In Patients With Well-Differentiated Neuroendocrine Tumours, There Is No Apparent Benefit of Somatostatin Analogues After Disease Control By Peptide Receptor Radionuclide Therapy

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Research Article

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Abstract

Purpose Peptide receptor radionuclide therapy (PRRT) and somatostatin analogues (SSAs) are commonly combined as primary treatment for neuroendocrine neoplasm (NEN), and SSAs given as maintenance treatment. We sought to evaluate whether sequential therapy with PRRT followed by SSAs has progression or survival benefits in patients with NEN.

Methods This prospective, randomised, single-centre study had as principal eligibility criteria: unresectable, locally-advanced, or metastatic, histologically-confirmed well-differentiated NEN; no symptoms of carcinoid syndrome; no SSAs or ≤ 3 months of SSAs before PRRT; and stable disease or partial/complete response after PRRT. Altogether 115 patients were randomised 2:1 to an SSA group (n=74) given octreotide acetate LAR every 4 weeks, or to a control group (n=41) receiving best supportive care. Octreotide treatment was to stop upon intolerable toxicity or patient refusal, or, at physician/patient discretion, upon progression. Primary study endpoint was progression-free survival (PFS).

Results Overall, median (25th-75th percentile) follow-up from the first PRRT activity to death or latest observation was 6.6 (3.18-10.22) years. During that time, 71/115 patients (62%) progressed, 52/74 (70%) in the SSA group, 19/41 (46%) in the control group ($p = 0.01$). Eighty-eight /115 (76%) patients died, 58/74 (78%) in the SSA group, 30/41 (73%) in the control group ($p = 0.52$). Median (95% CI) PFS was respectively, 4.7 (2.8-7.7) in the SSA group, and 6.4 (4.1-not reached) years in controls. Median OS was 6,6 years in whole group of patients. Neither PFS nor OS differed between groups ($p = 0.129$, $p = 0.985$, respectively).

Conclusions In patients with disease control after PRRT, subsequent SSA treatment appeared not to be associated with better PFS or OS. Whether to continue or stop SSA administration upon progression after PRRT requires evaluation in a prospective, randomised, controlled multicenter study with a relatively homogeneous sample.

Introduction

Somatostatin receptors (SSRs), particularly type 2 receptors, typically are over-expressed in neuroendocrine neoplasms (NEN)[1]. The introduction of somatostatin analogue (SSA) pharmacotherapy in the late 1980s was a breakthrough in treating patients with carcinoid syndrome [2, 3], and soon afterwards, in the therapy of NEN. Although experimental investigations demonstrated that SSAs exert cytostatic effects on tumour cells, the role of these agents in growth arrest was poorly defined and understood [4, 5]. For many years, the literature on treatment of NEN with SSAs was limited to reports of small, observational studies, which predominantly observed disease stabilisation [6]. The exception was one study from the early 1990's (N=84), in which 28% of treated patients (4/14) had partial remission [7]. The literature suggested that SSA antitumoural effects were restricted mainly to slow-growing tumours [8], and were unclear in malignancies other than NENs [9]. Results of prospective, randomised clinical trials of antiproliferative SSA treatment of NEN began to be published only starting some 10 years ago.

The first of these studies used octreotide LAR in metastatic midgut NENs [10], and more recently, a study was published regarding lanreotide autogel therapy of enteropancreatic NENs [11].

Another type of SSR-targeted treatment is peptide receptor radionuclide therapy (PRRT). In PRRT, SSAs serve as carrier molecules for any of a variety of radionuclides, most commonly lutetium 177 (^{177}Lu) or yttrium 90 (^{90}Y). Hence, in contrast to SSA pharmacotherapy, PRRT delivers cytotoxic radiation to cancer foci [12]. PRRT was first used in 1992 at Erasmus University of Rotterdam, The Netherlands [13], and initial publications showed about 20% partial remission (PR) and 60% disease stabilisation [12, 14]. Only in 2017 were results of a prospective randomised trial published clearly demonstrating significant improvement in progression-free survival (PFS) in patients treated with ^{177}Lu -labeled SSAs (hazard ratio [HR] [95% confidence interval [CI] 0.18 [0.13-0.33]) [15, 16].

At our Nuclear Medicine Department, we started to apply PRRT to treat well-differentiated NEN in 2002. Initially, we mainly used PRRT as first-line therapy, based on encouraging suggestions in the literature [14, 17] that the modality might often exert cytotoxic effects, in possible contrast to the primarily cytostatic effects of SSA therapy; additionally, reimbursement for PRRT had rapidly become available in Poland.

We soon faced the question of whether, and, if so, how, to give SSAs after the disease control, i.e., remission or stabilisation, that frequently was achieved after PRRT. Since data on the antiproliferative effect of SSAs were scarce, we decided to conduct the present study to evaluate whether SSA treatment after successful PRRT treatment would be beneficial regarding PFS or overall survival (OS).

Methods

Study design, endpoints, and ethics

This was a prospective, randomised, controlled single-centre trial with a treatment phase running from August 2004–November 2012. The inclusion criteria were unresectable, locally-advanced, or metastatic, histologically-confirmed well-differentiated NEN (Grades 1–2); no symptoms of carcinoid syndrome; World Health Organisation performance status 0–2; no SSA treatment, or ≤ 3 months of SSA treatment before PRRT; and disease control after a complete course of PRRT, as described below. Patients were excluded from the study if they had carcinoid syndrome, had malignancy other than NEN at randomisation, had not completed PRRT, or had progressed after PRRT.

Eight to 10 weeks after the last PRRT cycle, patients were evaluated scintigraphically, radiologically, and biochemically. Both after PRRT and during the randomised study, response was defined according to Response Criteria in Solid Tumours (RECIST) 1.0 and from 2009, RECIST 1.1 (based on computed tomography [CT]/magnetic resonance imaging [MRI]) [18].

Patients with disease control after PRRT, namely stable disease (SD), PR, or complete remission (CR), were enrolled into the study and randomised 2:1 to SSA treatment or best supportive care (“best supportive care group”) (Supplementary Figure S1). In cases of progressive disease (PD), defined as a

>20% increase in the sum of the longest tumour diameter or appearance of new metastatic lesions, post-PRRT treatment was left to the discretion of the treating physician and patient, and took place outside this study.

The study's primary endpoint was PFS and the secondary endpoint, OS, as defined in the "Statistics" subsection below. No formal safety assessment was made because it was felt that the literature had demonstrated the good safety and tolerability of SSA treatment of NEN.

The protocol was approved by our institutional Ethics Committee; all patients provided written informed consent before entry.

Patients

One hundred fifteen patients were enrolled. Their median (minimum–maximum) age at NEN diagnosis was 54 (12–78) years, and there was a slight predominance of males. Primary tumours were mainly in the gastrointestinal tract (GEP-NEN), but were in the lungs or other non-gastrointestinal sites in 18 patients (16%), and at unknown sites in 22 (19%). Median (25th -75th percentile) time from NEN diagnosis to study enrolment was 1.4 (0,5-3,9) years. At the time of randomisation, disease stabilisation had been achieved in 79% of patients (91/115), and PR, in 20% (23/115); including 1 patient who had progressed after PRRT and was mistakenly enrolled into the study.

Seventy-four patients were randomised to SSA treatment after PRRT, and 41 to best supportive care. The SSA group included the patient with PD after PRRT, who, in line with intention-to-treat principles, was included in statistical analyses of that group. Patient characteristics were well-balanced between the groups (Table 1).

Table 1
Treatment group characteristics

Characteristic	SSA group (%) (n = 74)	Observation group (%) (n = 41)	p value (χ ²)
Sex			
Male	56.8% (42)	78.0% (32)	0.40
Age at NEN diagnosis, years			
Median (range)	55.4 (49.5 - 63.7)	53.94 (45.31 - 61.42)	0.53
<45	24.3% (18)	17.1% (7)	0.49
45–65	60.8% (45)	61.0% (25)	
>65	14.9% (11)	22.0% (9)	
Time from diagnosis to start of PRRT (yr), median (25th –75th percentile)	1.4 (0.6-3.9)	1.2 (0.6–3.0)	1.00
NEN differentiation			
G1	54.1% (40)	56.1% (23)	0.80
G2	45.9% (34)	43.9% (18)	
Primary tumour site			
Any GEP	67.6% (50)	63.4% (26)	0.80
<i>Pancreas</i>	<i>18.9% (14)</i>	<i>14.6% (6)</i>	
<i>Small intestine</i>	<i>39.2% (29)</i>	<i>31.7% (13)</i>	
<i>Large intestine</i>	<i>9.5% (7)</i>	<i>9.5% (7)</i>	
Lungs	8.1% (6)	12.2% (5)	
Other	5.4% (4)	7.3% (3)	
Unknown	18.9% (14)	19.5% (8)	
Disseminated disease at diagnosis			
Present	71.6% (53)	65.9% (27)	0.50

Because of rounding, not all percentages may add to 100%.

90Y 90 yttrium, *177Lu* 177 lutetium, *G1* grade 1, *G2* grade 2, *NEN* neuroendocrine neoplasm(s), *PRRT*, peptide receptor radionuclide therapy

Characteristic	SSA group (%) (n = 74)	Observation group (%) (n = 41)	p value (χ ²)
Site(s) of dissemination at diagnosis			
Locoregional only	28.4% (21)	36.6% (15)	0.70
Liver only	27.0% (20)	24.4% (10)	
Bones only	2.7% (2)	2.4% (1)	
>2 sites	27.0% (20)	29.3% (12)	
Other therapies before PRRT			
No treatment	64.8% (48)	82.9% (34)	0.16
SSA treatment (≤3 months)	12.2% (9)	4.9% (2)	
Chemotherapy	20.3% (15)	9,8% (4)	
MIBG therapy	2.7% (2)	2.4% (1)	
PRRT regimen			
4 x 90Y-DOTATATE	43.2% (32)	26.8% (11)	0.08
4 x 90Y-DOTATATE	56.8% (42)	73.2% (30)	
+ 1 x 177Lu-DOTATATE			
Response to PRRT			
Partial remission	20.3% (15)	19.5% (8)	0.70
Stable disease	78.4% (58)	80.5% (33)	
Progression	1.4% (1)	0% (0)	
Because of rounding, not all percentages may add to 100%.			
90Y 90 yttrium, 177Lu 177 lutetium, G1 grade 1, G2 grade 2, NEN neuroendocrine neoplasm(s), PRRT, peptide receptor radionuclide therapy			

Peptide Receptor Radionuclide Therapy

PRRT was routinely administered to patients with well-differentiated NEN with sufficient SSR expression, as confirmed with SSA positron emission tomography/CT (PET/CT) performed ≤3 months before PRRT. Octreotide, tectrotide, or gallium 68-DOTATATE were used, depending on availability at the time. Uptake in liver lesions that was higher than healthy liver tissue uptake, and uptake at other sites that was at least

equal to healthy liver tissue uptake was considered to be adequate for PRRT. Well-preserved bone marrow function (haemoglobin ≥ 10 g/dL, white blood cell count $\geq 3 \times 10^9$ /L, platelet count $\geq 90 \times 10^9$ /L), liver function (bilirubin $\leq 1.5 \times$ upper limit of normal [ULN], alanine aminotransferase $< 2.5 \times$ ULN) and kidney function (creatinine clearance > 40 mL/min) also was an eligibility criterion for PRRT.

Of the 115 enrolled patients, the first 43 (37%) had been given 4 cycles each of 2.96 GBq ^{90}Y -labeled DOTATATE (Polatom, Otwock, Poland) every 8–12 weeks. From 2007 as a separate study, an additional single “boost” of 7.4 GBq ^{177}Lu -DOTATATE (Polatom) was given 6–8 weeks after the last ^{90}Y -DOTATATE administration. Toxicity was the only grounds for reduction in the planned PRRT regimen, which occurred 17 (23%) in SSA group and 11 patients (27%) in best supportive group. Patients with reduced PRRT activities were considered to have completed PRRT if they received the planned number of administrations.

The radiopharmaceuticals were administered via indwelling catheter over a maximum of 30 minutes. Before each radiopeptide infusion, patients received a commercially available nephroprotective amino acid infusion (Aminsteril N-Hepa, Fresenius Kabi, Bad Homburg, Germany). After the treatment patients were hospitalised for 48 hours.

Somatostatin Analogue Treatment And Follow-up

In the treated (“SSA”) group, octreotide acetate LAR injection (Sandostatin LAR, Novartis, Basel, Switzerland), 30 mg, was administered subcutaneously every 4 weeks, until the first of intolerable toxicity, patient refusal or disease progression. There was no SSA treatment in the best supportive care group unless disease progression.

For patients in both study groups, physical examination was performed every 4–6 months. Radiological examination and chromogranin A was performed every 4–6 months for the first 2 years after randomisation and every 6–12 months thereafter. Following disease progression, the start of any new therapy was left to discretion of the treating physician and patient. To monitor safety, biochemical evaluation of bone marrow, liver, and kidney, function was performed at least yearly.

Statistics

No formal sample size calculation was performed. Continuous variables are reported as means and standard deviation or medians (minimum–maximum). Two-group comparisons were calculated with Student’s t-test or the Wilcoxon-Mann-Whitney test, whereas comparisons among > 2 groups were evaluated with analysis of variance or the Kruskal-Wallis test, respectively, in the cases of data that were normally-distributed or non-normally-distributed, as per the Shapiro-Wilk test. Categorical variables are reported as counts (percentages) or vice versa, and between-group differences in categorical variables were calculated using the χ^2 test.

OS and PFS were analysed using the Kaplan-Meier method and log-rank test. Since we in essence were evaluating combined (sequential) PRRT/SSA therapy, the first PRRT administration was used as the starting point to calculate these outcomes. Specifically, PFS was defined as the interval from the first PRRT administration to the date that radiological progression was first documented or if no progression to death. OS was defined as the interval from that administration to the date of death, or, absent mortality, the last date of follow-up through 31/12/2020. The Statistics Poland registry (<https://stat.gov.pl/en/>) was consulted to confirm dates of death.

For each study outcome (PFS and OS), Cox proportional hazards regression was utilised to find potential predictive factors, including SSA treatment or no SSA treatment after PRRT. For the respective endpoint, factors with $p \leq 0.30$ in univariate analysis were included in the multivariate Cox proportional hazards model. HRs and their 95% CIs are presented.

P values < 0.05 were considered to be statistically significant. All analyses were performed with SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Somatostatin analogue administration

No patient terminated SSA treatment due to toxicity or personal preference in the absence of PD. There were no serious side effects related the SSA but 6 (5.2%) patients had renal toxicity and required haemodialysis 2 (1.7%) myelodysplastic syndrome and 2 (1.7%) acute leukaemia but they were related to PRRT or chemotherapy treatment rather than to SSA therapy.

Progression-free survival and overall survival

The median (95% CI) time from the first PRRT administration to the first documented NEN progression or death, was respectively, 4.7 (2.8-7.8) years and 6.4 (4.1-not reach) years in SSA and control and did not differ statistically between the study groups ($p = 0.13$). (Figure 1A). Altogether, 71/115 patients (62%) progressed, 52/74 (70%) in the SSA group and 19/41 (46%) in the best supportive care group ($p = 0.01$).

Median (25th-75th percentile) duration from the first PRRT activity to death or the last observation, i.e., OS, was 6.6 (3.18-10.22) years for the overall study sample, and also did not differ between the study groups (Figure 1B, $p = 0.99$). Eighty-eight (76%) patients died, 58/74 (78%) in the SSA group, 30/41 (73%) in the best supportive care group ($p = 0.52$). Twenty seven patients died without radiological progression and 6 (22.2%) withdraw from the study.

Univariable analysis

Table 2 reveals the results of the univariate analyses regarding PFS and OS. Variables with significant HRs >1 were associated with worse outcomes, while those with significant HRs <1 were associated with better outcomes.

Table 2 Univariate analyses of potential factors associated with each of PFS and OS

Factor	PFS	<i>p</i>	O	OS	<i>p</i>
	HR (95% CI)		HR (95% CI)		
Sex (male vs female)	1.28 (0.78–2.06)	0.26	0.91 (0.59–1.38)		0.66
Age at diagnosis (per year)	1.00 (0.97–1.01)	0.22	1.02 (1.00–1.03)		0.01
Time from diagnosis to PRRT (per year)	1.01 (0.96–1.07)	0.89	0.99 (0.94–1.04)		0.81
Age at PRRT (per year)	0.99 (0.97–1.01)	0.20	1.03 (1.01–1.04)		0.02
Differentiation (G2 vs. G1)	1.48 (0.92–2.36)	0.09	1.58 (1.03–2.40)		0.03
Primary tumour site ^a					
Lung	1.81 (0.86–3.81)	0.11	1.80 (0.90–3.50)		0.08
Small intestine	0.55 (0.32–0.91)	0.02	0.74 (0.40–1.10)		0.16
Large intestine	1.65 (0.86–3.17)	0.13	1.16 (0.60–2.20)		0.64
Other	1.65 (0.51–5.30)	0.39	3.76 (1.70–8.40)		0.002
Unknown	0.79 (0.43–1.46)	0.46	0.55 (0.29–1.01)		0.05
Site of distant involvement (liver only vs other)	2.07 (1.27–3.37)	0.004	1.50 (1.00–2.30)		0.08
Number of PRRT cycles (4 vs. 5)	1.02 (0.63–1.66)	0.92	0.83 (0.50–1.30)		0.38
SSA therapy after PRRT (no vs. yes)			1.00 (0.1.		
	1.50 (0.88–2.54)	0.13	1.0 (0.6	1.00 (0.64–1.56)	0.98

HR (95% CI) and *p* values for factors with *p* < 0.05 are given in bold type.

CI confidence interval, G1 grade 1, G2 grade 2, HR hazard ratio, OS overall survival PFS progression-free survival, PRRT peptide receptor radionuclide therapy

^a Each of the listed primary tumour sites was compared against all other sites combined

In the univariate analysis, there was no association with PFS of SSA treatment versus best supportive care after disease control by PRRT. Patients with primary tumour located in the small intestine had significantly better prognosis compared to other patients; prognosis was significantly worse in those with multiorgan involvement (liver and ≥1 other site). Other factors, namely sex, ages at diagnosis or at the first PRRT administration, degree of tumour differentiation, or number of PRRT cycles (4 vs. 5) were not significantly associated with PFS.

As additionally seen in Table 2, presence or absence of SSA treatment following PRRT also lacked association with OS; the only studied factors significantly associated with this outcome were older age at NEN diagnosis, grade 2 versus grade 1 tumour differentiation, and primary tumour not in the intestines or lungs, all of which were negative prognostic factors.

Multivariate analysis

Table 3 displays factors found in multivariate analysis to have significant independent relationships with the study endpoints. As in the univariate analysis, significant HRs >1 or <1 denoted negative or positive prognostic factors, respectively.

Table 3 Multivariate analysis: factors independently associated with each of PFS and OS

Factor	PFS HR (95% CI)	<i>p</i>	OS HR (95% CI)	<i>p</i>
Primary tumour in lung vs. other site	2.00 (1.01–3.80)	0.045	2.60 (1.30–5.20)	0.020
Distant involvement of >1 organ	2.10 (1.30–3.50)	0.002	1.60 (1.02–2.40)	0.048
Age at PRRT (per year)	NS		1.02 (1.01–1.04)	0.007

HRs >1 indicate worse prognosis, while those <1 equal better prognosis

CI confidence interval, *HR* hazard ratio, *NEN* neuroendocrine neoplasm(s), *NS* not significantly associated with outcome, *OS* overall survival, *PFS* progression-free survival

As seen in Table 3, only primary tumour in the lung and metastatic involvement of more than two organs were independently associated with PFS, foretelling a negative outcome. Only these factors as well as older age at the first PRRT administration had independent associations with OS, also presaging a negative outcome. Presence or absence of SSA after disease control by PRRT had no relationship with either study outcome.

Discussion

Since the introduction of biotherapy with SSAs and PRRT, different approaches and strategies have been explored in order to optimize effectiveness of each modality. In the case of PPRT, these strategies have included improving tumour perfusion to allow better distribution of the radiopharmaceutical [19], combining the modality with DNA-damaging drugs [20–22], and radiosensitisation through inhibiting essential processes such as DNA damage repair [23, 24].

Another potential approach to increase effectiveness of PRRT is combining the modality with SSA treatment. Indeed, how to do so has been a “hot question” in the management of NEN. SSAs act as cytostatic agents, whilst PRRT is cytotoxic and active in dividing cells [25]. In favour of combining SSAs and PRRT are biodistribution studies in which prior SSA administration seems to produce a better image contrast between target lesion and normal tissues, i.e., to increase tumour uptake whilst decreasing uptake in healthy tissues [26]. However, to reduce potential mutual interference of these two SSR-targeted therapies, the joint European Association of Nuclear Medicine/Society of Nuclear Medicine and Molecular Imaging/International Atomic Energy Agency PRRT procedure guidelines recommend a 4-week interval between SSA and PRRT administrations [27].

The primary goal of the present study was to evaluate effectiveness of biotherapy with SSAs after disease control by PRRT, defined as SD, PR, or CR. According to our clinical experience, SSA therapy seemed to be safe and well-tolerated in our patients after PRRT. However, in our study we did not demonstrate any significant differences in the two study endpoints, PFS or OS, between patients receiving such treatment versus those given only best supportive care.

To our knowledge, no published studies have investigated molecular interaction in sequential PRRT and SSA therapy. In the clinical setting, a significant decrease in SSR expression has been observed after PRRT [28]. Also, recent data from a mouse model demonstrated a strong reduction in the number of NEN cells expressing high levels of SSR type 2 on days 5 and 11 after a single ¹⁷⁷Lu-DOTATATE administration. Whether this finding remains true in the longer run is to be determined. However, if so, this observation could at least theoretically explain decreased activity of SSAs post-PRRT, in the form of diminished anti-proliferative effects [29].

Evidence from some retrospective studies suggests that combination of PRRT plus SSA maintenance therapy provides a survival benefit compared to PRRT alone [30, 31]. In their analysis of patients with well-differentiated NEN, Yordanova et al. [31] demonstrated that this form of combination therapy was associated with increased median OS, i.e., 91 months compared to 47 months in patients not given such maintenance treatment ($p < 0.0001$). The PFS was respectively 48 and 27 months ($p=0.012$). In univariate analysis, these investigators observed such benefit across all studied subgroups, irrespective of Ki 67 proliferation index if below 20%, of tumour burden, or of tumour functionality. Even more interesting, the differences were more pronounced regarding OS than PFS.

In our prospective study, we randomised patients with disease control after PRRT either to SSA or best supportive care. In contrast to Yordanova, we did not note any intergroup differences regarding PFS or OS. Here, we must stress that apart from presence or absence of randomisation, our studies differed in patient population. At the time our trial was initiated, SSAs already had become the main component of treatment of carcinoid syndrome. Therefore, we excluded patients suffering from this syndrome from this study. However, in Yordanova et al's retrospective evaluation, nearly 60% of patients, almost equally distributed between the two treatment groups, had functioning carcinoid tumours. This study sample characteristic could have worsened results in these investigators' observation group, in which patients with carcinoid syndrome had no symptomatic treatment. It is well-established that SSA treatment increases both quality-of-life and survival in patients with symptomatic carcinoid syndrome [32, 33].

On the other hand, our study, unlike that of Yordanova et al, enrolled patients with well-differentiated NEN that was heterogeneous in origin, including, apart from GEP-NEN, 16% of patients with primary tumours in the lung or other non-gastrointestinal sites, and 19% with unknown primary tumour sites. When our study started, the role of SSAs in NENs was less well-understood than is now the case. Thus patients with good SSR expression were included, irrespective of primary tumour origin. However, presently, strong evidence of beneficial effects of SSAs exists mainly in GEP-NEN; indeed, in prospective, randomised studies, the best results in anti-proliferative treatment with SSAs have been achieved in that setting [10, 34]. By contrast, for other NEN primary tumour sites, only retrospective observational data have been published, which suggest less benefit of SSAs [35, 36] [37, 38]. Interestingly, findings of our univariate analysis align with these observations: in that analysis, the best prognosis after PRRT appeared to be in patients with primary tumour in the small intestine, and the worst, in those with primary tumour in lung.

Major strengths of our study were its prospective, randomised controlled nature, and its long observation period that allowed meaningful calculation of both PFS and OS. However, the trial started almost two decades ago, and had related limitations beyond including patients with well-differentiated NEN originating from various sites. Among these was exclusion of patients with PD after PRRT. Many untreated patients with nonresectable NEN can have SD for many years. Thus PRRT currently is second-line therapy indicated after disease progression, while first-line therapy in most cases consists of SSAs [39, 40]. Further, since pathological evaluation mostly took place before 2010, the Ki67 proliferation index was not assessed in many patients. Therefore grade of differentiation, but not Ki 67 value, was included in our univariate analyses. This variable was non-significant in our multivariate analyses of PFS and OS.

However, we cannot exclude that in patients with low Ki 67, sequential PRRT and SSA therapy could have had an additive effect, as was seen in the PROMID and CLARINET studies [10, 11]. Of note is the fact that there were also patients who died without radiological progression. These were elderly patients with comorbidities.

Given our study's inclusion of patients with primary tumours of non-GEP origin, its exclusion of those with PD after PRRT, its limited Ki 67 testing, as well as its single-center nature, our results regarding the apparent absence of survival benefits of SSA maintenance therapy post-PRRT must be regarded as suggestive rather than definitive.

In summary, in this prospective, randomised controlled study in patients with disease control by PRRT, we did not demonstrate that sequential therapy with that modality followed by SSAs resulted in better PFS or OS than was noted in patients not receiving SSAs. Since the start of our study, indications for initiation of PRRT and SSA therapy have changed, so that PRRT now is usually given after progression on SSAs. To continue or stop SSAs after disease progression remains an open question. In our opinion, results of the present study underline the urgent need to further evaluate the role of SSAs after PRRT.

Declarations

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Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study protocol was approved by the institutional Ethical Committee.

References

1. Reubi JC. Peptide receptor expression in GEP-NET [eng]. *Virchows Arch.* 2007; doi:10.1007/s00428-007-0443-2.
2. Ahlman H, Wängberg B, Nilsson O, Grimelius L, Granérus G, Modlin IM, et al. Aspects on diagnosis and treatment of the foregut carcinoid syndrome [eng]. *Scand J Gastroenterol.* 1992; doi:10.3109/00365529209000106.

3. Oberg K, Ferone D, Kaltsas G, Knigge U-P, Taal B, Plöckinger U. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biotherapy [eng]. *Neuroendocrinology*. 2009; doi:10.1159/000183751.
4. Schally AV. Oncological applications of somatostatin analogues [eng]. *Cancer Res*. 1988;48(24 Pt 1):6977–85.
5. Patel YC, Greenwood MT, Panetta R, Demchyshyn L, Niznik H, Srikant CB. The somatostatin receptor family [eng]. *Life Sci*. 1995; doi:10.1016/0024-3205(95)02082-t.
6. Delaunoit T, Rubin J, Neczyporenko F, Erlichman C, Hobday TJ. Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine tumors [eng]. *Mayo Clin Proc*. 2005; doi:10.4065/80.4.502.
7. Eriksson B, Skogseid B, Lundqvist G, Wide L, Wilander E, Oberg K. Medical treatment and long-term survival in a prospective study of 84 patients with endocrine pancreatic tumors [eng]. *Cancer*. 1990; doi:10.1002/1097-0142(19900501)65:9<1883::aid-cncr2820650902>3.0.co;2-3.
8. Aparicio T, Ducreux M, Baudin E, Sabourin JC, Baere T de, Mitry E, et al. Antitumour activity of somatostatin analogues in progressive metastatic neuroendocrine tumours [eng]. *Eur J Cancer*. 2001; doi:10.1016/s0959-8049(01)00073-9.
9. Hejna M, Schmidinger M, Raderer M. The clinical role of somatostatin analogues as antineoplastic agents: much ado about nothing? *Ann Oncol*. 2002; doi:10.1093/annonc/mdf142.
10. Rinke A, Müller H-H, Schade-Brittinger C, Klose K-J, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group [eng]. *J Clin Oncol*. 2009; doi:10.1200/JCO.2009.22.8510.
11. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors [eng]. *N Engl J Med*. 2014; doi:10.1056/NEJMoa1316158.
12. Jong M de, Valkema R, Jamar F, Kvols LK, Kwekkeboom DJ, Breeman WAP, et al. Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings [eng]. *Semin Nucl Med*. 2002; doi:10.1053/snuc.2002.31027.
13. Krenning EP, Kooij PP, Bakker WH, Breeman WA, Postema PT, Kwekkeboom DJ, et al. Radiotherapy with a radiolabeled somatostatin analogue, 111In-DTPA-D-Phe1-octreotide. A case history [eng]. *Ann N Y Acad Sci*. 1994; doi:10.1111/j.1749-6632.1994.tb17300.x.
14. Paganelli G, Bodei L, Handkiewicz Junak D, Rocca P, Papi S, Lopera Sierra M, et al. 90Y-DOTA-D-Phe1-Tyr3-octreotide in therapy of neuroendocrine malignancies [eng]. *Biopolymers*. 2002; doi:10.1002/bip.10349.
15. Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al. Phase 3 Trial of (177)Lu-Dotatate for Midgut Neuroendocrine Tumors [eng]. *N Engl J Med*. 2017; doi:10.1056/NEJMoa1607427.
16. Strosberg JR, Caplin ME, Kunz PL, Ruszniewski PB, Bodei L, Hendifar AE, et al. Final overall survival in the phase 3 NETTER-1 study of lutetium-177-DOTATATE in patients with midgut neuroendocrine

- tumors. *J Clin Oncol*. 2021; doi:10.1200/JCO.2021.39.15_suppl.4112.
17. Jong M de, Valkema R, Jamar F, Kvols LK, Kwekkeboom DJ, Breeman WAP, et al. Somatostatin receptor-targeted radionuclide therapy of tumors: preclinical and clinical findings [eng]. *Semin Nucl Med*. 2002; doi:10.1053/snuc.2002.31027.
 18. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009; doi:10.1016/j.ejca.2008.10.026.
 19. Bison SM, Haeck JC, Bol K, Koelewijn SJ, Groen HC, Melis M, et al. Optimization of combined temozolomide and peptide receptor radionuclide therapy (PRRT) in mice after multimodality molecular imaging studies [eng]. *EJNMMI Res*. 2015; doi:10.1186/s13550-015-0142-y.
 20. Claringbold PG, Brayshaw PA, Price RA, Turner JH. Phase II study of radiopeptide 177Lu-octreotate and capecitabine therapy of progressive disseminated neuroendocrine tumours [eng]. *Eur J Nucl Med Mol Imaging*. 2011; doi:10.1007/s00259-010-1631-x.
 21. Claringbold PG, Price RA, Turner JH. Phase I-II study of radiopeptide 177Lu-octreotate in combination with capecitabine and temozolomide in advanced low-grade neuroendocrine tumors [eng]. *Cancer Biother Radiopharm*. 2012; doi:10.1089/cbr.2012.1276.
 22. Yordanova A, Ahrens H, Feldmann G, Brossart P, Gaertner FC, Fottner C, et al. Peptide Receptor Radionuclide Therapy Combined With Chemotherapy in Patients With Neuroendocrine Tumors [eng]. *Clin Nucl Med*. 2019; doi:10.1097/RLU.0000000000002532.
 23. Purohit NK, Shah RG, Adant S, Hoepfner M, Shah GM, Beauregard J-M. Potentiation of (177)Lu-octreotate peptide receptor radionuclide therapy of human neuroendocrine tumor cells by PARP inhibitor [eng]. *Oncotarget*. 2018; doi:10.18632/oncotarget.25266.
 24. Cullinane C, Waldeck K, Kirby L, Rogers BE, Eu P, Tothill RW, et al. Enhancing the anti-tumour activity of (177)Lu-DOTA-octreotate radionuclide therapy in somatostatin receptor-2 expressing tumour models by targeting PARP [eng]. *Sci Rep*. 2020; doi:10.1038/s41598-020-67199-9.
 25. Bodei L, Schöder H, Baum RP, Herrmann K, Strosberg J, Caplin M, et al. Molecular profiling of neuroendocrine tumours to predict response and toxicity to peptide receptor radionuclide therapy [eng]. *Lancet Oncol*. 2020; doi:10.1016/S1470-2045(20)30323-5.
 26. Aalbersberg EA, de Wit-van der Veen, B J, Versleijen MWJ, Saveur LJ, Valk GD, Tesselaar MET, et al. Influence of lanreotide on uptake of (68)Ga-DOTATATE in patients with neuroendocrine tumours: a prospective intra-patient evaluation [eng]. *Eur J Nucl Med Mol Imaging*. 2019; doi:10.1007/s00259-018-4117-x.
 27. Bodei L, Mueller-Brand J, Baum RP, Pavel ME, Hörsch D, O'Dorisio MS, et al. The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours [eng]. *Eur J Nucl Med Mol Imaging*. 2013; doi:10.1007/s00259-012-2330-6.
 28. Oh S, Prasad V, Lee DS, Baum RP, Chen X. Effect of Peptide Receptor Radionuclide Therapy on Somatostatin Receptor Status and Glucose Metabolism in Neuroendocrine Tumors: Intraindividual

- Comparison of Ga-68 DOTANOC PET/CT and F-18 FDG PET/CT. *International Journal of Molecular Imaging*. 2011; doi:10.1155/2011/524130.
29. Feijtel D, Doeswijk GN, Verkaik NS, Haeck JC, Chicco D, Angotti C, et al. Inter and intra-tumor somatostatin receptor 2 heterogeneity influences peptide receptor radionuclide therapy response [eng]. *Theranostics*. 2021; doi:10.7150/thno.51215.
 30. Sowa-Staszczak A, Stefanska A, Chrapczynski P, Trofimiuk-Müldner M, Szura M, Hubalewska-Dydejczyk A. Does combination of "cold" and "hot" somatostatin analogs prolong survival of patients with neuroendocrine neoplasms? [eng]. *Endocr J*. 2017; doi:10.1507/endocrj.EJ16-0219.
 31. Yordanova A, Wicharz MM, Mayer K, Brossart P, Gonzalez-Carmona MA, Strassburg CP, et al. The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy [eng]. *Clin Cancer Res*. 2018; doi:10.1158/1078-0432.CCR-18-0947.
 32. Kvols LK, Reubi JC. Metastatic Carcinoid Tumors and the Malignant Carcinoid Syndrome. *Acta Oncologica*. 1993; doi:10.3109/02841869309083912.
 33. Ruszniewski P, Ducreux M, Chayvialle JA, Blumberg J, Cloarec D, Michel H, et al. Treatment of the carcinoid syndrome with the longacting somatostatin analogue lanreotide: a prospective study in 39 patients. *Gut*. 1996; doi:10.1136/gut.39.2.279.
 34. Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study [eng]. *Endocr Relat Cancer*. 2016; doi:10.1530/ERC-15-0490.
 35. Sullivan I, Le Teuff G, Guigay J, Caramella C, Berdelou A, Leboulleux S, et al. Antitumour activity of somatostatin analogues in sporadic, progressive, metastatic pulmonary carcinoids [eng]. *Eur J Cancer*. 2017; doi:10.1016/j.ejca.2016.11.034.
 36. Lenotti E, Alberti A, Spada F, Amoroso V, Maisonneuve P, Grisanti S, et al. Outcome of Patients With Metastatic Lung Neuroendocrine Tumors Submitted to First Line Monotherapy With Somatostatin Analogs [eng]. *Front Endocrinol (Lausanne)*. 2021; doi:10.3389/fendo.2021.669484.
 37. Kulke MH, Ruszniewski P, van Cutsem E, Lombard-Bohas C, Valle JW, Herder WW de, et al. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial [eng]. *Ann Oncol*. 2017; doi:10.1093/annonc/mdx078.
 38. Ferolla P, Brizzi MP, Meyer T, Mansoor W, Mazieres J, Do Cao C, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial [eng]. *Lancet Oncol*. 2017; doi:10.1016/S1470-2045(17)30681-2.
 39. Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site [eng]. *Neuroendocrinology*. 2016; doi:10.1159/000443167.

40. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up [eng]. Ann Oncol. 2020; doi:10.1016/j.annonc.2020.03.304.

Figures

Figure 1

PFS (Panel A) and OS (Panel B) by treatment group. After a median (95% CI) follow-up of 6.6 (0.7–16.1) years, median (95% CI) PFS was 4.7 (2.8–7.7) years for the SSA group and 6.4 (4.1–not reached) years for the best supportive care group ($p = 0.129$). Corresponding values for OS were 4.9 (2.7–7.9) years for the SSA group and 4.2 (2.6–6.8) years for the best supportive care group ($p = 0.98$).

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