Somatostatin Receptor Expression in Lung Neuroendocrine Tumors: An Analysis of DOTATATE PET Scans

Taymeyah Al-Toubah¹, Jaime Montilla-Soler², Ghassan El-Haddad², Mintallah Haider¹, and Jonathan Strosberg¹

¹Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida; and ²Department of Diagnostic Imaging, Nuclear Medicine, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida

Somatostatin receptor (SSTR) expression in metastatic lung neuroendocrine tumors (NETs) has not been well characterized using PET imaging. Understanding the degree and uniformity of SSTR expression is important to establish the role of SSTR-targeted treatments in lung NETs. Methods: A retrospective institutional review of patients with metastatic lung NETs who underwent DOTATATE PET imaging from March 2017 to February 2023 was performed. Results: In total, 48 patients with metastatic lung NETs who underwent ⁶⁸Ga- or ⁶⁴Cu-DOTATATE PET imaging were identified. Four had completely negative SSTR expression, and 10 had very weak expression (less than in a normal liver). Among the remaining 34 patients, 21 had uniformly positive DOTATATE PET scans, and 13 had heterogeneous expression. Only 44% had uniformly positive receptor expression, identifying them as candidates for peptide receptor radionuclide therapy. Conclusion: Most metastatic lung NETs lack uniform SSTR expression and are thus suboptimal candidates for SSTR-targeted therapy. SSTR imaging in lung NETs should be evaluated carefully for uniformity of expression.

Key Words: neuroendocrine tumors; lung NETs; ⁶⁸Ga-DOTATATE; ⁶⁴Cu-DOTATATE; somatostatin expression

J Nucl Med 2023; 64:1895–1898 DOI: 10.2967/jnumed.123.266185

ell-differentiated neuroendocrine tumors (NETs) are characterized by the expression of somatostatin receptors (SSTRs) on the cell surface. SSTRs are G-protein–coupled receptors with 7 transmembrane domains that regulate hormone secretion and cellular proliferation. Among the 5 subtypes of SSTRs, receptor subtype 2 is most frequently expressed, followed by subtype 5 (1). SSTR expression is highly relevant for treating advanced NETs, because somatostatin analogs (SSAs) and radiolabeled SSAs induce cytostatic and cytotoxic effects by binding to SSTRs (2,3). Radiolabeled SSA therapy is a form of peptide receptor radionuclide therapy (PRRT) in which a peptide coupled to a radioisotope delivers radiation to a peptide receptor expressing malignancy.

Lung NETs, also known as bronchial carcinoid tumors, are a relatively common subtype of well-differentiated NETs, representing approximately one quarter of the total population of gastroenteropancreatic and thoracic NETs (4). Pathologically, lung NETs are subdivided into typical NETs (characterized by a mitotic rate of <2 per 10 high-powered fields and the absence of necrosis) and atypical NETs (indicated by a mitotic rate of 2–10 per 10 highpowered fields or evidence of tumor necrosis on pathology) (5). The typical and atypical categories roughly correspond to grade 1 and 2 gastroenteropancreatic NETs. Well-differentiated lung NETs with a mitotic rate greater than 10 have not been appropriately categorized in current classifications but can also be considered atypical NETs with relatively high proliferation (6,7).

The SSTR expression of lung NETs has not been well described in the literature (8–10). Evidence that SSTR expression may be relatively low in this patient population includes the poor enrollment of patients with lung NETs in studies evaluating SSA and radiolabeled SSA. For example, the phase III SPINET trial comparing lanreotide versus placebo in advanced lung NETs was closed early for low accrual (11). Moreover, in large cohort studies of the radiolabeled SSA ¹⁷⁷Lu-DOTATATE in gastroenteropancreatic and thoracic NETs, only 5%–13% of the patients treated carried the diagnosis of lung NETs (12,13).

SSTR expression can be assessed in several ways. Immunohistochemical analysis of a biopsy specimen may accurately indicate expression at a particular location but cannot account for intraand intertumoral heterogeneity. Therefore, a preferred method of assessment is SSTR imaging. In the past, ¹¹¹In-pentetreotide scintigraphy (Octreoscar; Mallinckrodt Pharmaceuticals) was a standard method of whole-body evaluation of SSTR expression (2). The Krenning scale, designed to compare tumoral expression with uptake in normal organs such as the liver and spleen, was developed to standardize ¹¹¹In-pentetreotide reports (*14*). A Krenning score of 2, equivalent to normal liver uptake, often indicated a positive ¹¹¹In-pentetreotide scan. For radiolabeled SSA therapy, a Krenning score of 2 or higher in all measurable tumors was required for treatment eligibility.

Over the past decade, SSTR imaging using PET scans has largely replaced ¹¹¹In-pentetreotide scintigraphy. ⁶⁸Ga-DOTATATE, ⁶⁸Ga-DOTATOC, and ⁶⁴Cu-DOTATATE PET scans, typically fused with CT, represent the most common SSTR imaging tests and offer substantially improved sensitivity and resolution compared with scintigraphic scans (15). SUV scores can be precisely measured for individual tumors, although the comparison with normal organ uptake is still required to contextualize the results. According to some guidelines, SSTR expression greater than normal liver expression on SSTR PET imaging is a minimum requirement for PRRT (16). Studies suggest SSTR expression roughly twice that of the normal liver predicts response (17). It is important to emphasize that SSTR expression generally should be observed in all measurable lesions. SSTR-negative tumors tend to be more aggressive and can proliferate rapidly during PRRT, thus negating any beneficial effect in SSTR-positive tumors.

Received Jun. 13, 2023; revision accepted Sep. 16, 2023.

For correspondence or reprints, contact Jonathan Strosberg (jonathan. strosberg@moffitt.org).

Published online Oct. 5, 2023.

COPYRIGHT © 2023 by the Society of Nuclear Medicine and Molecular Imaging.

Studies evaluating SSTR expression in lung NETs are limited. A retrospective study evaluated 25 patients with localized lung tumors, of which only 11 were typical or atypical lung NETs (18). Of the 25 Octreoscans in this patient population, only 20 were described as positive. A more recent retrospective series evaluating the correlation between SSTR PET/CT imaging and immunohistochemical staining for SSTRs (subtypes 2 and 5) in 32 patients with lung NETs demonstrated a correlation between SSTR subtype 2 immunohistochemical staining and SSTR PET/CT imaging in 75% of the cases (9). In total, SSTR PET (68Ga-DOTATOC and ⁶⁸Ga-DOTANOC) was reported to be positive in 28 of 32 patients (87.5%), although the Krenning score was relatively low (grade 1) in 12 patients (37.5%). There were no cases of immunohistochemically positive but SSTR PET/CT-negative tumors. Tumor heterogeneity in SSTR expression was not described. A similar study evaluated SSTR types 2a and 3 using immunohistochemical analysis in 218 well- and poorly differentiated lung neuroendocrine neoplasms (24 typical, 73 atypical) and correlated results with SSTR imaging where available (19). SSTR type 2a was overexpressed in typical NETs compared with atypical NETs. SSTR expression by immunohistochemical analysis correlated with the corresponding Octreoscan in 20 of the 28 cases where it was available. Another study evaluating SSTRs in lung NETs using immunohistochemical staining noted that tumors expressing SSTR subtypes 1 and 2 had improved outcomes compared with those expressing SSTR subtypes 3 and 4 (20).

A more thorough understanding of SSTR expression in lung NETs is essential to contextualize the role of SSAs and radiolabeled SSAs in this patient population to accurately predict the potential for clinical trial enrollment. In addition, since systemic treatments are generally administered for advanced disease, a focus on metastatic tumors is critical for evaluating intertumoral heterogeneity in SSTR expression.

MATERIALS AND METHODS

All patients who underwent ⁶⁸Ga- or ⁶⁴Cu-DOTATATE PET at Moffitt Cancer Center between March 2017 and February 2023 were analyzed to identify patients with primary lung NETs. The standard imaging protocol included a 68Ga-DOTATATE injection of 1,998 kBq/kg (≤199,800 kBq) or a ⁶⁴Cu-DOTATATE injection of 148,000 kBq 1h before PET/CT imaging. The imaging protocol consisted of low-dose CT imaging from the skull apex to the mid thigh and PET imaging using a Discovery MI time-of-flight scanner (GE Healthcare). The data were then processed using GE Healthcare Advanced Workspace software to include multiplanar reconstructions of the CT, PET, and overlayed (fused) data for interpretation. Incubation time was 60 min, and acquisition time per bed position was 3 min for ⁶⁸Ga and 4-5 min for ⁶⁴Cu depending on body mass index. We used a matrix size of 192×192 for 68 Ga and 256×256 for 64 Cu. All examinations were compared with the most recent anatomic imaging (CT, MRI) available. ⁶⁸Ga-DOTATATE PET scans were done until the point of ⁶⁴Cu-DOTATATE PET approval in the United States, when most scans performed were with ⁶⁴Cu-DOTATATE. The Krenning score was prospectively used as part of the examination interpretation. Clinicopathologic data collected included demographics, tumor stage, grade and differentiation, SSTR expression, presence of functional hormonal syndrome, sites of disease, prior therapies, and vital status.

Radiographic scans were reviewed by a nuclear medicine radiologist to assess SSTR expression. Institutional Review Board approval was obtained for this analysis, and patient consent was not required because of the study's retrospective nature.

TABLE 1 Patient and Tumor Characteristics

Parameter	Ν	%
Female	29	60
Male	19	40
Ki-67		
≤2%	10	21
3%–20%	29	60
>20%	6	13
Unknown	3	6
Atypical	30	63
Typical	18	37
Hormone syndrome		
Yes	9	19
No	39	81

RESULTS

Among 1,978 patients who underwent ⁶⁸Ga- or ⁶⁴Cu-DOTA-TATE PET between March 2017 and February 2023, 48 patients with metastatic NETs originating in the lung were identified. Among these patients, 30 had atypical NETs and 18 had typical lung NETs. Patient and tumor characteristics are summarized in Table 1.

Four patients (8%) had a complete absence of tumoral SSTR expression, 2 patients (4%) had uniformly weak expression (less than in a normal liver), 8 patients (17%) had a heterogeneous mixture of absent and weakly expressing tumors, and 13 patients (27%) had a heterogeneous mixture of strongly avid tumors combined with the absence or near absence of SSTR expression in measurable tumors. Only 21 patients (44%) had uniformly strong SSTR expression in all their tumors (Table 2). Of the 18 patients with typical NETs, 12 (67%) had positive uniformly strong SSTR expression, 4 (22%) had heterogeneous expression, 1 (5%) had weak expression, and 1 (5%) had absent SSTR expression. Among the 30 atypical NETs, only 9 (30%) had uniformly strong expressive tumors, 17 (57%) had heterogeneous SSTR expression, 3

 TABLE 2

 Breakdown of SSTR Expression in Each Tumor Type

SSTR expression	Typical	Atypical	Total (%)
Absent	1	3	4 (8%)
Uniformly present low expression (<liver)< td=""><td>1</td><td>1</td><td>2 (4%)</td></liver)<>	1	1	2 (4%)
Uniformly present high expression (>liver)	12	9	21 (44%)
Heterogeneous low expression (mixture of low and absent expression)	2	6	8 (17%)
Heterogeneous strong expression (mixture of high and absent expression)	2	11	13 (27%)
Total	18	30	48



FIGURE 1. Strong SSTR expression on PET/CT (A) corresponding to metastatic lesions on contrast-enhanced CT (B).

(10%) had absent SSTR expression, and 1 (3%) had uniform but weak SSTR expression. Only 21 of 48 patients (44%) had uniformly strong positive receptor expression, which would render them candidates for treatment with PRRT. All patients in this latter category had tumors with an SUV_{max} at least double that in a normal liver, except for 1 patient with an SUV_{max} slightly above that in a normal liver.



FIGURE 2. Heterogeneous SSTR expression on PET/CT (A) compared with metastatic lesions on contrast-enhanced CT (B).



FIGURE 3. Absent SSTR expression on PET/CT (A) compared with metastatic lesions on contrast-enhanced CT (B).

Breakdown of SSTR expression in each tumor type is summarized in Table 2. Examples of strong, heterogeneous, and absent tumor expression are shown in Figures 1–3.

DISCUSSION

Understanding the unique patterns of SSTR expression in advanced lung NETs is essential when considering the role of SSTR-targeting systemic treatments. However, prior data were limited and included heterogeneous histologies (well- and poorly differentiated neoplasms) and stages (localized and metastatic). Our analysis focused on a relatively homogeneous population of patients with metastatic well-differentiated lung NETs who underwent SSTR PET/CT imaging using ⁶⁸Ga- or ⁶⁴Cu-DOTATATE PET scans.

Our findings suggest that SSTR expression in lung NETs, particularly atypical lung NETs, differs from that in well-differentiated gastroenteropancreatic NETs. Although completely absent SSTR expression is relatively uncommon, heterogeneous expression is frequent. Nearly a third of SSTR PET/CT scans (13/48) showed a heterogeneous pattern with both strongly positive and strongly negative SSTR expression in different tumors.

These results suggest that SSAs, particularly radiolabeled SSAs, may play a relatively limited role in lung NETs versus gastroenteropancreatic NETs. Although SSAs can be considered for treating patients with heterogeneous SSTR expression, PRRT is relatively contraindicated in this scenario. The low rates of uniform-avidity SSTR expression (44% in our cohort) also explain the relatively poor accrual of patients with lung NETs to studies of SSAs and potential difficulties in the accrual of this patient population to PRRT trials.

The main limitation of our study is the relatively small sample size of patients, particularly with typical NETs. The relatively low incidence of metastatic, differentiated lung NETs as well as the lower rates of referral to neuroendocrine specialty centers for lung NETs than for gastroenteropancreatic NETs may be the cause. Larger studies would be helpful to corroborate our findings. Clinical trials evaluating PRRT in lung NETs, such as A021901 (NCT04665739), will be important for evaluating the efficacy of PRRT in this rare patient population.

CONCLUSION

Metastatic lung NETs often demonstrate a heterogeneous pattern of SSTR expression, with relatively few tumors showing high levels of uniform expression on SSTR PET/CT scans. This information suggests that most lung NETs may be ineligible for PRRT using radiolabeled SSAs.

DISCLOSURE

Ghassan El-Haddad receives consulting fees from Bayer Healthcare, Boston Scientific Corp., Canon Medical Systems Corp., Novartis Pharmaceuticals Corp., and Terumo Medical Corp; is on the advisory board and receives consulting fees from NorthStar Medical Radioisotopes; and is a stockholder in Johnson & Johnson. Jonathan Strosberg is on the Speakers' Bureau of Ipsen and Tersera and is a consultant for Novartis. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What are the SSTR expression patterns of metastatic lung NETs?

PERTINENT FINDINGS: Most metastatic lung NETs express SSTR weakly or heterogeneously, potentially rendering patients ineligible for SSTR-based therapies.

IMPLICATIONS FOR PATIENT CARE: DOTATATE PET images should be carefully evaluated in patients with lung NETs to ensure strong uniform expression of SSTRs when considering treatment with radiolabeled SSAs.

REFERENCES

- Cives M, Strosberg JR. Gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin. 2018;68:471–487.
- Kwekkeboom DJ, Krenning EP. Radiolabeled somatostatin analog scintigraphy in oncology and immune diseases: an overview. *Eur Radiol*. 1997;7:1103–1109.
- Lamberts SW, Bakker WH, Reubi JC, Krenning EP. Somatostatin receptor imaging in vivo localization of tumors with a radiolabeled somatostatin analog. J Steroid Biochem Mol Biol. 1990;37:1079–1082.

- Dasari A, Shen C, Halperin D, et al. Trends in the incidence, prevalence, and survival outcomes in patients with neuroendocrine tumors in the United States. JAMA Oncol. 2017;3:1335–1342.
- Travis WD. Pathology and diagnosis of neuroendocrine tumors: lung neuroendocrine. *Thorac Surg Clin.* 2014;24:257–266.
- Rubino M, Scoazec JY, Pisa E, et al. Lung carcinoids with high proliferative activity: further support for the identification of a new tumor category in the classification of lung neuroendocrine neoplasms. *Lung Cancer*. 2020;148:149–158.
- Centonze G, Maisonneuve P, Simbolo M, et al. Lung carcinoid tumours: histology and Ki-67, the eternal rivalry. *Histopathology*. 2023;82:324–339.
- Tafreshi NK, Pandya DN, Tichacek CJ, et al. Preclinical evaluation of [²²⁵Ac]Ac-DOTA-TATE for treatment of lung neuroendocrine neoplasms. *Eur J Nucl Med Mol Imaging*. 2021;48:3408–3421.
- Rufini V, Lorusso M, Inzani F, et al. Correlation of somatostatin receptor PET/CT imaging features and immunohistochemistry in neuroendocrine tumors of the lung: a retrospective observational study. *Eur J Nucl Med Mol Imaging*. 2022;49:4182–4193.
- Pirayesh E, Amoui M, Assadi M. Uptake difference by somatostatin receptors in a patient with neuroendocrine tumor: ^{99m}Tc-octreotide uptake in the lung without uptake in liver lesions. *Mol Imaging Radionucl Ther.* 2015;24:128–131.
- Baudin E, Horsch D, Singh S, et al. 1096O lanreotide autogel/depot (LAN) in patients with advanced bronchopulmonary (BP) neuroendocrine tumors (NETs): results from the phase III SPINET study [abstract]. *Ann Oncol.* 2021;32(suppl 5): S906.
- Brabander T, van der Zwan WA, Teunissen JJM, et al. Long-term efficacy, survival, and safety of [¹⁷⁷Lu-DOTA⁰,Tyr³]octreotate in patients with gastroenteropancreatic and bronchial neuroendocrine tumors. *Clin Cancer Res.* 2017;23: 4617–4624.
- Bodei L, Kidd M, Paganelli G, et al. Long-term tolerability of PRRT in 807 patients with neuroendocrine tumours: the value and limitations of clinical factors. *Eur J Nucl Med Mol Imaging*. 2015;42:5–19.
- Krenning EP, Bakker WH, Breeman WA, et al. Localisation of endocrine-related tumours with radioiodinated analogue of somatostatin. *Lancet.* 1989;1:242–244.
- Forbes S, Baghdadi Y, Parkar F, Abraham T, Love C. Evaluating Ga-68 DOTA-TATE images: SUVmax vs Krenning score [abstract]. *J Nucl Med.* 2019;60(suppl 1): 1535.
- Hope TA, Abbott A, Colucci K, et al. NANETS/SNMMI procedure standard for somatostatin receptor-based peptide receptor radionuclide therapy with ¹⁷⁷Lu-DOTATATE. J Nucl Med. 2019;60:937–943.
- Kratochwil C, Stefanova M, Mavriopoulou E, et al. SUV of [⁶⁸Ga]DOTATOC-PET/CT predicts response probability of PRRT in neuroendocrine tumors. *Mol Imaging Biol.* 2015;17:313–318.
- Papotti M, Croce S, Bellò M, et al. Expression of somatostatin receptor types 2, 3 and 5 in biopsies and surgical specimens of human lung tumours. Correlation with preoperative octreotide scintigraphy. *Virchows Arch.* 2001;439:787–797.
- Righi L, Volante M, Tavaglione V, et al. Somatostatin receptor tissue distribution in lung neuroendocrine tumours: a clinicopathologic and immunohistochemical study of 218 'clinically aggressive' cases. *Ann Oncol.* 2010;21:548–555.
- Vesterinen T, Leijon H, Mustonen H, et al. Somatostatin receptor expression is associated with metastasis and patient outcome in pulmonary carcinoid tumors. *J Clin Endocrinol Metab.* 2019;104:2083–2093.