an intensively avid thyroid nodule is primarily classified as SSTR-RADS-3C (see below; no previous imaging or other work-up), then biopsied and found to be an adenoma, this finding would be re-scored as SSTR-RADS-1B.

SSTR-RADS-1B might help the reader to describe a region of increased uptake but without raising a concern of malignancy (17). PRRT is definitely not considered.

### **SSTR-RADS-2**

The SSTR-RADS-2 category describes lesions with uptake (level 1) in *soft-tissue sites atypical* for metastatic NET (e.g., axillary lymph nodes) or uptake in *bone lesions atypical* for NET (e.g. strongly suspected to be degenerative in nature, Fig. 3). In brief, SSTR-RADS-2 includes those lesions with low levels of SSTR expression and/ or non-specific radiotracer uptake and that are atypical sites for NET lesions. SSTR-RADS-2 lesions are almost certainly benign; PRRT is definitely not considered.

### **SSTR-RADS-3**

SSTR-RADS-3 includes those imaging findings that require further work-up (biopsy, if sampling is possible, or follow-up (f/u) imaging). Many of these lesions are suggestive of, but not definitive for, NET tumors. SSTR-RADS-3A signifies level 1-2 uptake in soft-tissue sites *typical for NET metastases*, such as in regional *lymph nodes* (Fig. 4), whereas SSTR-RADS-3B refers to level 1-2 uptake in *bone lesions not atypical* for NET (Fig. 5). In both cases, initial f/u imaging (SSTR-PET or whole-body magnetic resonance imaging) might be necessary to confirm definitive diagnosis, although the final interpretation may also depend on Ki-67/ Grading (21). Similar to PSMA-RADS, we would recommend f/u imaging after 3-6 months (3,22); any progression of the lesions would lead to an “upgrade” to either SSTR-RADS-4 or SSTR-RADS-5 (17). However, the Ki-67 index/histopathological grading has to be taken into account in the context of NET; in case of an increased proliferation index, f/u imaging after 3 months would be preferred. For SSTR-RADS-3B, the treatment algorithm should depend on the biology and number of positive lesions: Single positive lesions might rather be followed or treated with a locoregional procedure, whereas an increased number of growing, SSTR-expressing metastases might guide the treating physician to consider PRRT (3,23).

SSTR-RADS-3C suggests another non-NET malignant process and involves intense uptake (level 3) in a site highly atypical for a NET lesion, e.g. radiotracer uptake in the breast (Fig. 6) (20). In many cases, histologic diagnosis (if feasible) can help guide the selection of therapeutic options, as necessary.

SSTR-RADS-3D lesions have a high likelihood for a malignancy (e.g. dedifferentiated NET or other malignant process), but they are negative on a SSTR-PET scan. In other words, anatomic findings highly suggestive of being malignant, but demonstrating no SSTR-targeted radiotracer uptake, would be categorized as SSTR-RADS-3D. A common clinical scenario would be dedifferentiation of single NET liver lesions (in a patient with known G2 disease) demonstrating distinct heterogeneous characteristics on a subsequent 2-deoxy-2-(18F)fluoro-D-glucose (18F-FDG) PET scan (SSTR-PET negative, but 18F-FDG PET positive) (24). Different uptake patterns on 68Ga-DOTATATE and 18F-FDG scan normally indicate more aggressive disease (Fig. 7) (6,25). Hence, in terms of NET lesions suspicious for dedifferentiation, 18F-FDG PET could be performed (11,26,27). Tissue biopsy to confirm the diagnosis and to gain additional prognostic information about the non-SSTR-expressing site of disease may be of value in certain circumstances. PRRT might not be considered, but this depends on grading, overall tumor burden, kidney and bone marrow function, and overall SSTR expression on a whole-patient level. An example would be a G2 NET with the majority of lesions demonstrating SSTR expression, but a single dedifferentiated SSTR-negative, 18F-FDG positive lesion. A combined treatment of PRRT together with a locoregional procedure, such as selective internal radiotherapy or transarterial chemoembolization, could be performed (28,29). In some cases, SSTR-RADS-3D lesions are indicative of a non-NET malignant process (i.e. a coexisting second primary tumor with or without metastatic disease). If this is suspected, biopsy to establish the identity of the potential second malignancy is crucial to guide further imaging work-up and therapy.

#### **SSTR-RADS-4**

SSTR-RADS-4 describes those findings having intense uptake in sites typical for NET lesions, but without definitive findings on conventional imaging. An example would be intense uptake in a locoregional lymph node (level 3), but without confirmatory findings on anatomic imaging (i.e. small lymph node or marrow-based bone lesions, which are non-suspicious on a CT scan, Fig. 8). Given the high sensitivity and specificity of SSTR-targeted radiotracers, these lesions are likely to represent sites of NET. In brief, the main difference between SSTR-RADS-4 and SSTR-

RADS-5 (see below) is the lack of anatomic correlate for SSTR-RADS-4 lesions, adding a slight uncertainty to the diagnosis of a NET lesion. Further confirmation by biopsy is generally not necessary, unless prognosis or other precision medicine metrics can be gained by analyzing a tissue specimen. That being said, many of these lesions classified as SSTR-RADS-4 would be difficult to biopsy because of small size (e.g. an intensively avid small lymph node that would be difficult to target on CT guidance). On the assumption of a typical distribution of NET, PRRT can be considered (3,23).

### **SSTR-RADS-5**

SSTR-RADS-5 lesions show intense uptake (level 3) in sites typical for NET and with corresponding findings on conventional imaging (e.g. a liver lesion demonstrating SSTR-uptake and typical appearance on CT, Fig. 9). The likelihood of a mis-diagnosis is low; hence, similar to PSMA-RADS-5 or BI-RADS-5, biopsy failing to yield a definitive diagnosis has a high risk of being false-negative (15,17). As such, in these lesions, biopsy is unlikely to be of value in confirming the diagnosis, but again may be useful in certain circumstances as described in the SSTR-RADS-4 section. PRRT can definitely be considered (3,23).

## **DISCUSSION**

In this manuscript, we aimed to establish a standardized reporting system for the clinically most relevant SSTR imaging agents, namely SSTR-RADS version 1.0.

In analogy to PSMA-RADS, reporting on a SSTR-PET scan requires a minimum of clinical and imaging acquisition information, which should be mentioned in the clinical report (Suppl. Table 1). If *less than/equal to 5 positive lesions* can be identified, all of these sites should be classified according to the above-mentioned SSTR-RADS classification (along with an anatomical description, maximum diameter for measurable lesions, and expressed mean/maximum standardized uptake value) (3,11,17). The impression could state the SSTR-RADS scores for those lesions, but also provide an overall SSTR-RADS score. An overall SSTR-RADS of 3 without mentioning an anatomical description of increased uptake is insufficient, as further work-up cannot be undertaken since the exact site of abnormal SSTR expression is still lacking (17). If *>5 positive lesions* can be detected, a dominant, representative lesion per “system” should be chosen (i.e. the largest or “hottest” lesion, such as primary tumor or “hottest” lymph node/organ metastasis); however, contrary to 18F-FDG imaging findings in NET malignancies (30), the role

of a dominant/"hottest" lesion on a SSTR-PET has not yet been fully investigated. Nevertheless, the "highest" SSTR-RADS lesion will also designate the overall PET score and might "overrule" "lower" lesions, i.e. if one lesion is classified as SSTR-RADS-3A or -3B, but the remaining lesions are SSTR-RADS-4 or -5, the findings for SSTR-RADS-3A or -3B lesions can be waived (17). If the overall score is SSTR-RADS-4 or SSTR-RADS-5, PRRT should be considered (Fig. 10) (3,23). Nevertheless, SSTR-RADS-3C and -3D are very important categories: SSTR-RADS-3C may trigger immediate further work-up, whereas in SSTR-RADS-3D further work-up is also required, but PRRT might be more widely applicable: if only one single dedifferentiated lesion is present, a combined treatment of peptide-based radiotherapy with locoregional procedure might be an option. However, a high tumor burden with several dedifferentiated lesions rules out PRRT (e.g. several SSTR(-)/  $^{18}\text{F}$ -FDG(+) liver metastases or several liver metastases which are negative on SSTR-PET but are present on magnetic resonance imaging) (11). Tumor heterogeneity (SSTR(-),  $^{18}\text{F}$ -FDG(+) lesions) should be reported and local treatment of SSTR non-avid lesions should be considered (28,29).

Despite the aforementioned goal of increasing the reader's confidence of evaluating SSTR-PET scans, the herein proposed SSTR-RADS system could be potentially applied in numerous clinical settings. Recent reports have investigated the pre-therapeutic uptake of SSTR-PET (Standardized Uptake Values) for outcome prediction in patients scheduled for PRRT, using either  $^{177}\text{Lu}$ - or  $^{90}\text{Y}$ -DOTATATE/-TOC (31-33). However, reliable outcome predictors are still intensively sought for: the *Delphic Consensus Assessment* for GEP-NET disease management reported on the limitations of Chromogranin A alterations as well as Ki-67 for identifying potential PRRT candidates (34). Moreover, SSTR-RADS could also be expanded to other SSTR-expressing, non-GEP tumors, such as small cell lung cancer or cancer of unknown primary (35-37). Hence, in light of the increased use of SSTR-PET outside of controlled clinical trials, SSTR-RADS could serve as a more sophisticated approach for outcome prediction in PRRT.

While adapting some aspects of the PSMA-RADS system to SSTR molecular imaging, we maintained the initial proposed five-point RADS scale for prostate molecular imaging: Once the underlying framework of PSMA-RADS has been successfully understood (17), it can now be readily applied for SSTR-PET using SSTR-RADS and imaging interpreters who are familiar with one system should be able to learn the other system. Nonetheless, the differences in the underlying biologies of both tumor entities have to be considered while reporting on either

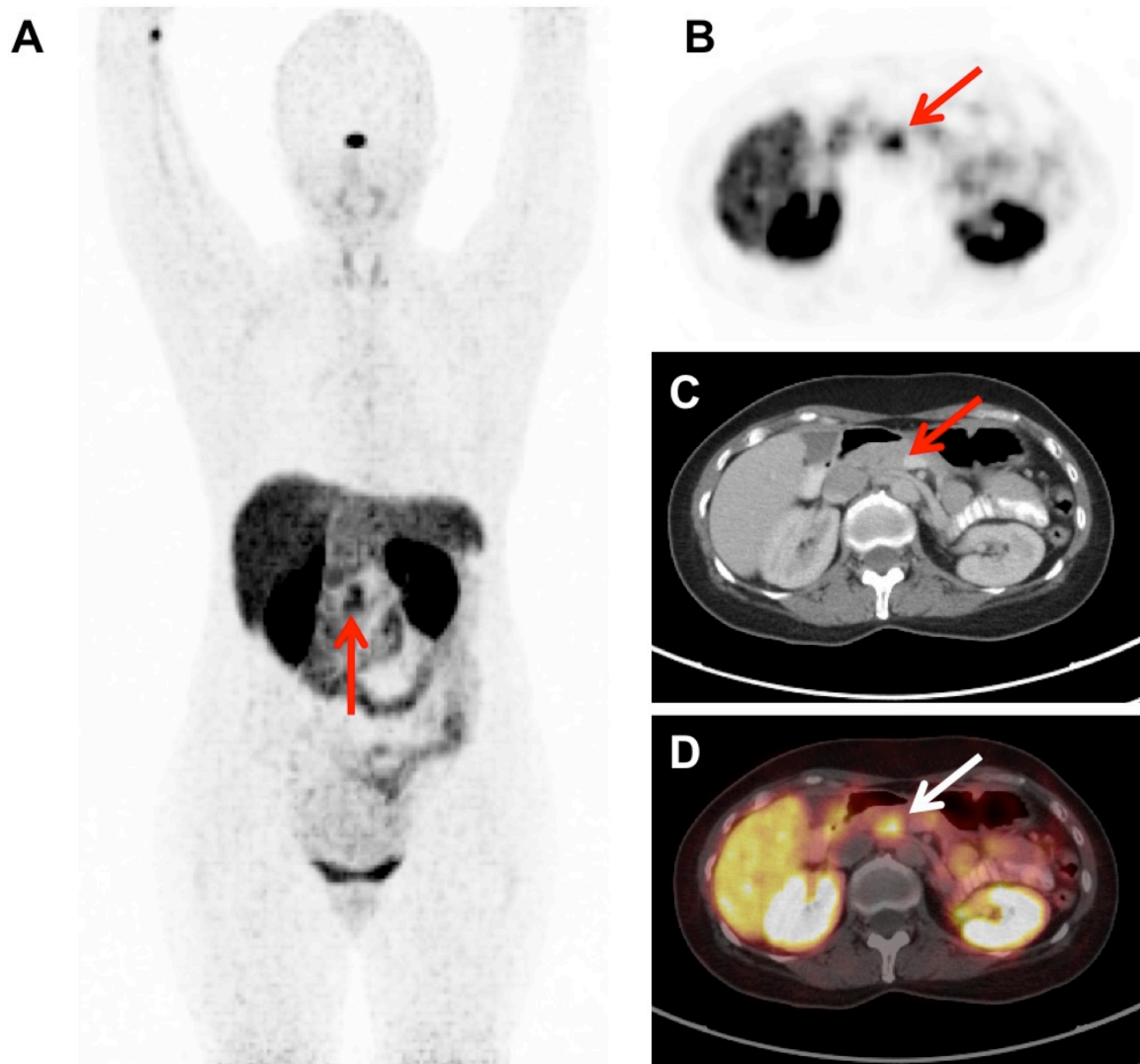


PSMA- or SSTR-PET scans. However, further analysis of inter-reader agreement is of utmost importance before SSTR-RADS can be implemented in clinical routine.

## **CONCLUSION**

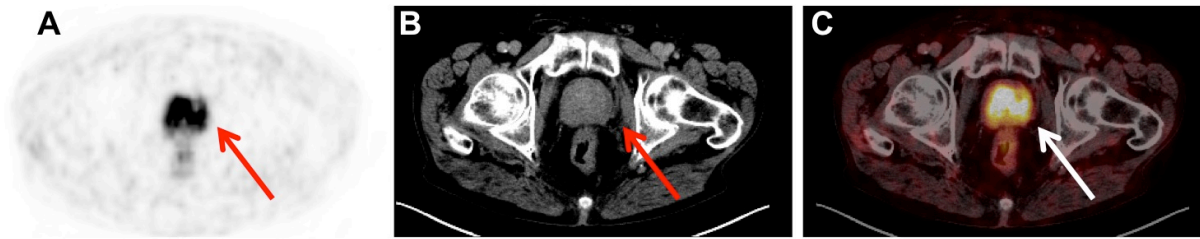
We herein propose a novel standardization system for SSTR-PET scans, which may have utility in identifying potential pitfalls in interpretation and measure the reader's confidence in the presence or SSTR-expressing tumor. This system may also guide the treating physician in selecting PRRT candidates. Further confirmatory work is needed to validate this proposed reporting system. Apart from that, we hope that the vision of SSTR-RADS as a way towards standardization will be pursued in daily clinical routine. SSTR-RADS is subject to continuous development and therefore, we highly appreciate any further input by imaging specialists to improve this scoring system.

## FIGURE and FIGURE LEGENDS



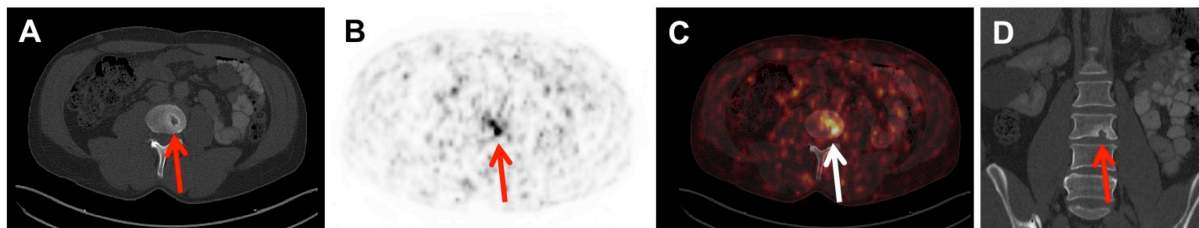
**Figure 1. SSTR-RADS-1A.**

Coronal  $^{68}\text{Ga}$ -DOTATOC PET whole-body maximum intensity projection (A) demonstrating physiological tracer distribution. No sites of abnormal uptake can be appreciated. Normal biodistribution of agent is seen, including uptake in pituitary gland, thyroid, adrenal glands, bowel, liver and spleen (18,19). Radiotracer is excreted via urinary tract. Arrow indicates physiological finding in the uncinate process, which is also demonstrated by axial  $^{68}\text{Ga}$ -DOTATOC PET (B), axial CT (C) and axial  $^{68}\text{Ga}$ -DOTATOC PET/CT (D).



**Figure 2. SSTR-RADS-1B.**

Image of a patient with increased Chromogranin A levels, referred for initial staging. Axial 68Ga-DOTATOC PET (A), axial CT (B) and axial 68Ga-DOTATOC PET/CT (C) demonstrating increased uptake in the prostate (arrow), e.g. caused by prostatitis or due to benign prostatic hyperplasia (BPH).



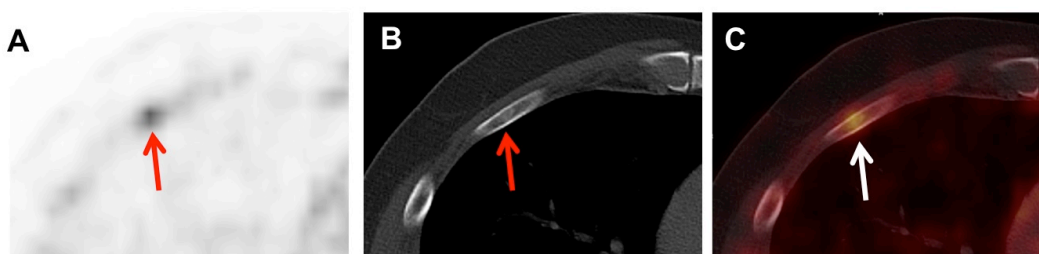
**Figure 3. SSTR-RADS-2.**

Likely benign skeletal finding with uptake in a patient suffering from NET of pancreatic origin (G1, Ki-67=2%). Axial CT (A), axial 68Ga-DOTATOC PET (B), axial 68Ga-DOTATOC PET/CT (C) and coronal CT (D) showing a lytic-appearing lesion involving the inferior endplate of a lumbar vertebral body (arrow). Strongly suspected to be degenerative (a Schmorl's node), this intravertebral disc herniation would be classified as SSTR-RADS-2.



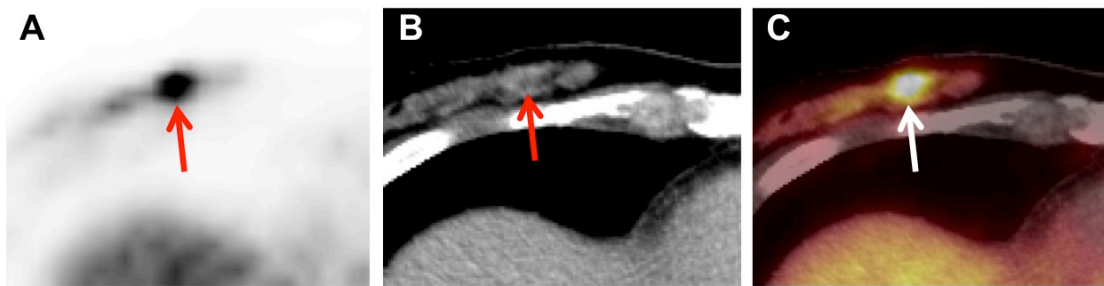
**Figure 4. SSTR-RADS-3A.**

Low-level uptake in a mesenteric lymph node in the mid-abdomen of a patient diagnosed with an ileal NET (G1, Ki-67=2%). Axial 68Ga-DOTATOC PET (A), axial CT (B), axial 68Ga-DOTATOC PET/CT (C) show a small (short-axis diameter, <0.5 cm) mesenteric lymph node (arrow). Degree of focal uptake was above bloodpool but lower than liver (not shown) and follow-up imaging (after 3 months) was recommended. Depending on local practice pattern, biopsy might be considered (although biopsy of this site is difficult).



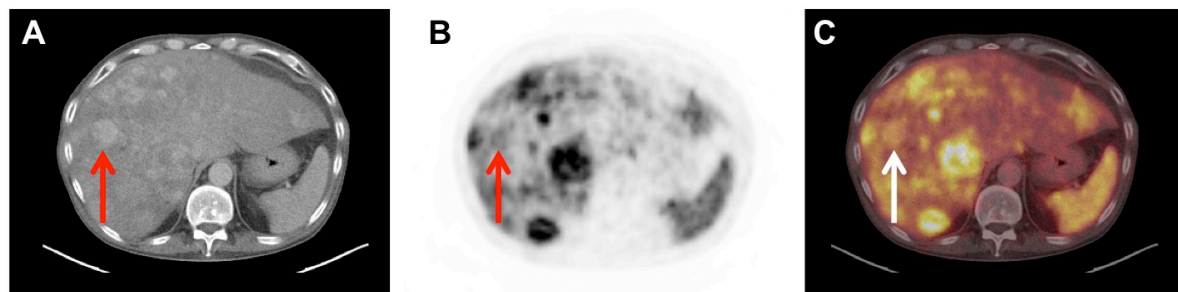
**Figure 5. SSTR-RADS-3B.**

Moderate uptake in a bone lesion in a patient with small bowel NET (G2). Axial 68Ga-DOTATOC PET (A), axial CT (B), axial 68Ga-DOTATOC PET/CT (C) show radiotracer uptake in the right 5<sup>th</sup> rib (arrow). Due to the CT findings along with moderate uptake on PET, follow-up imaging was recommended.



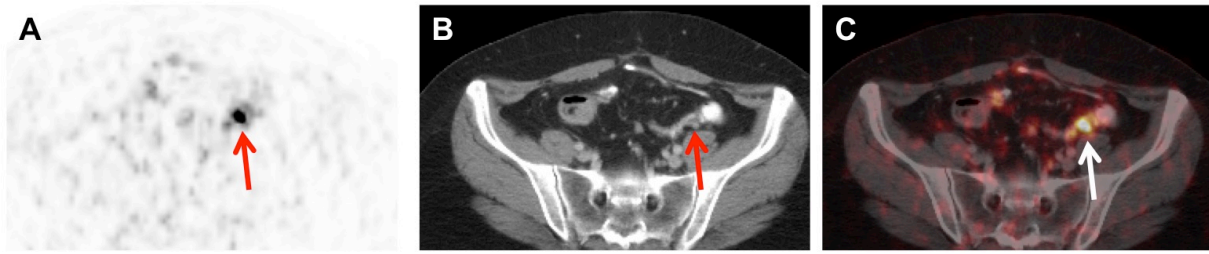
**Figure 6. SSTR-RADS-3C.**

Patient suffering from right invasive, lobular breast cancer (pT3, N1, M1 (liver)). As a site highly atypical for a NET lesion, axial 68Ga-DOTATOC PET (A), axial CT (B) and axial 68Ga-DOTATOC PET/CT (C) demonstrating intense uptake in the remaining right breast (arrow, level 3).



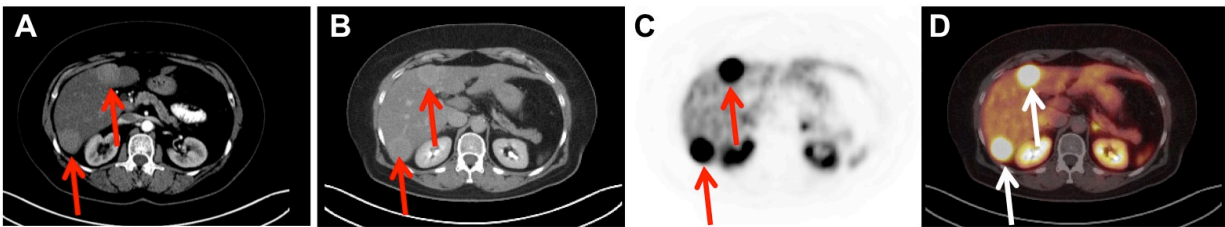
**Figure 7. SSTR-RADS-3D.**

Non-radiotracer avid liver lesion in patient with a G2 NET of pancreatic origin with a history of “cold” and “hot” somatostatin analog treatment (2 cycles of Peptide Receptor Radionuclide Therapy, cumulative activity, 15.4 GBq  $^{177}\text{Lu}$ -DOTATOC). Axial CT (A), axial 68Ga-DOTATOC PET (B), axial 68Ga-DOTATOC PET/CT (C) show a 2.8 cm hepatic metastasis with negligible uptake above liver background (arrow).  $^{18}\text{F}$ -FDG PET was recommended to assess underlying intratumoral heterogeneity/dedifferentiation, with the eventual need for PET-guided biopsy being likely.



**Figure 8. SSTR-RADS-4.**

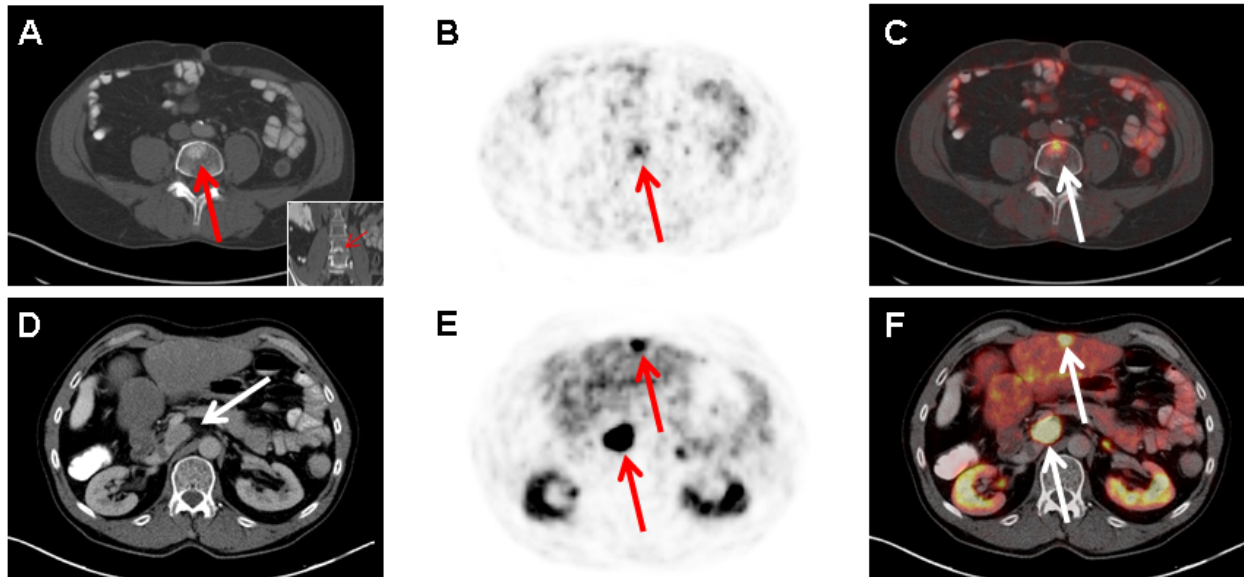
Patient suffering from an ileocecal NET (Ki-67 2%, G1), with radiotracer-avid lymph node in the lower left abdomen that is too small to consider definitively disease-involved on conventional imaging. Axial 68Ga-DOTATOC PET (A), axial CT (B) and axial 68Ga-DOTATOC PET/CT (C) images show a degree of uptake consistent with a metastatic NET lesion (arrow, level 3). However, because short-axis diameter of lymph node was 0.6 cm (i.e. <1.0 cm), this node would generally not be considered pathologically enlarged on CT.



**Figure 9. SSTR-RADS-5.**

Image of a patient with extensive, SSTR-positive liver lesions. Axial CT (A and B), axial 68Ga-DOTATOC PET (C) and axial 68Ga-DOTATOC PET/CT (D) clearly demonstrating two intrahepatic lesions with intense radiotracer uptake (level 3) and corresponding findings on CT (arrow). This scan would be categorized as SSTR-RADS-5. PRRT could definitely be considered.





**Figure 10. Defining an Overall SSTR-RADS Score.**

Example of a patient with colorectal NET (Ki-67<2%, G1 NET). Axial/Coronal (insert) CT (A), axial  $^{68}\text{Ga}$ -DOTATOC PET (B), axial  $^{68}\text{Ga}$ -DOTATOC PET/CT (C) reveal equivocal tracer uptake in a degenerative, intravertebral disc herniation (most likely a Schmorl's node, SSTR-RADS-2, arrow). However, axial  $^{68}\text{Ga}$ -DOTATOC PET (E) and axial  $^{68}\text{Ga}$ -DOTATOC PET/CT (F) clearly demonstrate intense uptake in a liver lesion in segment III which cannot be detected on (D) axial CT (SSTR-RADS-4), highly consistent with liver metastasis. Additionally, intense uptake in a pathologically enlarged lymph node close to the hilum of the liver (arrow) can be also identified on both imaging modalities. As the latter would be classified as SSTR-RADS-5, the "highest" SSTR-RADS lesion will also designate the overall PET score (i.e. SSTR-RADS-5 in this case, "overruling" the other lesions). PRRT could be considered.

	Findings	Uptake level <sup>1</sup>	PRRT? <sup>2</sup>
<b>1 (benign)</b>	Known to be benign (confirmed by previous biopsy or with pathognomonic appearance on conventional/anatomic imaging).		
<b>1A</b>	Benign lesion, characterized by biopsy or in accordance to anatomic imaging and <i>without</i> any abnormal uptake (Fig. 1).	1	Not to be considered.
<b>1B</b>	Benign lesion, characterized by biopsy or in accordance to anatomic imaging but <i>with</i> increased (focal) uptake (e.g. prostatitis, benign prostatic hyperplasia (Fig. 2), or thyroid adenoma (Suppl. Fig. 1)).	2-3	Not to be considered.
<b>2 (likely benign)</b>	<i>Soft-tissue site atypical</i> of metastatic NET (e.g., axillary lymph nodes); equivocal uptake in <i>bone lesion atypical</i> for NET (e.g. strongly suspected to be degenerative, Fig. 3).	1	Not to be considered.
<b>3</b>	<i>Further work-up (biopsy, if sampling is possible) or follow-up (f/u) imaging might be required.</i>		
<b>3A</b>	<i>Suggestive of, but not definitive for NET.</i> Equivocal uptake in soft-tissue sites <i>typical for NET metastases</i> , such as in regional lymph nodes (LN, Fig. 4). Biopsy or initial f/u imaging (SSTR-PET or whole-body magnetic resonance imaging after 3 months) might confirm diagnosis, also depending on Ki-67/ Grading (21).	1-2	Not to be considered.
<b>3B</b>	<i>Suggestive of, but not definitive for NET.</i> Uptake in <i>bone lesions not atypical</i> for NET (Fig. 5). Initial f/u imaging (SSTR-PET or whole-body magnetic resonance imaging f/u after 3 months) might confirm diagnosis, also depending on Ki-67/ Grading (21).	1-2	Single lesions: locoregional procedure; increased number of lesions: PRRT.
<b>3C</b>	<i>Suggestive of an SSTR-expressing, non-NET benign tumor or malignant process.</i> Intense uptake in a site ( <i>highly</i> ) <i>atypical</i> for NET, e.g. breast uptake (Fig. 6) (20). Tissue confirmation of tumor histology should be considered.	3	Not to be considered.
<b>3D</b>	<i>High likelihood for malignant NET lesion, but negative on a SSTR-PET scan.</i> Anatomic imaging representing lesion highly suggestive of being malignant (dedifferentiated NET or another type of malignancy), but demonstrating no SSTR uptake (e.g., single dedifferentiated liver metastasis, Fig. 7, or a non-NET malignancy) (6,25). 2-deoxy-2-18F-fluoro-D-glucose PET might be of value (11,26,27). Tissue confirmation of tumor histology should be considered.	n/a	Not to be considered <sup>3</sup> .
<b>4 (NET highly likely)</b>	<i>Positive uptake in site typical for NET lesion, but lacking definitive findings on anatomic imaging.</i> Intense uptake in common site typical for NET lesion, but <i>without</i> confirmatory findings on anatomic imaging (e.g. bone lesions or small LN, which is non-suspicious on a conventional CT scan, Fig. 8). Due to high sensitivity and specificity of SSTR-PET imaging, further confirmation by biopsy might be not necessary.	3	To be considered <sup>4</sup> .
<b>5 (NET almost certainly present)</b>	<i>Intense uptake in site typical for NET with corresponding findings on conventional imaging.</i> An example would be a SSTR-expressing liver lesion <i>with</i> corresponding findings on a CT scan (Fig. 9).	3	Definitely to be considered.



**Table 1. Overview of SSTR-RADS 1-5.** PRRT = Peptide Receptor Radionuclide Therapy, n/a = not available, NE Neuroendocrine Tumor, f/u = follow-up, SSTR-PET = somatostatin receptor positron emission tomography, C computed tomography.

<sup>1</sup> Uptake Levels, a three-point qualitative assessment for defining the level of uptake (Table 2).

<sup>2</sup> Peptide Receptor Radionuclide Therapy (PRRT) using <sup>177</sup>Lu-/<sup>90</sup>Y-radiolabelled somatostatin analogues. Inclusion and exclusion criteria according to The Joint IAEA, EANM, and SNMMI Practical Guidance as well as The ENETS Consensus Guidelines still apply (3,23).

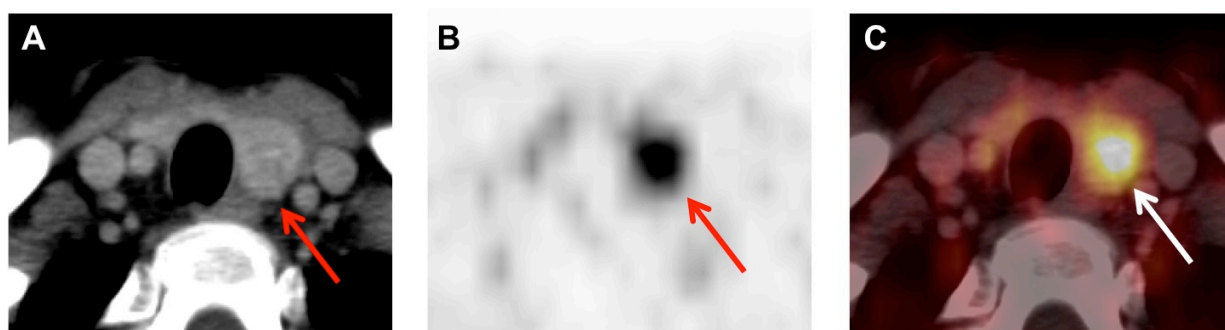
<sup>3</sup> Depends on grading, overall tumor burden, kidney and bone marrow function and overall SSTR expression (e.g. G2 NET patient with entirely all lesions demonstrating SSTR expression, but a single dedifferentiated lesion. A combined treatment of PRRT together with a locoregional procedure could be considered) (28,29).

<sup>4</sup> On the assumption that a SSTR-PET avid lesion in a typical distribution has a very high probability of representing NET, PRRT might be considered.

<b>Uptake Scores</b>	<b>Relative Uptake</b>
<b>Level 1</b>	$\leq$ bloodpool
<b>Level 2</b>	uptake > bloodpool but $\leq$ physiological liver uptake
<b>Level 3</b>	uptake > physiological liver uptake

**Table 2.** A three-point qualitative assessment scoring for defining the uptake level in a SSTR-avid lesion on a SSTR-PET scan.

## SUPPLEMENTARY FIGURE



**Supplementary Figure 1. SSTR-RADS-1B.**

Axial 68Ga-DOTATOC PET (A), axial CT (B) and axial 68Ga-DOTATOC PET/CT (C) showing intense focus of uptake in the thyroid (arrow). Patient had a history of thyroid adenoma.

## SUPPLEMENTARY TABLE

<b>Patient's History</b>	<ul style="list-style-type: none"> <li>✓ Primary tumor origin</li> <li>✓ Date of tumor biopsy and Ki-67/ Grading</li> <li>✓ Date of primary diagnosis</li> <li>✓ Presence of any symptoms</li> <li>✓ Previous therapies (incl. SSA and PRRT)</li> <li>✓ Previous conventional and/or functional imaging including SSTR- and 18F-FDG PET scans</li> <li>✓ History and treatment of other malignancies</li> <li>✓ Laboratory test results (NSE, CgA), if available</li> </ul>
<b>Imaging Data</b>	<ul style="list-style-type: none"> <li>✓ Injected amount/ activity</li> <li>✓ Uptake time</li> <li>✓ Field of view</li> </ul>

**Supplementary Table 1.** Minimum required data in a clinical report. SSA = somatostatin analogues, PRRT = Peptide Receptor Radionuclide Therapy, 18F-FDG = 2-deoxy-2-(18F)fluoro-D-glucose, NSE = neuron-specific enolase, CgA = Chromogranin A.

## DISCLOSURE

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