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^{111}In-Pentetreotide Scintigraphy Versus ^{68}Ga-DOTATATE PET: Impact on Krenning Scores and Effect of Tumor Burden

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Eligibility for somatostatin receptor (SSTR) radionuclide therapy uses the qualitative Krenning score based on ^{111}In-pentetreotide planar scintigraphy as was performed in the NETTER-1 trial. The purpose of this study was to determine the effect of using SSTR PET–based Krenning score in comparison to ^{111}In-pentetreotide. **Methods:** This was a post hoc head-to-head comparison of ^{68}Ga-DOTATATE–based and ^{111}In-pentetreotide–based Krenning scores in 150 patients included in a prospective phase 2 study (NCT01967537). Patients were imaged using ^{68}Ga-DOTATATE PET/CT, ^{111}In-pentetreotide planar scintigraphy, and SPECT/CT within 1 wk. SSTR ligand uptake was graded using the Krenning score independently by 3 readers. **Results:** The detection rate of SSTR-expressing disease (Krenning scores 2–4) was 23%, 38%, and 72% with planar imaging, SPECT, and SSTR PET, respectively. The Krenning score was higher with SSTR PET (2.71 ± 1.74) than with planar imaging (0.75 ± 1.37; $P < 0.001$) or SPECT (1.23 ± 1.57; $P < 0.001$). In patients with a Krenning score of at least 3 on SSTR PET, the detection rate of planar imaging and SPECT was lower for lesions smaller than 2 cm than lesions 2 cm or larger: 15% and 24% versus 78% and 89%, respectively ($P < 0.001$). For lesions larger than 5 cm, Krenning scores between SSTR PET and ^{111}In-pentetreotide were nearly equivalent. Lesion size did not have an impact on SSTR PET Krenning scores. Interreader agreement was higher for SSTR PET than for planar imaging or SPECT (0.79 vs. 0.67 and 0.50, respectively). **Conclusion:** SSTR PET results in higher Krenning scores than ^{111}In-pentetreotide, particularly when lesions measured 2 cm or less. Small lesion size resulted in low Krenning scores using ^{111}In-pentetreotide, but lesion size did not affect SSTR PET–based Krenning scores. The results of the NETTER-1 trial cannot be directly applied to patients with small lesions. Further study of peptide receptor radionuclide therapy in patients with small lesions negative on ^{111}In-pentetreotide imaging and positive on SSTR PET is warranted.

Key Words: ^{111}In-pentetreotide; ^{68}Ga-DOTATATE; PET/CT; Krenning score; neuroendocrine tumor

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Somatostatin receptor (SSTR) expression is a prerequisite for successful treatment using peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE in patients with progressive neuroendocrine tumors (*1*). To determine whether a patient is a candidate for therapy, one can use either ^{111}In-pentetreotide scintigraphy or PET agents such as ^{68}Ga-DOTATATE or ^{68}Ga-DOTATOC to assess the SSTR expression. The most commonly used method for characterizing the degree of SSTR expression on imaging is the Krenning score based on ^{111}In-pentetreotide uptake (*2*). SSTR PET has been shown to have a better detection sensitivity than ^{111}In-pentetreotide, and it is unclear how this increased sensitivity affects the Krenning score (*3–5*).

Although guidelines have suggested using SSTR PET to select patients for PRRT, there is limited literature on how to use such imaging studies for patient selection (*6,7*). For example, in the NETTER-1 trial, the inclusion criteria relied on interpretation of the ^{111}In-pentetreotide scintigraphy results using the Krenning score (eligible if the highest lesion uptake equaled or exceeded liver uptake) (*8*). European centers have used both ^{111}In-pentetreotide scintigraphy and SSTR PET for patient selection (*9,10*). The common approach for characterizing uptake on SSTR PET is to use a modified Krenning score in which the same qualitative approach (comparison to liver uptake) is applied to SSTR PET (*6,11*). It is unclear if the Krenning score is equivalent between modalities.

To understand possible limitations in the applicability of data from the NETTER-1 trial when patients are selected for ^{177}Lu-DOTATATE PRRT using Krenning scores derived from each imaging modality, we performed a head-to-head comparison of ^{68}Ga-DOTATATE–based and ^{111}In-pentetreotide–based Krenning score in the same cohort of patients included in a prospective phase 2 study (NCT01967537).

MATERIALS AND METHODS

This post hoc retrospective study was approved by the National Cancer Institute Institutional Review Board (approval 13C-0193J). All patients provided written informed consent to participate in the parent prospective phase 2 study (NCT01967537). From October 2013 to July 2015, 227 patients with suspicion of neuroendocrine tumor on imaging (CT/MRI/^{18}F-FDG PET) or with biochemical evidence of neuroendocrine tumor or with mutation in MEN1 or VHL were enrolled in the study and underwent ^{68}Ga-DOTATATE PET/CT. A study analysis of 131 patients was previously published and did not include

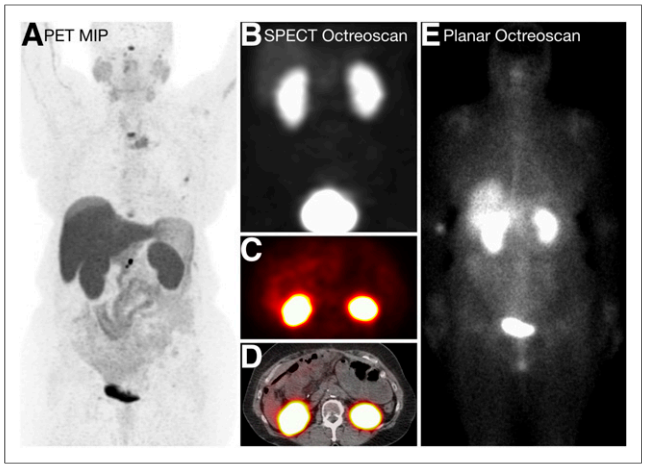

FIGURE 1. Example of SSTR PET demonstrating higher Krenning score than ^{111}In-pentetreotide in low-volume disease. This patient was graded as having Krenning score of 4 on SSTR PET (A) but 0 on SPECT (B–D) and planar imaging (E). Extent of disease was graded as 1 by 3 readers (e.g., 1–3 lesions smaller than 2 cm). MIP = maximum-intensity projection.

evaluation of the Krenning score (*5*). We included in this head-to-head comparison the 150 patients who underwent both ^{68}Ga-DOTATATE PET/CT and ^{111}In-pentetreotide imaging (planar imaging and SPECT) within a span of less than 1 wk (mean time interval, 1.9 ± 2.5 d; range, 0–7).

Image Acquisition and Analysis

The imaging acquisition parameters can be found in the original publication (*5*). Planar imaging was acquired using 2.5 million counts per head at 1.3 mm per second after 5 min after the first bed position. The SPECT acquisition was performed with 120 frames and 35 s per frame. DICOM images were anonymized before transfer. All anonymized images were analyzed by 3 nuclear medicine physicians experienced in imaging of patients with neuroendocrine tumors and masked to any clinical data. Readers were not masked to the ^{68}Ga-DOTATATE PET/CT findings while interpreting the ^{111}In-pentetreotide studies, and vice versa.

All 3 imaging studies (planar imaging, SPECT, and PET) were graded using the Krenning score based on the lesion with the highest SSTR ligand uptake (H-lesion): 0, no uptake; 1, very low uptake; 2, uptake less than or equal to that of the liver; 3, uptake greater than the liver; and 4, uptake greater than that of the spleen (*2*). The Krenning score was originally developed for scintigraphy using ^{111}In-pentetreotide SPECT and was applied identically to ^{68}Ga-DOTATATE PET. Readers were not masked to the ^{68}Ga-DOTATATE PET results while interpreting the ^{111}In-pentetreotide imaging studies. The studies were reviewed after grading, and a consensus grade was created for each study.

Additionally, the volume and extent of tumor burden were graded with a 5-grade tumor burden score: 1, 1–3 lesions measuring less than 2 cm; 2, greater than 3 lesions measuring less than 2 cm; 3, multiple lesions measuring between 2 and 5 cm; 4, less than 5 lesions but with at least 1 measuring greater than 5 cm; and 5, greater than 5 lesions with at least 1 measuring greater than 5 cm. Finally, 1 reader quantitatively measured the size and the SUV_{max} of the lesion with the greatest ^{68}Ga-DOTATATE uptake (H-lesion) and the SUV_{max} of the spleen, the liver, and the kidneys with a 3-dimensional volume of interest. Tumor-to-liver, tumor-to-spleen, and tumor-to-kidney ratios were calculated.

Statistical Analysis

Tabular results are provided by reader, and the Krenning score among the 3 readers was calculated and compared with tumor burden score, lesion size, and SUV_{max} on ^{68}Ga-DOTATATE PET. The Wilcoxon rank signed rank test was used to compare Krenning scores using the 3 imaging modalities. A linear mixed-effects model (lmer function in R Package lme4) accounting for repeated measures was used to assess the effect of tumor burden score, size, and SUV_{max} on the Krenning score for each of the 3 imaging modalities. A Fisher exact test was used to compare the detection rate of large and small lesions using planar imaging and SPECT. Interreader agreement was measured using the Fleiss κ. R, version 3.4.2, was used for analysis.

RESULTS

Krenning Score Interpretation

Based on the Krenning score, the detection rate of SSTR-positive disease (Krenning scores 2–4) was 23%, 38%, and 72% with ^{111}In-pentetreotide planar imaging, SPECT, and ^{68}Ga-DOTATATE PET, respectively. There was no patient with a negative ^{68}Ga-DOTATATE PET scan and a positive ^{111}In-pentetreotide scan. Of the patients with positive ^{68}Ga-DOTATATE PET scans, ^{111}In-pentetreotide planar imaging and SPECT were positive in 32% and 53% of patients, respectively. Results broken down by individual readers are provided in Tables 1 and 2. The Krenning score was significantly higher with ^{68}Ga-DOTATATE PET (2.71 ± 1.74) than with ^{111}In-pentetreotide planar scintigraphy (0.75 ± 1.37) or SPECT (1.23 ± 1.57) ($P < 0.001$ for both). Interreader agreement was moderate to substantial, with a κ-value of 0.67, 0.50, 0.78, and 0.69 for planar imaging, SPECT, PET, and tumor burden score, respectively. Supplemental Table 1 depicts the anatomic localization of the ^{68}Ga-DOTATATE PET–positive findings and of the H-lesions (supplemental materials are available at http://jnm.snmjournals.org). Pancreas, abdominal lymph node, and liver were the most common sites of SSTR-expressing disease and of the H-lesion.

SSTR PET Semiquantitative Analyses

The median SUV_{max} of the H-lesion was 57.0 (mean, 76.6; range, 14.7–321.0) with a median size of 1 cm (mean, 1.6 cm;

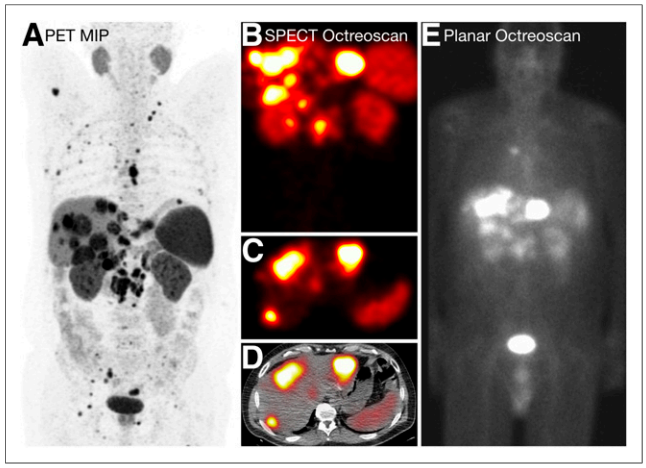

FIGURE 2. Example of agreement. All 3 imaging studies were read by all readers as having Krenning score of 5. SSTR PET demonstrates more lesions (A), particularly in bones, than SPECT (B–D) and planar imaging (E). Extent of disease was graded as 5 by all readers (i.e., at least 1 lesion larger than 5 cm and more than 5 lesions). MIP = maximum-intensity projection.

TABLE 1
Krenning Scores Broken Down by Reader and Imaging Modality Across All Patients Imaged

	Reader 1			Reader 2			Reader 3		
Krenning score	Planar	SPECT	PET	Planar	SPECT	PET	Planar	SPECT	PET
0–1 (*n*)	117 (78%)	93 (62%)	42 (28%)	106 (71%)	83 (55%)	43 (29%)	119 (79%)	102 (68%)	45 (30%)
2 (*n*)	5	16	0	13	17	3	4	5	3
3 (*n*)	17	23	25	18	31	17	14	24	14
4 (*n*)	11	18	83	13	19	87	13	19	88
2–4 (*n*)	33 (22%)	57 (38%)	108 (72%)	44 (29%)	67 (45%)	107 (71%)	31 (21%)	48 (32%)	105 (70%)

range, 0.4–12 cm). Supplemental Table 2 reports the tumor-to-organ ratios. In patients with a Krenning score of 3, the tumor-to-kidney and tumor-to-spleen ratios were neutral (1.0) whereas the mean tumor-to-liver ratio was 2.3. In patients with a Krenning score of 4, the mean tumor-to-kidney, tumor-to-spleen, and tumor-to-liver ratios were 3.3, 3.4, and 7.7, respectively.

Effect of Volume, Tumor Burden, and Uptake

Breakdown of Krenning score by tumor burden score for each individual reader is provided in Table 3. In patients with a Krenning score of at least 3 on SSTR PET, the detection rate of ^{111}In-pentetreotide planar imaging and SPECT was significantly lower with lesions smaller than 2 cm than with lesions 2 cm or larger: 15% and 24% versus 78% and 89%, respectively ($P < 0.001$) (Figs. 1 and 2). ^{111}In-pentetreotide–based Krenning score was associated with tumor burden score and SUV_{max} for both planar imaging and SPECT (planar imaging, $P = 0.002$ for tumor burden score and $P = 0.01$ for SUV_{max}; SPECT, $P < 0.001$ for tumor burden score and $P = 0.007$ for SUV_{max}). For ^{68}Ga-DOTATATE PET, the Krenning score was not significantly associated with tumor burden score but was associated with SUV_{max} ($P = 0.30$ for tumor burden score and $P = 0.002$ for SUV_{max}).

DISCUSSION

We have demonstrated in neuroendocrine tumor patients that using SSTR PET substantially increases the Krenning score compared with ^{111}In-pentetreotide planar imaging and SPECT. The difference in Krenning score was most marked in patients with lesions that measured less than 2 cm, and the Krenning score based on SSTR PET was independent of tumor size.

The results of trials such as the NETTER-1 trial should not be directly applied to patients with smaller lesions, as small lesions (i.e., less than 2 cm) are typically negative on ^{111}In-pentetreotide scintigraphy. Ninety percent of patients in the NETTER-1 trial had Krenning 3–4 disease on ^{111}In-pentetreotide scintigraphy (*8*). In patients with small lesions, most patients with Krenning 3/4 disease on ^{68}Ga-DOTATATE PET would not have qualified for the NETTER-1 trial, and caution must be taken to apply criteria used in the NETTER-1 trial to ^{68}Ga-DOTATATE PET results. Currently, it is unclear whether patients with low-volume disease benefit as greatly from PRRT as do patients with larger-volume disease, but given the rate of myelodysplastic syndrome and leukemia, the risk–benefit in these patients is likely different from those with larger-volume disease (*12*). It may be that patients with numerous small lesions will benefit from ^{177}Lu-DOTATATE therapy, and there may be an advantage to using ^{68}Ga-DOTATATE PET, which can detect these smaller lesions.

Interreader agreement was higher in SSTR PET than in either ^{111}In-pentetreotide planar imaging or SPECT. SSTR PET is known to have high interreader agreement (*13*), which presumably results from the increased tumor-to-background ratio seen compared with ^{111}In-pentetreotide scintigraphy. It might be suggested that ^{111}In-pentetreotide scintigraphy should be used to select patients for PRRT given that existing data use this imaging study, but we believe that SSTR PET should be preferred because of the ease and reproducibility of interpretation. The results from this work, by clarifying the differences in the Krenning score when applied to these different imaging studies, should help guide clinicians in how to apply the findings on SSTR PET to patient selection.

It is not surprising the SUV_{max} strongly correlated with Krenning score for all 3 imaging modalities, as Krenning score is a qualitative assessment of uptake, furthermore highlighted by the tumor-to-organ ratios. What is somewhat unexpected is that size was not correlated with Krenning score for SSTR PET but was strongly

TABLE 2
Krenning Scores Broken Down by Reader and Modality in Patients with Evidence of SSTR-Positive Disease on ^{68}Ga-DOTATATE PET

	Reader 1			Reader 2			Reader 3		
Krenning score	Planar	SPECT	PET	Planar	SPECT	PET	Planar	SPECT	PET
0–1	69%	47%	0%	59%	37%	0%	70%	54%	0%
2	5%	15%	0%	12%	16%	3%	4%	5%	3%
3	16%	21%	23%	17%	29%	16%	13%	23%	13%
4	10%	17%	77%	12%	18%	81%	12%	18%	84%
2–4	31%	53%	100%	41%	63%	100%	29%	46%	100%

TABLE 3
Number of Planar Imaging– and SPECT-Positive ^{111}In-Pentetreotide Scans Broken Down by Tumor Burden Score in Patients with SSTR-Positive Disease on ^{68}Ga-DOTATATE PET

Tumor burden score < 3						Tumor burden score ≥ 3					
Planar			SPECT			Planar			SPECT		
R1	R2	R3	R1	R2	R3	R1	R2	R3	R1	R2	R3
14	10	15	24	21	31	14	21	12	17	29	12
17%	13%	17%	29%	28%	35%	58%	72%	86%	71%	100%	86%

R1 = reader 1; R2 = reader 2; R3 = Reader 3.

correlated for ^{111}In-pentetreotide scintigraphy. This result is likely due to the higher detection sensitivity and uptake with SSTR PET than with planar imaging and SPECT: mean size of the H-lesion was 1 cm (among 108 measures), and some H-lesions of less than 0.8 cm even had an SUV_{max} greater than 300. Again, this finding highlights the point that smaller lesions on SSTR PET will have a higher Krenning score than on ^{111}In-pentetreotide scintigraphy.

The main limitation of this study is that the patients enrolled do not represent patients being screened for potential PRRT. Twenty-nine percent of patients had no evidence of disease, and there was a bias toward patients with disease of lower volume than would be seen in potential PRRT patients. Nonetheless, this cohort is instructive in that it highlights that patients with small lesions can have markedly higher Krenning scores with SSTR PET than with ^{111}In-pentetreotide scintigraphy. The strength of this study is that all patients had paired SSTR PET and ^{111}In-pentetreotide scintigraphy within a maximum of 8 d of each other. An additional limitation is related to the ^{111}In-pentetreotide imaging protocol. For example, the acquisition time per step in the SPECT protocol was 35 s rather than 45 s as recommended in the European Association of Nuclear Medicine guidelines (*14*). The planar acquisition was performed at 1.3 mm per second, compared with 3 cm per minute in the European Association of Nuclear Medicine guidelines. These differences may have affected the sensitivity for smaller lesions on ^{111}In-pentetreotide.

CONCLUSION

In this post hoc comparison of SSTR PET–based and ^{111}In-pentetreotide–based Krenning score in 150 patients, SSTR PET resulted in higher Krenning scores than did ^{111}In-pentetreotide, in particular when lesions measured 2 cm or less. When lesions measured greater than 5 cm, Krenning scores between SSTR PET and ^{111}In-pentetreotide scintigraphy were nearly equivalent. Given the uncertainty in the risk–benefit of PRRT in subjects with low ^{111}In-pentetreotide–based Krenning scores, when using SSTR PET to select patients for PRRT it would be prudent to consider the volume and extent of tumor burden in addition to Krenning score.

DISCLOSURE

Thomas Hope was supported by the Prostate Cancer Foundation (2017 Jonathan Kovler Young Investigator Award) and the National Institutes of Health (grant R01CA212148); receives grant support from GE Healthcare, Philips, and Advanced Accelerator Applications; and participated on an advisory board for Ipsen. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: How does the Krenning score used in the NETTER-1 trial translate to somatostatin receptor (SSTR) PET and what is the potential impact of this in guiding the decision for peptide receptor radionuclide therapy (PRRT)?

PERTINENT FINDINGS: A retrospective analysis was conducted on 150 patients imaged in NIH with ^{68}Ga-DOTATATE PET/CT and ^{111}In-pentetreotide PET/CT within 1 wk. The Krenning score was significantly higher with SSTR PET than with planar or SPECT ^{111}In-pentetreotide. This discrepancy was most pronounced for lesions <2 cm; lesion size did not affect SSTR PET score.

IMPLICATIONS FOR PATIENT CARE: Most patients with lesions <2 cm would not have qualified for PRRT based on ^{111}In-pentetreotide but appear as candidates based on SSTR PET. This implies the possibility that patients with numerous small lesions could benefit from PRRT. Integration of size, volume, and extent of tumor burden with the Krenning score might prove of benefit when selecting patients for PRRT based on SSTR PET.

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