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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Abstract

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

Methods This prospective, randomised, single-centre study had as principal eligibility criteria: unresectable, locally advanced, or metastatic, histologically confirmed well-differentiated NEN; no symptoms/biochemical diagnosis of carcinoid syndrome; no SSAs or ≤3 months of SSAs before PRRT; and stable disease or partial or 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 a control group (n = 41) receiving only best supportive care. Octreotide treatment was to stop upon intolerable toxicity or patient refusal, or, at physician/patient discretion, upon NEN progression. The primary endpoint was progression-free survival (PFS), the secondary endpoint, and overall survival (OS).

Results 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, and 19/41 (46%) in the control group (p = 0.01). Eighty-eight/115 patients (76%) died, 58/74 (78%) in the SSA group, and 30/41 (73%) in the control group (p = 0.52). Median (95% CI) PFS was 4.7 (2.8–7.7) years in the SSA group, and 6.4 (4.1–not reached) years in controls. Overall, median OS was 6.6 years. 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 SSA administration upon progression after PRRT requires evaluation in a prospective, randomised, controlled multicentre study with a relatively homogeneous sample.

Keywords Neuroendocrine malignancies · Peptide receptor radionuclide therapy · Somatostatin analogues · Sequential treatment · Survival
Introduction

Somatostatin receptors (SSRs), particularly type 2 receptors, typically are over-expressed in neuroendocrine neoplasm(s) (NEN) [1]. The introduction of SSR-targeted treatment in the form 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 1990s (N= 84), in which 28% of treated patients (4/14) had partial remission [7]. The literature suggested that SSA antitumoral effects were restricted mainly to slow-growing tumours [8], and were unclear in malignancies other than NEN [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 NEN [10], and more recently, a study was published regarding lanreotide auto-gel therapy of enteropancreatic NEN [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 (177Lu) or yttrium 90 (90Y). Hence, as internal radiotherapy, and in contrast to SSA pharmacotherapy, PRRT exerts cytotoxic effects at 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 177Lu-labelled 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 [12, 14] 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 to November 2012. As summarised in Supplementary Table S1, the inclusion criteria were unresectable, locally advanced, or metastatic, histologically confirmed well-differentiated NEN (grades 1–2); no symptoms or biochemical diagnosis of carcinoid syndrome; age ≥ 18 years; World Health Organisation performance status 0–2; Common Terminology Criteria for Adverse Events bone marrow and liver toxicity grade ≤ 2 at randomisation; 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 symptoms or biochemical diagnosis of carcinoid syndrome, had malignancy other than NEN at randomisation, had not completed PRRT, had progressed after PRRT, or if they did not provide informed consent to participate.

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, initially version 1.0 and from 2009, version 1.1 (based on computed tomography [CT]/magnetic resonance imaging) [17].

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 alone (“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 sufficiently 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); the study sample included 1 patient who had progressed after PRRT and was mistakenly enrolled into the trial.

Seventy-four patients were randomised to SSA treatment after PRRT, and 41 to best supportive care alone. 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).

Peptide receptor radionuclide therapy

PRRT was routinely administered to patients with well-differentiated NEN with sufficient SSR expression, as confirmed with SSA receptor imaging performed ≤3 months before PRRT. Octreotide, tectotride, or gallium 68-DOTATATE were used, depending on availability. 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 were considered to be adequate for PRRT. Well-preserved bone marrow function (haemoglobin ≥10 g/dL, white blood cell count ≥3 × 10^9/L, platelet count ≥90 × 10^9/L), liver function (bilirubin ≤1.5 × upper limit of normal [ULN], alanine aminotransferase <2.5 × 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%) were given 4 cycles each of 2.96 GBq 90Y-DOTATATE (Polatom, Otwock, Poland) every 6–12 weeks. From 2007 as part of a separate study, an additional single “boost” of 7.4 GBq 177Lu-DOTATATE (Polatom) was given 6–8 weeks after the last 90Y-DOTATATE administration. Toxicity was the only grounds for reduction in the planned PRRT regimen, which occurred in 17 patients (23%) in the SSA group and in 11 patients (27%) in the best supportive care 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 min. Before each radiopeptide infusion, patients received a commercially available nephroprotective amino acid infusion (Aminosteril N-Hepa, Fresenius Kabi, Bad Homburg, Germany). After the treatment, patients were hospitalised for 48 h.

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 progressed.

For patients in both study groups, physical examination was performed every 4–6 months. Radiological examination and chromogranin A (CgA) testing were 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 the 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 χ² 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 there was no progression, until death or last observation through 31/12/2020. OS was defined as the interval from the first PRRT administration to the date of death, or, absent mortality, until 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 hazard regression was utilised to find potential predictive factors, including SSA treatment or no SSA treatment after PRRT. For the respective endpoint, factors with p ≤ 0.30 in univariate analysis were included in the multivariate
| Characteristic                                                                 | SSA group (%) | Observation group (%) | p value ($\chi^2$) |
|-------------------------------------------------------------------------------|---------------|-----------------------|-------------------|
| Sex                                                                           |               |                       |                   |
| Male                                                                          | 57% (42)      | 78.0% (32)            | 0.40              |
| Age at NEN diagnosis, years                                                  |               |                       |                   |
| Median (range)                                                               | 55 (50–64)    | 55 (45–61)            | 0.53              |
| <45                                                                           | 24% (18)      | 17.1% (7)             | 0.49              |
| 45–65                                                                         | 61% (45)      | 61% (25)              |                   |
| >65                                                                           | 15% (11)      | 22% (9)               |                   |
| Time from NEN 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% (40)      | 56% (23)              | 0.80              |
| G2                                                                            | 46% (34)      | 44% (18)              |                   |
| Primary tumour site                                                           |               |                       |                   |
| Any GEP                                                                       | 68% (50)      | 63% (26)              | 0.80              |
| Pancreas                                                                      | 19% (14)      | 15% (6)               |                   |
| Small intestine                                                              | 39% (29)      | 32% (13)              |                   |
| Large intestine                                                              | 10% (7)       | 10% (7)               |                   |
| Lungs                                                                         | 8% (6)        | 12% (5)               |                   |
| Other                                                                         | 5% (4)        | 7% (3)                |                   |
| Unknown                                                                       | 19% (14)      | 20% (8)               |                   |
| Disseminated disease at diagnosis                                            |               |                       |                   |
| Present                                                                       | 72% (53)      | 66% (27)              | 0.50              |
| Site(s) of dissemination at diagnosis                                         |               |                       |                   |
| Locoregional only                                                            | 28% (21)      | 37% (15)              | 0.70              |
| Liver only                                                                    | 27% (20)      | 24% (10)              |                   |
| Bones only                                                                    | 3% (2)        | 2% (1)                |                   |
| >2 sites                                                                      | 27% (20)      | 29% (12)              |                   |
| Ratio of CgA value to upper limit of normal, median (25th–75th percentile)   |               |                       |                   |
| At 1st cycle of PRRT                                                        | 2.9 (1.1–11.3)| 2.3 (1.2–7.4)         | 1.0               |
| At last cycle of PRRT                                                        | 2.2 (1.0–8.8) | 2.0 (1.1–5.2)         | 1.0               |
| Other therapies before PRRT                                                   |               |                       |                   |
| No treatment                                                                  | 65% (48)      | 83% (34)              | 0.16              |
| SSA treatment (for ≤3 months)*                                                | 12% (9)       | 4% (2)                |                   |
| Chemotherapy                                                                  | 20% (15)      | 10% (4)               |                   |
| 131I-MIBG therapy                                                            | 3% (2)        | 2% (1)                |                   |
| PRRT regimen                                                                  |               |                       |                   |
| 4×90Y-DOTATATE                                                                | 43% (32)      | 27% (11)              | 0.08              |
| 4×90Y-DOTATATE+1×177Lu-DOTATATE                                               | 57% (42)      | 73% (30)              |                   |
| Response to PRRT                                                             |               |                       |                   |
| Partial remission                                                            | 20% (15)      | 20% (8)               | 0.70              |
| Stable disease                                                                | 78% (58)      | 81% (33)              |                   |
| Progression                                                                   | 1% (1)        | 0% (0)                |                   |

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

90Y 90 yttrium, 131I-MIBG, 131-iodine meta-iodobenzylguanidine, 177Lu 177 lutetium, CgA chromogranin A, G1 grade 1, G2 grade 2, NEN neuroendocrine neoplasm(s), PRRT peptide receptor radionuclide therapy

*Per inclusion criteria, no patient given >3 months of SSA therapy before PRRT could be included in the study
Cox proportional hazard model. HR and their 95% CI are presented.

Due to non-normal distribution, changes in time of the chromogranin concentration were analysed with the use of nonparametric methods proposed for factorial designs with repeated measures.

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**

**Progression-free survival and overall survival**

The median (95% CI) time from the first PRRT administration to the first documentation of NEN progression or, if progression was absent, to death or last observation, was 4.7 (2.8–7.8) years in the SSA group and 6.4 (4.1–not reached) in controls. PFS did not differ

![Graph A](image1.png)

**Fig. 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)

| SSA (n) | 74 | 34 | 21 | 16 | 8 | 6 | 2 |
|---------|----|----|----|----|---|---|---|
| no SSA (n) | 41 | 54 | 37 | 27 | 21 | 14 | 6 |

![Graph B](image2.png)
statistically between these groups \((p = 0.13)\) (Fig. 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 to 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 (Fig. 1B, \(p = 0.99\)). Altogether, 88 patients (76\%) died, 58/74 (78\%) in the SSA group, and 30/41 (73\%) in the best supportive care group \((p = 0.52)\). Twenty-seven patients died without radiological progression and 6 (22\%) withdrew from the study, with their vital status confirmed via the Statistics Poland registry as alive at latest follow-up.

### Univariate analysis

Table 2 reveals the results of univariate analyses regarding association of individual potential predictive factors with PFS or OS. Variables with significant \(HR > 1\) were associated with worse outcomes (progression or death, respectively), whilst those with significant \(HR < 1\) were associated with better outcomes.

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 patients with other primary site localization; prognosis was significantly worse in those with multiorgan involvement (liver and \(\geq 1\) other site) than in those with only monofocal dissemination of the tumour. 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 \(HR > 1\) or \(< 1\) denoted negative or positive prognostic factors, respectively.

As seen in Table 3, only primary tumour in the lung and metastatic involvement of more than two organs were independently associated with PFS, both 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

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

| Factor                              | PFS HR (95\% CI) | \(p\)   | OS HR (95\% CI) | \(p\)   |
|-------------------------------------|------------------|--------|----------------|--------|
| 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** | 10.74 (0.40–1.10) | 0.16   |
| Large intestine                     | 1.65 (0.86–3.17) | 0.13   | 11.16 (0.60–2.20) | 0.64   |
| Other                               | 1.65 (0.51–5.30) | 0.39   | **3.76 (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   |
| Chemotherapy or 131I-MIBG before PRRT | 6.57 (1.96–9.75) | 0.73   | 6.18 (1.95–9.82) | 0.32   |
| 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) | 1.50 (0.88–2.54) | 0.13   | 1.00 (0.64–1.56) | 0.98   |

\(HR > 1\) indicate worse prognosis, while those \(< 1\) equal better prognosis

\(p\) values for factors with \(p < 0.05\) are given in bold type

131I-MIBG, 131-iodine meta-iodobenzylguanidine, 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
SSAs after disease control by PRRT had no relationship with either study outcome.

**Chromogranin A response to PRRT and somatostatin analogues**

Since the methods used to quantify CgA and normal values for this analyte changed during the study period, the ratio of measured CgA values to the upper limit of normal values (ULN) was studied. The ratio of the measured CgA value to the ULN value did not differ between the SSA and best supportive care groups at either the first or last PRRT administrations (Table 1). The CgA concentration at the last PRRT activity had no associations with PFS or OS (Table 2). However, there was a statistically significant interaction between randomisation and relative CgA concentration (p < 0.001); i.e. the relative value of CgA changed over time, but differently in the SSA group and the best supportive care group (Fig. 2).

**Toxicity of SSA treatment and PRRT**

No patient terminated SSA treatment for reasons unrelated to PD, i.e. due to toxicity or personal preference. No serious side effects were noted that were considered to be related to SSAs, but 10 patients (9%) developed late serious side effects that were judged to be most probably related to PRRT. In 6 patients (5%), renal toxicity requiring haemodialysis was diagnosed during PRRT. Two patients (2%) suffered from myelodysplastic syndrome (in both cases, diagnosed 1 year after PRRT and in the absence of previous chemotherapy) and 2 (2%) developed acute leukaemia (diagnosed 8 years and 5 years after the end of PRRT). One of the patients with acute leukaemia had been treated with platinum-based chemotherapy 10 years before leukaemia diagnosis; the other patient had no history of chemotherapy.

### Randomisation:

| Time         | SSA group HR (95% CI) | p    | Best supportive group HR (95% CI) | p    |
|--------------|-----------------------|------|----------------------------------|------|
| 1st PRRT     | 2.9 (1.1-11.3)        | 0.34 | 2.3 (1.2-7.4)                    | 0.19 |
| Last PRRT    | 2.2 (1.0-8.3)         | 0.67 | 2.0 (1.1-5.2)                    | 0.08 |
| 3-6 months after PRRT | 1.2 (0.7-3.4) | 0.60 | 2.5 (1.2-8.6)                    | 0.08 |
| 8-12 months after PRRT | 1.5 (0.9-5.0) | 0.84 | 2.3 (1.3-8.7)                    | 0.08 |
| 22-26 months after PRRT | 1.6 (0.9-5.7) | 0.25 | 3.7 (1.2-14.6)                   | 0.08 |

HR > 1 indicate worse prognosis, whilst 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

**Fig. 2** Changes in CgA concentration (relative value, e.g. x upper limit of normal was calculated due to changes in CgA measurement methods and normal values over the course of the study)
Discussion

Since the introduction of biotherapy with SSAs and PRRT, different approaches and strategies have been explored in order to optimise effectiveness of each modality. In the case of PRRT, these strategies have included improving tumour perfusion to allow better distribution of the radiopharmaceutical [18], combining the modality with DNA-damaging drugs [19–21], and inhibiting essential processes such as DNA damage repair so as to promote radiosensitisation [22, 23].

Another potential approach to increase effectiveness of PRRT is combining the modality with SSA treatment [24]. 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 using SSR PET, 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].

There are also concerns with long-lasting SSA therapy. The first relates to tachyphylaxis—i.e. resistance to therapy developing when patients are treated to control symptoms of hormone overproduction. Second, after lengthy SSA treatment, loss of SSR expression or change in SSR pharmacokinetics can be observed [28], which in turn may result in loss of antiproliferative tumour response to SSA treatment. One can try to overcome these issues using SSA dose escalation; however, literature to date suggests that with this strategy, improvement can be expected only in under 20% of patients [29]. Thus, there is a need for large prospective trials to prove that SSA dose escalation is safe, well-tolerated, and effective [30]. Another way to overcome SSA resistance could be combinations of SSAs and other treatments [31] or introduction of SSAs that are more potent and directed against SSR types beyond type 2 [30]. There are observations that well-differentiated NEN co-express SSR and type 2 dopamine receptor [32], and inhibition of both receptors could be an interesting therapeutic option. In view of the risk of resistance to SSAs, the question of whether to start SSA treatment directly after completion of other, effective treatment or only after tumour progression, is important, since waiting to start SSAs could delay development of SSA resistance.

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 in this trial, 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 endpoints, PFS or OS, between patients receiving SSAs versus those given only best supportive care.

To our knowledge, until recently, no published non-clinical studies have investigated molecular interaction in sequential PRRT and SSA therapy [24]. In the clinical setting, a significant decrease in SSR expression has been observed after PRRT [33]. 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 [34].

Evidence from some retrospective studies suggests that the combination of PRRT plus SSA maintenance therapy provides survival benefits compared to PRRT alone [35, 36]. In their analysis of patients with well-differentiated NEN, Yordanova et al. [36] 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). PFS was respectively 48 and 27 months (p = 0.012). In univariate analysis, these investigators observed benefit of sequential PRRT/SSA therapy regarding both these survival endpoints 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 regarding PFS.

In our prospective study, we randomised patients with disease control after PRRT 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 than apart from use of randomisation, our studies differed in patient population. At the time that 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 our 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 [37, 38].

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 NEN 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, 39]. By contrast, for other NEN primary tumour sites, only retrospective observational data have been published, which suggest less benefit of SSAs [40–43]. 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.

Of several potential clinical prognostic factors evaluated in our study, only a few proved to be statistically significant (Tables 2 and 3). The site of primary tumour was important regarding both PFS and OS, and as alluded to above, NEN in the small intestine has been documented elsewhere to have the best prognosis [44], whilst lower tumour differentiation (G2) is associated with worse OS [45]. On the other hand, previous cytotoxic therapy—chemotherapy or 131-iodine meta-iodobenzylguanidine—had no significant association with survival outcomes in our analysis, yet the number of previously treated patients was small, especially in the best supportive care group. Although it has been claimed in some studies that high CgA concentration may be a negative prognostic factor in patients with NEN [46], that observation was not confirmed in our study. Trends in CgA changes over time suggested that PRRT did not influence CgA concentration, in contrast to what was the case with SSA treatment (Fig. 2). However, CgA may not always be a reliable NEN marker, as about 30–50% of patients with NEN show normal CgA, and a wide range of conditions, both benign and malignant, can generate false-positive results [47]. Thus, circulating NEN transcripts may be more specific and, ultimately, more useful, as a prognostic and predictive factor [48].

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 heterogeneous sites. Among these limitations was exclusion of patients with PD after PRRT. Many untreated patients with unresectable NEN can have SD for many years. Thus, PRRT currently is second-line therapy indicated after disease progression, whilst first-line therapy in most cases consists of SSAs [49, 50]. A further limitation was that, since pathological evaluation mostly took place before 2006, the Ki67 proliferation index was not assessed in many patients. Data on the Ki67 index were unavailable in 49 of our patients (43%), including 11 (22%) who were diagnosed before 2001. This problem was also noticed in other studies, e.g. one of the German Neuroendocrine Tumour registry [51]. Therefore, grade of differentiation, but not Ki 67 value, was included in our univariate analyses. Although significant in those analyses, tumour differentiation was non-significant in our multivariate analyses of PFS and OS. However, given the limited data on Ki 67 in our study sample, 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 in our study who died without radiological progression. These were elderly patients with co-morbidities.

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, and its single-centre 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 NEN who had 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 receiving only best supportive care. 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.

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**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 Ethics Committee.
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