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ORIGINAL RESEARCH

Pulmonary neuroendocrine tumours and somatostatin receptor status: an assessment of unlicensed use of somatostatin analogues in the clinical practice

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Background: The use of somatostatin analogues (SSAs) has not been formally approved in pulmonary neuroendocrine tumours (NETs) in the absence of positive controlled trials, even though it is recommended as a potential therapeutic option in recent guidelines.

Patients and methods: We have assessed the use of SSA in the general practice in Austria by retrospectively analysing patients with pulmonary NETs referred to our European Neuroendocrine Tumor Society centre in Vienna for second opinion or further therapy. In addition, we have analysed the somatostatin receptor (SSTR) expression of those patients by immunohistochemistry (IHC) and SSTR imaging, e.g. ^{68}Ga-DOTANOC-positron emission tomography/computed tomography, and whether such analyses had been carried out before referral at our centre.

Results: Out of 34 patients (19 atypical and 15 typical carcinoids) with metastatic or advanced disease, 10/34 (29%) had been prescribed SSA before referral. No IHC for SSTR had been carried out, and only 9/34 (27%) had undergone SSTR imaging by nuclear medicine. Sufficient material for IHC was available in 29/34 (85%) patients and SSTR-IHC was rated negative in 13/29 (45%), weakly positive in 4/29 (14%), moderately positive in 5/29 (17%) and strongly positive in 7/29 (24%) patients. On SSTR imaging, 8/34 patients (24%) were positive, 13/34 (38%) negative and 13/34 patients (38%) showed a mix of positive and negative NET lesions. In 11/29 (38%) patients with both IHC and imaging available, discordance of SSTR expression on imaging and histological assessment was detected.

Conclusions: These data show that uncritical use of SSA should be discouraged, and assessment of SSTR, preferably by imaging, is mandatory before prescription of SSA in pulmonary NETs.

Key words: somatostatin analogues, pulmonary neuroendocrine tumours, carcinoid

INTRODUCTION

Pulmonary neuroendocrine tumours (NETs) are increasing in incidence, and—according to data published by the Surveillance, Epidemiology, and End Results (SEER) registry—are the most commonly diagnosed NETs.[1] To the current knowledge, they account for 1%-3% of all malignant lung tumours but constitute 25%-30% of all NETs.[1-4] Based on the 2015 World Health Organization (WHO) classification, differentiated pulmonary NETs are classified as typical carcinoids (TCs) and atypical carcinoids (ACs), according to stringent pathological criteria taking into account the number of mitoses and presence of necrosis (<2 mitoses, no necrosis for TC and 2-10 mitoses or necrosis for AC).[4,5] Aggressive neuroendocrine carcinomas (large cell and small cell) are not related to differentiated NETs and represent a distinct entity approached by a completely different treatment algorithm. An analysis of the National Cancer Database (NCDB) carried out in patients undergoing resection for pulmonary NET between 2004 and 2014 demonstrated a pronounced female predominance in the 6673 patients registered with 30% being male and 70% being female.[6] The distribution between TC and AC was in favour of the more commonly diagnosed TC (n = 5880, 88%) as opposed to only 793 patients with AC (12%). In terms of prognosis, lung NETs usually present with an indolent clinical course and outcome is favourable in localized disease with 10-year survival rates of >80% reported for TC while AC faces a poorer prognosis at

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40%-50%.[3,7] Even in advanced disease, survival rates are in the range of 40%-60% at 5 years.[7,8]

Surgery remains the mainstay of treatment, as it is the only curative option for patients diagnosed with pulmonary NETs,[8] but up to 25% present with primary metastatic disease and relapses including distant metastases following curative surgery are frequent, thus underlining the need for effective systemic therapies.[7,9] Platinum-based chemotherapies in analogy to small-cell lung cancer had been applied in the past, with modest rates of success and progression-free survival (PFS) in the range of 7-8 months.[8] Recent series suggest oxaliplatin-based therapy to be superior in PFS and tolerability compared to cisplatin or carboplatin.[10] Several small studies have also evaluated temozolomide-based regimens and have suggested response rates of up to 30% with the methylation status of the MGMT promoter discussed as a potential biomarker.[11-13]

More recently, the mammalian target of rapamycin (mTOR) inhibitor everolimus was approved as the first agent for therapy of pulmonary NETs based on results of the phase III RADIANT-4 study.[14] In this trial, 302 patients were randomized between everolimus and placebo, resulting in a significantly prolonged time to progression not only in the overall collective, but also in the subgroup of patients with pulmonary NETs.[14,15] In view of this, everolimus is widely being used in patients with TC and AC and has also been included in the European Neuroendocrine Tumor Society (ENETS) consensus published in 2015 and the guideline of the European Society for Medical Oncology (ESMO) renewed in 2021.[8,16] In the same papers, however, also the use of somatostatin analogues (SSAs) has been recommended for first-line therapy not only in (the low percentage of) symptomatic patients presenting with relevant hormone production, but also for tumour control in both TC and AC, albeit in the absence of data from a randomized controlled trial.

The SSAs octreotide (OCT) and lanreotide (LAN) are widely being used for antiproliferative treatment mostly as depot forms every 28 days in gastroenteropancreatic NETs (GEP-NETs) due to positive phase III data leading to approval in these indications,[17,18] but have not formally been licensed for antiproliferative treatment in pulmonary NETs in Austria. This is further complicated by the fact that the expression of somatostatin receptors (SSTRs), which constitutes the main rationale for SSA use, does not appear to be as uniform as in gastrointestinal NETs, which might be a further obstacle for the successful application in this disease.[19] In view of this, we have tried to assess the use of SSA in the general practice in Austria by retrospectively analysing patients with pulmonary NETs referred to our ENETS Centre of Excellence in Vienna for second opinion or further therapy between 2016 (after publication of the ENETS consensus) and December 2019. In addition to collecting basic clinical data, we have analysed the SSTR expression of those patients by immunohistochemistry (IHC) and SSTR imaging, e.g. ^{68}Ga-DOTANOC-peptide positron emission tomography (PET)/computed tomography (CT), and whether such analyses had been carried out before referral at our centre.

Patients and methods

We have retrospectively analysed all patients with advanced pulmonary NETs referred at our institution, a certified tertiary referral centre for neuroendocrine neoplasms (ENETS Centre of Excellence) and we identified patients seen for further therapy after initial treatment or second opinion after a multidisciplinary tumour board. In all patients, histological samples were (re)evaluated according to the most recent WHO classification by a reference pathologist at our institution (PM), and if enough material was available, further staining for SSTRs was carried out.[4] Basic clinical characteristics extracted from our routine medical records included sex, age, extent of disease and therapy. If applicable, type of SSA (OCT or LAN), dose/regimen, response to treatment and adverse events were documented. Finally, also the presence and results of external SSTR imaging using either DOTA-PET/CT or OctreoScan (^{111}In-pentetreotide scintigraphy) were analysed, and in all patients with no prior SSTR imaging, a ^{68}Ga-DOTANOC-PET/CT was routinely carried out at our institution. The current analysis had been approved by the local ethical board of the Medical University of Vienna (EK-No.: 2409/2020).

Assessment of SSTR status on tissues

Immunohistochemical analyses (IHC) for expression of somatostatin receptor 2 (SSTR2) and somatostatin receptor 5 (SSTR5) were carried out according to the manufacturer's guidelines. No other isoforms of SSTR were assessed due to the current lack of diagnostic and therapeutic relevance.[20] In brief, tumour tissue was fixed in 4% buffered formalin and submitted to histologic routine procedure. Sections of 3-µm thickness were cut from the tumour blocks and transferred to silanized sections, which were used for haematoxylin–eosin staining as well as for IHC. IHC was carried out using the avidin-biotinylated peroxidase complex method. Antibodies against SSTR2 (Abcam®, Cambridge, UK, dilution ratio: 1 : 500) and SSTR5 (Abcam®, dilution ratio: 1 : 200) were used after heat-induced epitope antigen retrieval, according to the manufacturer's instructions. SSTR expression was graded as absent (0), weak (+), intermediate (++) and strong (+++) by the reference pathologist (see Figure 1). For easier comparison, we additionally used a semi-quantitative approach based on a well-established weighted histoscoring method. Histoscoring was based on the above-explained staining intensity of all cells of the full slide and in the following calculation was done according to the formula: 1 × percentage (%) of cells staining weakly positive + 2 × % of cells staining moderately positive + 3 × % of cells staining strongly positive. The resultant score ranges between 0 (no staining at all) and 300 (all cells are strongly positive). For further analyses, expression was classified into '+++' corresponding to an SSTR histoscore >200, '++' corresponding to a histoscore from 100 to 200 and '+' corresponding to a histoscore from >20 to <100.

SSTR imaging and analysis of SSTR expression on PET/CT

PET/CT at our centre was carried out 45-60 min after intravenous administration of 160-180 MBq of ^{68}Ga-DOTANOC

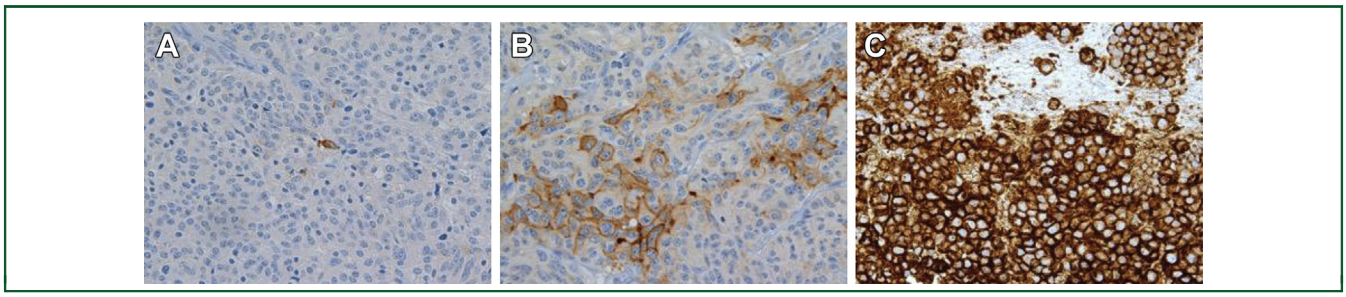

Figure 1. Immunohistochemical stainings for SSTR2 expression.
Immunohistochemical slides from pulmonary neuroendocrine tumour (NET) showing (A) lack of somatostatin receptor 2 (SSTR2) expression, (B) weak SSTR2 and (C) strong SSTR2 expression (original magnification ×400).

(conjugate of the SSA 1-Nal3-OCT and ^{68}Ga-labelled 1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid) using a 64-row multi-detector, hybrid PET/CT system (Biograph TruePoint TrueView 64; Siemens, Erlangen, Germany). Imaging was carried out at 4 min/bed position, and images were reconstructed using the point-spread function-based reconstruction algorithm TrueX, with 4 iterations and 21 subsets, 5-mm slice thickness and a 168 × 168 matrix size. Contrast-enhanced venous-phase CT was used for attenuation correction and was carried out following an intravenous injection of 90-120 ml of a tri-iodinated, non-ionic contrast medium at a rate of 4 ml/s, with a reference tube current of 230 mA, a tube voltage of 120 kVp, a collimation of 64 × 0.6 mm, a 5-mm slice thickness with a 3-mm increment and a 512 × 512 matrix. Since radiotracer uptake is not comparable quantitatively between patients undergoing different types of imaging (i.e. scintigraphy and PET/CT), a qualitative strategy of SSTR image analysis was pursued: (i) assessment of SSTR-positive and -negative lesions, i.e. focal uptake, or lack thereof, relative to the surrounding tissue uptake, at known sites of disease or sites of disease confirmed by CT; and based on these findings (ii) assessment of heterogeneity in terms of positivity/negativity between anatomic sites in patients with multifocal or multiorgan NET involvement.

RESULTS

Basic characteristics

A total of 34 patients with non-secretory, advanced pulmonary NETs were referred at the Department of Medicine I, Division of Oncology at the Medical University of Vienna for second opinion or further therapy between January 2016 and December 2019. The majority of patients were female ($n = 22$, 65%) and only 12 patients were male ($n = 12$, 35%) with the median age being 78 years (range: 28-88 years). Distant organ metastases were present in 56% of patients (19/34), while the remaining patients had locally advanced and unresectable disease. Out of these patients, a high percentage of patients (56%, 19/34) were classified as having AC (4 males, 15 females), while 15 patients (44%; 8 males, 7 females) were diagnosed with TC.

SSTR-IHC results

None of the patients had had IHC analysis of SSTR expression on biopsy tissues before referral to our centre, and sufficient material for testing was available in 29/34 cases (86%). SSTR expression was assessed on the primary tumour of the lung in 20/29 (69%) available tissues, while in the remaining 9 patients tissues of metastases (organ or lymph node) were used for staining. For detailed overview on results, see Table 1. According to the criteria given in the Patients and methods section, 13/29 (45%) were rated negative, 4/29 (14%) weakly positive (all in the lung) (+), 5/29 (17%) moderately positive (++) and the remaining 7/29 (24 %) strongly positive (+++). Eight out of the 13 patients rated negative had AC and only 5 TC, and 2 patients rated positive had TC and 2 AC. Amongst the more intensively SSTR-expressing tumours, three patients presented with expression classified as ++ had AC and two TC, while in the seven patients with strongly positive tumours, i.e. +++, four patients had TC and three AC, respectively. The staining pattern was membranous in all positive cases, with some cases with strong expression also showing additional cytoplasmic staining.

SSTR imaging results

All patients underwent SSTR imaging. The large majority had a ^{68}Ga-DOTANOC-PET/CT at our institution (25/34, 74%), while the remaining nine (26%) had already undergone SSTR imaging at the referring centre, including one patient with an OctreoScan, two with ^{99m}Tc-Tektrotyde imaging and six with DOTA-peptide-PET/CT using ^{64}Cu in two and ^{68}Ga as radionuclide in four cases. The results of SSTR imaging were heterogeneous, and to a larger than expected extent negative: in total, only 8 patients (24%) were rated positive, while 13/34 (38%) were classified negative. Notably, 13/34 patients (38%) showed a mix of positive and negative NET lesions on SSTR imaging, with 8 having AC and 5 TC (Figures 2 and 3).

Combining SSTR imaging and IHC data, seven patients were SSTR negative on IHC but were at least in some lesions SSTR positive by imaging and contrarily, four patients who were weakly SSTR positive (one '+' and three '++') were completely negative on the SSTR PET scan. Thus, in 11/29 (38%) patients with IHC and imaging data available, a discordance of SSTR expression on imaging and histological assessment was detected.

SSA treatment

A total of 10 patients (29%) had been prescribed SSA before referral at our institution, with 4 having received OCT

Table 1. Characteristics of 34 patients with pulmonary neuroendocrine tumours including somatostatin receptor status

No.	Sex/age	Histology	Site of disease	Prior SSA therapy	SSTR-IHC	SSTR imaging
1	f/38	TC	Lung	No	++ (lung)	Neg
2	m/75	AC	Lung, liver	No	Neg (lung)	+ (lung)/− (liver)
3	f/71	AC	Lung, liver	No	+++ (lung)	+ (lung)/− (liver)
4	m/81	TC	Lung, orbit, bone, LNN	No	Neg (orbit)	+ (orbit, lung, bone)/− (lung, bone)
5	m/77	TC	Lung	OCT	+++ (lung)	+
6	f/64	TC	Lung, LNN	No	Neg (LNN)	Neg
7	m/62	AC	Lung, LNN, liver	LAN	Neg (liver)	+ (lung, LNN)/− (lung, LNN, liver)
8	f/28	AC	Lung, bone	No	Neg (lung)	Neg
9	f/78	AC	Lung, LNN	No	Neg (LNN)	Neg
10	f/59	TC	Lung, LNN	No	Neg (LNN)	Neg
11	f/65	AC	Lung	No	+++ (lung)	+
12	f/48	AC	Lung, orbit, liver, LNN, heart, thyroid	LAN	+++ (thyroid)	+
13	m/72	AC	Lung, liver, LNN	No	Neg (liver)	+ (LNN)/− (lung, liver, LNN)
14	f/81	AC	Lung, LNN	No	Neg (lung)	+ (LNN)/− (lung)
15	m/83	TC	Lung, liver, bone, LNN, spleen	LAN	+++ (liver)	+
16	f/62	AC	Lung, LNN, liver, ovary	No	n.d.	Neg
17	m/78	TC	Lung, liver, LNN, bone	No	Neg (lung)	+ (LNN, liver, bone)/− (lung, liver)
18	m/75	TC	Lung, LNN, bone, soft tissue	No	Neg (lung)	+ (LNN, soft tissue, bone)/− (lung, LNN)
19	f/62	AC	Lung	No	Neg (lung)	Neg
20	f/75	AC	Lung, liver, peritoneum	No	++ (lung)	+ (liver, peritoneum)/− (liver, lung)
21	f/76	AC	Lung	No	n.d.	Neg
22	f/74	AC	Lung	No	n.d.	Neg
23	f/82	TC	Lung, liver, LNN	OCT	n.d.	+ (lung)/− (liver, LNN)
24	m/88	AC	Lung, liver, LNN	No	++ (liver)	+ (liver, LNN)/− (lung, LNN)
25	f/64	TC	Lung	No	+ (lung)	Neg
26	m/80	TC	Brain, LNN, bone	No	n.d.	+ (brain, LNN)/− (LNN, bone)
27	m/76	TC	Lung, liver	OCT	++ (lung)	+
28	m/47	TC	Lung (lung)	No	+++ (lung)	+
29	f/85	AC	Lung, LNN	OCT	+ (lung)	Neg
30	f/72	AC	Lung, bone, soft tissue	LAN	Neg (lung)	Neg
31	f/77	TC	Lung, liver, bone	LAN	+++ (lung)	+
32	f/72	TC	Lung, LNN	No	+ (lung)	Neg
33	f/80	AC	Lung, LNN	LAN	++ (lung)	+
34	f/82	AC	Lung, LNN, bone	No	+ (lung)	+ (lung, LNN)/− (lung, LNN, bone)

AC, atypical carcinoid; f, female; IHC, immunohistochemistry; LAN, lanreotide; LNN, lymph nodes; m, male; n.d., no data; neg, negative; No., ID number; OCT, octreotide; SSA, somatostatin analogue; SSTR, somatostatin receptor; TC, typical carcinoid.

long-acting release 30 mg and 6 LAN autogel (2 at a dose of 60 mg and 4 at 120 mg every 28 days). In 4 of those 10 patients, no SSTR imaging had been carried out before application of the SSA. Following imaging at our centre, two were found to be negative on PET/CT, with one being also negative on IHC while SSTR-IHC of the other was only rated weakly positive; two patients were subsequently rated PET positive in the lung but had a negative PET/CT result in the multiple liver lesions. There was not enough material left for SSTR analysis in one patient, while the other was negative on IHC from a liver biopsy. The remaining six patients were rated positive on SSTR imaging, and all patients had at least (++) results on IHC. Thus, in summary, six patients treated with SSA had a clear SSTR expression confirmed by at least one method, while three had weak positivity or discrepant findings only and one was negative on both IHC and imaging. Treatment duration was between 3 and 11 months. In terms of response, four patients progressed, while six had stable disease. No objective remissions were seen with application of the SSAs. As expected, tolerability was excellent with no major toxicities documented according to available records.

DISCUSSION

Differentiated NETs of the lung are the most commonly diagnosed neuroendocrine neoplasms. Having been graded as TC and AC in the past, the classification is now increasingly more in analogy to NETs of the GEP system, i.e. NET G1 and G2, respectively.[4,21] Despite the lack of formal approval and positive phase III evidence, current guidelines state that SSA can be considered for the treatment of lung NETs in particular circumstances.[8,16] In detail, both the ESMO and the ENETS guidelines state long-acting SSA as a potential treatment option for (first-line) systemic treatment of locally advanced or metastatic lung NET patients with a low proliferation index and positive SSTR expression.

In view of this and the fact that particularly the latter is not considered in the majority of available series on SSA use in pulmonary NET, despite a considerable lower percentage classified as SSTR positive in lung NET compared to GEP-NET,[22] the primary objective of our analysis was to establish the impact of the ENETS 2015 consensus on the practical management of patients initially treated outside of referral centres in Austria. Therefore, we have analysed patients referred at our centre for second opinion or after first-line

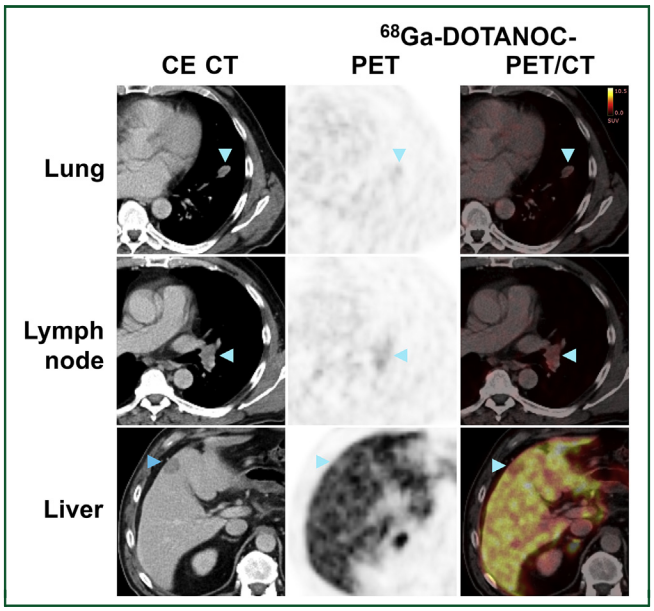

Figure 2. A 71-year-old male patient with metastatic pulmonary neuroendocrine tumour (NET) (arrowheads). On ^{68}Ga-DOTANOC-positron emission tomography (PET), only the left hilar lymph node metastasis shows a clear focal, moderate tracer accumulation [i.e. somatostatin receptor (SSTR) overexpression], whereas the pulmonary lesion that is visible on contrast-enhanced (CE) computed tomography (CT) shows very faint uptake, and the liver lesion no focal tracer uptake, relative to the surrounding tissues.

therapy for use/prescription of SSA treatment as well as data on SSTR imaging before use/recommendation. Assessment of response was not the focus of this series. For timeline, we refer to the period following the ENETS consensus publication, as this was the very first official recommendation for off-label SSA use in advanced pulmonary NETs, while the ESMO guideline was only recently renewed.[8,16] Whereas we cannot rule out differences in the pre-analytic handling of NET tissues at other centres, SSTR assessment was exclusively carried out at the Medical University of Vienna following a standardized protocol, thus minimizing a potential bias regarding staining and quantification methods.

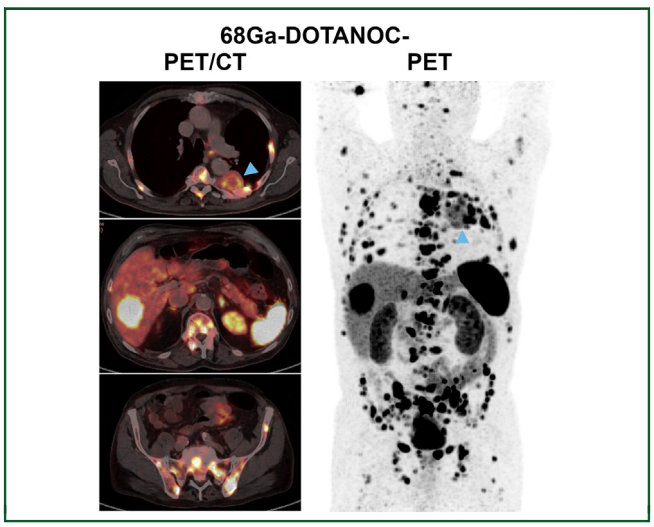

Figure 3. A 79-year-old patient with metastatic left pulmonary neuroendocrine tumour (NET). The primary tumour in the left lung (arrowheads) shows clearly lower ^{68}Ga-DOTANOC uptake than the multiple bone metastases and the liver metastasis on ^{68}Ga-DOTANOC-positron emission tomography (PET)/computed tomography (CT) and the PET maximum intensity projection, suggesting variability of somatostatin receptor (SSTR) expression between sites of disease.

SSAs have been reported to have pleiotropic modes of action including anti-angiogenic effects mediated via interaction with the tumour environment, but there is widespread consensus that the main activity is exerted by interaction with SSTR2 and SSTR5 located on the tumour cells and that expression of SSTRs is thus a prerequisite for antineoplastic activity.[22,23] This has been adopted by the ENETS and ESMO recommendation, stating that SSA should be used in SSTR-positive tumours only, while the method of assessment, i.e. imaging or IHC, is not clearly recommended.[8,16] In view of this, our results referring to the lower than expected rate of SSTR imaging are of interest, as >70% of patients had either a negative result or a diverging uptake within different sites. In addition, nearly 50% lacked SSTR expression on IHC. A potential bias might be introduced by the high percentage of patients with AC/NET G2 in our series, with the rate of AC in the total incidence of pulmonary NETs reported to be up to 10% in larger series, versus 53% in our collective.[6] Nevertheless, these data underline that SSTR expression cannot be assumed '*per se*' in a real-world setting but needs to be tested in lung NETs before treatment initiation.

Our findings are supported by related studies in the literature, including a large series of 24 TCs and 73 ACs, where 49% of ACs and 29% of metastatic TCs lacked SSTR2A expression.[19] Metastatic TCs had a significantly higher SSTR expression as compared to localized TC. The concordance rate of SSTR2A IHC expression and OCT scintigraphy was 69%, but imaging was only carried out in a low number of cases. A further series reported a sensitivity of 86% for ^{68}Ga-DOTANOC tracer uptake in 28 lung NET patients but concluded that the main influence of imaging was regarding detection of further sites, while only in one patient the scan had explicit therapeutic implications.[24] Another problem in imaging lung NETs appears to be that particularly in AC 20% of lesions have been reported to be detectable only in the PET component whereas they were absent on the CT scan.[25] Also, the phenomenon of mixed expression patterns, i.e. SSTR imaging-positive and -negative lesions in one patient, has been previously documented in 8% of TC and 27% of AC in a series of 27 patients. In our cohort, an even higher number of 38% of patients had mixed results on PET/CT imaging. Interestingly, we found the lung more often positive in patients with diverging results than other sites including the liver. This also begs the question whether imaging of lung lesions is in fact always due to binding of the radiotracer to tumour cells or imaging of an inflammatory background in the lung, as also reactive lesions including infections and tuberculosis have been reported to be positive due to activation of SSTRs on inflammatory cells.[26] Furthermore, this also suggests a potential problem with IHC SSTR assessment from a single biopsy in patients with multiple metastatic localizations, if there is indeed a

difference in SSTR expression according to site in individual patients. This appears reasonable, as also for Ki67 a relevant heterogeneity between primary and metastases was postulated in NETs.[27] Data regarding IHC SSTR expression in lung NET primaries and metastases are limited but a small series has reported a high concordance rate of SSTR2 and SSTR5 expression in 15/17 (88%) investigated cases of lung NET primaries and corresponding metastases.[28] Finally, while currently lacking therapeutic implications, the use of novel PET radionuclide tracers with higher SSTR affinity or targeting a broader SSTR spectrum could be helpful in cases with discrepant or negative SSTR findings on imaging.[29]

Treatment algorithms for GEP-NETs have been well established and are based on data from randomized phase III studies assessing the use of the SSAs OCT and LAN, the mTOR inhibitor everolimus, the tyrosine kinase inhibitor sunitinib as well as peptide receptor radionuclide therapy within the NETTER-1 trial.[14,17,18,30-33] As opposed to this, the only formally approved agent for treatment of pulmonary NETs is everolimus based on a cohort of 90 patients included in the RADIANT-4 trial,[14,15] while SSAs have not been formally approved in this indication.[17,18] A randomized phase III for LAN 120 mg every 4 weeks was stopped early for insufficient recruitment, and data published so far in abstract form only did not show a statistically significant difference in PFS for LAN versus placebo (NCT02683941).[34] Previously available evidence for use of SSA in lung NETs derives from small phase II studies or retrospective analyses. For instance, a retrospective series assessed SSA use in 61 patients (67% AC) including 48% with functioning tumours.[35] The best objective response observed was stable disease in 77%, the median PFS was 17.4 months [95% confidence interval (CI) 8.7-26 months] and the estimated OS was 58.4 months (95% CI 44.2-102.7 months). Patients previously classified as slowly progressing or patients with functioning tumours had a significantly longer PFS when compared to the rest of the cohort. Comparable series reported 2-fluoro-2-deoxy-D-glucose positivity and pre-treatment with other strategies to be associated with a shorter response to SSA.[36,37] Phase II evidence derives from the LUNA study, which evaluated the SSA pasireotide ± everolimus.[38] The median PFS was 8.5 months (95% CI 5 months-not reached) for the pasireotide cohort, including 41 patients with documented progression before treatment start but also these data did not translate into clinical practice.

Our data suggest a high acceptance of the ENETS recommendation in view of the fact that 10/34 patients (29%) had been prescribed SSA therapy. Academically, however, this impairs recruitment of future prospective evidence for SSA use in lung NETs as already evidenced by termination of a phase III study due to low recruitment rates.[34] Planning of comparable studies is unlikely if SSA off-label is widely accessible in this indication. Of note is also that, against the official recommendation, almost half of the patients received SSA therapy without prior assessment of SSTR expression.

To conclude, SSAs are commonly being used for pulmonary NETs outside of clinical trials, in a sometimes uncritical manner. We detected highly heterogeneous profiles of SSTR expression on imaging/IHC and a considerable amount of TC and AC lacking SSTR expression. Thus, assessment of SSTR expression should be a prerequisite before SSA initiation, and owing to the heterogeneous expression within sites, our data suggest that ^{68}Ga-PET/CT imaging should be the preferred method in clinical practice. While the favourable toxicity profile and the extensive experience deriving from GEP-NETs suggest SSA as an attractive treatment option, the lack of positive randomized data and approval should be taken into account when prescribing SSA for lung NETs.

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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