Treatment sequence in patients with neuroendocrine tumours: a nationwide multicentre, observational analysis of the Swiss neuroendocrine tumour registry

Kollár Attila[a], Bütikofer Lukas[b], Ochsenbein Adrian[a], Stettler Christoph[c], Trepp Roman[c]

[a] Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern, Switzerland
[b] CTU Bern, Switzerland
[c] Department for Diabetes, Endocrinology, Nutritional Medicine and Metabolism (UDEM), Inselspital, Bern University Hospital, Switzerland

Correspondence:
Dr Attila Kollár, MD, Department of Medical Oncology, Inselspital, Bern University Hospital, University of Bern,, Lory-Spital, CH-3010 Bern, attila.kollar[at]insel.ch

Summary

BACKGROUND: In recent years, several treatment modalities have proved to be effective in the treatment of neuroendocrine tumours (NETs). However, there is currently no consensus on the sequence in which these options are best used.

METHODS: In this observational study, we analysed the treatment modalities and sequences of all patients included in the Swiss NeuroEndocrine Tumour registry (SwissNET). SwissNET is a national registry, which has prospectively included patients with a NET from all regions of Switzerland since 2008.

RESULTS: The registry includes 1366 patients; 1063 had documented therapies after the main diagnosis and were included in the analysis. The median follow-up time was 1.86 years. The most common primary site was the small intestine (291 patients, 27%) followed by pancreas (254 patients, 24%), lung (172 patients, 16%) and appendix (163 patients, 15%). A total of 167 different therapy sequences were observed. In 708 (67%) patients, surgery was the only treatment. The sequence of surgery followed by chemotherapy was most frequently documented in poorly (G3) differentiated (24 patients, 60%) and pancreatic (15 patients, 34%) NETs. Tumours treated with surgery followed by biotherapy or followed by peptide receptor radionuclide therapy (PRRT) were predominantly well-differentiated G1 NETs of the small intestine. In patients who were treated with either PRRT or systemic therapy (chemotherapy or molecular therapy) or both, PRRT was used more frequently than systemic therapy in patients with a small intestinal NET (35 patients, 62% vs 30, 54%), whereas the opposite held true in pancreatic (44 patients, 59% vs 56, 70%) and lung NETs (6 patients, 14% vs 40, 97%). If both chemotherapy and molecular therapy were used, chemotherapy was applied prior to molecular therapy in 13 of 19 (68%) patients with a pancreatic NET.

CONCLUSION: Surgery represents the treatment of choice in most patients with a NET irrespective of tumour stage. In patients receiving additional treatment, an impressive variety of treatment sequences were documented. In small intestinal NETs, patients received PRRT more often than chemotherapy, whereas the opposite holds true for patients with pancreatic and lung NETs.

Keywords: NET, neuroendocrine tumour, treatment, sequence, chemotherapy, PRRT

Introduction

Neuroendocrine tumours (NETs) represent a rare and highly heterogeneous tumour entity with increasing incidence [1]. Based on population-based registry data, approximately 50% of NETs arise from the gastrointestinal tract, one quarter from the lungs and, in third place, 6% from the pancreas [2]. The incidence rate of pancreatic NETs has significantly increased during the last decade, whereas the incidence rate of lung NETs is reported to be rather stable [3].

Goals of antiproliferative treatment options for patients with locally advanced and metastatic NETs include the reduction of tumour burden, delay of tumour progression, prolongation of life and improvement in quality of life. Current treatment modalities regularly used to achieve these aims consist mainly of surgery, antiproliferative drugs and peptide receptor radionuclide therapy (PRRT). Systemic drug therapy includes somatostatin analogues, cytotoxic drugs (chemotherapy) and targeted treatment options (molecular therapy). Because of the rarity of NET, large randomised, placebo-controlled trials assessing the efficacy of these treatments in the locally advanced, metastatic setting are limited. In the PROMID trial octreotide LAR significantly increased progression-free survival compared with placebo in patients with a metastatic midgut NET, irrespective of functionality [4]. Correspondingly, lanreotide significantly prolonged progression-free survival among patients with a well-differentiated (Ki-67 <10%) metastatic enteropancreatic NET in the ran-

domised, double-blind, placebo-controlled, multinational Clarinet trial [5]. Chemotherapy regimens (streptozocin, 5-fluorouracil, doxorubicin, capecitabine, temozolomide, oxaliplatin) were investigated in retrospective and small prospective phase II trials [6–8]. Sunitinib, an oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitor and everolimus, an inhibitor of mammalian target of rapamycin (mTOR) significantly improve progression-free survival in well-differentiated NETs [9, 10]. In the NET-TER-1 trial treatment with ^{177}Lu-Dotatate resulted in markedly longer progression-free survival and a significantly higher response rate than high-dose octreotide LAR among patients with an advanced midgut NET [11].

Currently, clinical trials addressing the issue of optimal treatment sequencing are limited. For example, the efficacy and safety of PRRT with ^{177}Lu-Edotreotide compared with targeted molecular therapy with everolimus is being studied in a prospective, randomised phase III trial in patients with inoperable NETs of gastroenteric or pancreatic origin (NCT03049189). Outside clinical trials, patient and tumour characteristics as well as treatment goals (disease stabilisation, tumour shrinkage) are taken into consideration to decide on the best treatment strategy. Additionally, physician expertise and regulatory issues with regard to access to novel treatments affect the choice of treatment. Based on those parameters, the ENETS (European Neuroendocrine Tumor Society) published guidelines to facilitate treatment decision [12]. In view of the lack of evidence regarding the optimal treatment sequence to improve patient outcome, assessing the presence of a potential treatment consent in daily clinics is valuable.

Primarily, this research project aims to illuminate the NET treatment sequence used in the clinical setting outside of clinical trials based on a large, national, prospectively conducted registry (SwissNET). Secondly, we assessed the sequence of systemic drug therapy (chemo- and molecular therapy) and PRRT on the one hand and the sequence of chemo- and molecular therapy in respect to the different primary NET sites.

Material and methods

Study design and population
The SwissNET registry is a nationwide prospective database documenting data on patients with NET in Switzerland since 2008. Ethical approval to run the registry was obtained from the lead ethics committee in Bern (Kantonale Ethikkommission Bern; No: 395/2014). Currently, 56 participating hospitals and private practices are providing SwissNET with their patient information. Accrual sites in the SwissNET registry are presented in supplementary figure S1 (appendix 1). All documented patients have signed a written informed consent form, agreed to their medical records being collected within SwissNET and agreed that the pseudonymised data can be used for research purposes. Patients with a NET of the aerodigestive tract with the exclusion of small/large cell neuroendocrine carcinoma of the lung are registered in SwissNET. The current classification is based on the revised World Health Organization (WHO) criteria 2010 for NETs of gastroenteropancreatic origin and the 2004 WHO classification for lung NETs [13]. Medical records are regularly screened and clinical

information, including NET treatment modalities are documented by trained study nurses.

The main outcome was defined by the description of the patients' demographics (age), tumour characteristics (primary site, tumour grade, functionality), all documented treatment modalities and sequence in the main analysis set representing the entire SwissNET cohort (cut-off date 25 July 2017). Treatment modalities were divided into surgery, biotherapy (somatostatin analogues), chemotherapy, molecular therapy (sunitinib, everolimus), PRRT and local ablative therapy (percutaneous radiotherapy, radiofrequency ablation, etc.). Treatment sequencing was based on the date of therapy start. Repeated therapies of the same type were pooled if the time between the consecutive therapy starts was less than 6 months.

Biotherapy, in particular the short-acting formulation, is often used concomitantly to other systemic therapies in functional NETs precluding sequence analysis with this regards [14]. The limited documentation in the medical history of exact treatment details regarding biotherapy (mainly treatment dose, interval and end) hampered proper analysis of biotherapy in this context. Therefore, the use of biotherapy was analysed separately.

Based on a secondary analysis set, we assessed sequences used for small intestinal, pancreatic and lung NETs and studied the order of use of systemic therapy (chemotherapy and/or molecular therapy) and PRRT and the sequence of molecular therapy (sunitinib, everolimus) and chemotherapy. Local ablative and biotherapy as such were excluded in the secondary analysis set. Both treatment modalities are often used concomitantly with chemo-, molecular therapy and PRRT hampering sequence analysis.

Statistical analysis
Patient and disease characteristics were analysed using descriptive statistics. We reported the number of non-missing observations for patient and tumour characteristics. For the treatment sequences, we were limited to documented treatments. However, we expect that the documentation of the treatments is complete as trained study nurses regularly update all entries.

Continuous and categorical variables are presented as median and interquartile range (IQR) or number and percentage of patients. All analyses were done in Stata Release 14 (Ref: StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

Results

Patient and tumour characteristics in the SwissNET cohort
The Swiss Neuroendocrine Tumor registry comprises 1366 patients, with documented therapies in 1063 cases. The median follow-up time was 1.86 years (interquartile range [IQR] 0.35–4.03). The most common primary site was the small intestine (291 tumours; 27%) followed by pancreas (254 tumours, 24%), lung (172 tumours; 16%) and appendix (163 tumours; 15%). A majority of the NET were well-differentiated G1 and G2 (78%). The detailed patient and tumour characteristics are presented in table 1.

Treatment sequences in the SwissNET cohort

The different treatment modalities given to the patients in the entire SwissNET cohorts are documented in table 2. Most of the patients underwent surgery (935 patients; 88%) in the course of their disease. Only a minority of patients were received non-surgical treatment modalities. Overall, 158 (15%), 156 (15%) and 113 (11%) patients received biotherapy, chemotherapy or PRRT, respectively.

A total of 167 different therapy sequences were observed (table 3). Out of these, 40 (24%) were used in more than one patient. In 708 (67%) patients, surgery was the only treatment appendical NETs, representing the most common primary tumour site treated with surgery only. Twenty patients (2%) and 12 patients (1%) were treated only with chemotherapy and biotherapy, respectively.

Overall, 311 patients (29%) received more than one treatment modality. For the first two treatment modalities the most common sequences were surgery followed by biotherapy in 45 (14%), surgery followed by chemotherapy in 44 (14%) and surgery followed by PRRT in 36 (12%) patients (table 4).

Treatment sequence according to primary tumour location in the secondary analysis set

Small intestinal neuroendocrine tumours

The treatment sequences of 288 small intestinal NET patients were analysed (figure 1). Surgery was the only treatment in 214 patients (74%). Systemic drug therapy only and PRRT only were given to 5 (2%) and 1 (0%) patients, respectively. After surgery, PRRT was applied most frequently (29 patients; 10%). Surgery followed by another tumour resection was noted in 21 (7%) and surgery followed by systemic drug therapy in 15 patients (5%).

The use of systemic drug therapy and PRRT and the use of chemo- or molecular therapy and the corresponding sequence of these two treatment modalities are shown in table 5. Fifty-six patients (19%) with small intestinal NETs

Table 1: Patient and tumour characteristics (n = 1063 patients).

		n (%) or median (IQR)
Age at diagnosis (years)		61 (50–71)
Sex	Female	504 (47%)
	Male	559 (53%)
Primary site	Small intestine	291 (27%)
	Pancreas	254 (24%)
	Lung	172 (16%)
	Appendix	163 (15%)
	Unknown	64 (6%)
	Colorectal	50 (5%)
	Stomach	38 (4%)
	Oesophagus	3 (0%)
	Other	26 (2%)
	Not documented	2 (0%)
Diagnosis	Neuroendocrine tumour	759 (71%)
	Neuroendocrine carcinoma	304 (29%)
Functioning	No	732 (69%)
	Yes	141 (13%)
	Not documented	190 (18%)
Tumour grade at baseline	G1	598 (56%)
	G2	229 (22%)
	G3	92 (9%)
	Not documented	144 (13%)
Tumour stage at baseline	I	184 (17%)
	II	81 (8%)
	III	117 (11%)
	IV	75 (7%)
	Not documented	606 (57%)
Follow-up time after major diagnosis (y)		1.86 (0.35–4.03)
IQR = interquartile range		

Table 2: Therapies in the main analysis set (n = 1063).

	n (%)
Surgery	935 (88%)
Biotherapy	158 (15%)
Chemotherapy	156 (15%)
PRRT	113 (11%)
Ablative therapy	111 (10%)
Molecular therapy	53 (5%)

PRRT = peptide receptor radionuclide therapy

were treated with either PRRT or systemic therapy (chemotherapy and/or molecular therapy) or both. In this cohort PRRT was used slightly more frequently than systemic therapy (35 patients [62%] vs 30 patients [54%]). When both modalities were used, PRRT was more frequently applied before systemic therapy than vice versa (8 patients [14%] vs 1 patient [2%]). Thirty patients (10%) with a small intestinal NET were treated with either molecular therapy or chemotherapy or both. Again, in this cohort, chemotherapy was used more frequently (22 patients [73%] vs 11 patients [37%]).

Pancreatic neuroendocrine tumours

In total, 251 pancreatic NET patients were analysed for their treatment sequence. Surgery was the only treatment for 169 patients (67%). Systemic drug therapy only and PRRT only were given to 4 (2%) and 3 (1%) patients, respectively. After surgery, systemic therapy was applied most frequently, in 17 patients (7%). The detailed treatment sequences are depicted in figure 2.

The use of systemic drug therapy and PRRT, and the use of chemo- or molecular therapy and the corresponding sequence of these two treatment modalities are shown in table 5. Seventy-five patients (30%) with a pancreatic NET were treated with either PRRT or systemic therapy or both. In this patient group, systemic therapy was used more frequently than PRRT (56 patients [75%] vs 44 patients [59%]). When both modalities were used, chemotherapy was more frequently applied before PRRT than vice versa (14 patients [19%] vs 11 patients [15%]). Fifty-six patients (22%) with a pancreatic NET were treated with either molecular therapy or chemotherapy or both. Thereby, chemotherapy was used more frequently than molecular therapy (50 patients [89%] vs 25 patients [45%]) and more frequently before than after (13 patients [23%] vs 6 patients [11%]).

Lung neuroendocrine tumours

In total, 170 lung NET patients were analysed for their therapy sequence. Surgery was the only treatment for 127 patients (75%). Systemic drug therapy only and PRRT only were given to 17 (10%) and 1 (1%) patients, respectively. Further treatment sequences are illustrated in figure 3.

The sequence whether systemic drug therapy or PRRT and whether chemo- or molecular therapy was given first are demonstrated in table 5. 41 patients (24%) with lung NET were treated with either PRRT or systemic therapy or both.

Table 3: All therapy sequences in the main analysis set (n = 1063).

Sequence	n (%)
S	708 (66.1%)
SB	25 (2.4%)
SC	22 (2.1%)
C	20 (1.9%)
SS	18 (1.7%)
SP	14 (1.3%)
B	12 (1.1%)
SA	9 (0.8%)
BS	8 (0.8%)
A, CA, P, SCC	6 (0.6%) × 4 = 24 (2.3%)
CC, PB, SSA	5 (0.5%) × 3 = 15 (1.4%)
SBB, SPB	4 (0.4%) × 2 = 8 (0.8%)
AS, CACA, CM, PC, SAC, SBS, SCA, SCAC, SPBB	3 (0.3%) × 9 = 27 (2.5%)
AC, BCCBC, BM, BPB, CAA, CAAC, CAC, PBP, PP, SAB, SAS, SPC, SSAS	2 (0.2%) × 13 = 26 (2.4%)
ABC, ACAC, ACPMA, ASA, ASB, ASBB, ASCA, BB, BCP, BMBPB, BMBPPMS, BMCMC, BPBBCBC, BPBC, BPBP, BPM, BPSA, BSASSSMC, BSB, BSBP, BSBPB, BSBSBPSPB, BSC, BSCM, BSP, BSPM, CAACA, CAACAC, CAACS, CAB, CABCPBM, CACACA, CACCC, CACSA, CAM, CASA, CBACA, CBCMBPBAPSCA, CBM, CBMC, CCCPP, CCS, CMAB, CMAMMAC, CMCAB, CMCCB, CPA, CPC, CPMAC, CPPMB, CS, CSABMP, CSAPBB, CSC, CSM, CSPP, MB, MBC, MBM, MSC, PBBBP, PBBM, PBBP, PBCBPC, PBM, PBPSPP, PCSCC, PMBPAC, PPB, PPP, PS, PSP, SAAPSBCMB, SABSBAMMCBC, SABSPPP, SACS, SAM, SAPAMSABM, SAPB, SAPBB, SASB, SASPMAM, SASSCCCP, SBABS, SBAS, SBBAP, SBC, SBM, SBMMMS, SBP, SBPBB, SBPBMA, SBPPBBMBSB, SBPPBCPBM, SBPS, SBSA, SCASPC, SCBCB, SCBCBCM, SCCB, SCCC, SCM, SCMBBA, SCPB, SCPBA, SCPBS, SMASCM, SPABC, SPBABB, SPBAS, SPBP, SPBPBPBPM, SPCB, SPCP, SPM, SPMCACCACPB, SPPP, SPS, SPSASPMBMB, SPSBB, SSAB, SSBMMB, SSBPBPBBS, SSP, SSPP, SSSAM, SSSS	1 (0.1%) × 127 = 127 (11.9%)

A = ablative therapy; B = biotherapy; C = chemotherapy; M = molecular therapy; P = PRRT = peptide receptor radionuclide therapy; S = surgery

Table 4: Patient characteristics for groups defined by the first two therapies in the main analysis set.

Group	Patients (n = 311) n (%)	Age at diagnosis in years Median (IQR)	Main primary site n (%)	Tumour grade n (%)	Functioning n (%)
SB	45 (14%)	66.0 (48.0–48.0)	Small intestine (33, 73%)	G1 (22, 54%)	13 (29%)
SC	44 (14%)	62.0 (54.8–54.8)	Pancreas (15, 34%)	G3 (24, 60%)	2 (5%)
SP	36 (12%)	60.5 (50.0–50.0)	Small intestine (18, 50%)	G1 (17, 53%)	8 (22%)
SS	32 (10%)	58.0 (51.0–51.0)	Small intestine (18, 56%)	G1 (19, 70%)	3 (9%)
SA	27 (9%)	61.0 (45.0–45.0)	Pancreas (12, 44%)	G2 (12, 52%)	3 (11%)
CA	25 (8%)	66.0 (59.0–59.0)	Lung (17, 68%)	G3 (11, 85%)	1 (4%)
BS	17 (5%)	65.0 (50.0–50.0)	Small intestine (8, 47%)	G1 (8, 62%)	8 (47%)
PB	13 (4%)	65.0 (54.0–54.0)	Unknown (5, 38%)	G1 (5, 63%)	3 (23%)

A = ablative therapy; B = biotherapy; C = chemotherapy; M = molecular therapy; P = PRRT; S = surgery Only combinations with >10 patients are shown

In this cohort systemic therapy was used more frequently than PRRT, in 40 patients (97%) vs 6 patients (14%), respectively. In the cohort treated with either molecular therapy or chemotherapy or both chemotherapy was used more frequently than molecular therapy (39 patients [98%] vs 5 patients [13%]).

Biotherapy (somatostatin analogues)

Treatment with somatostatin analogues was documented in 158 patients (15%). In 53 patients of these patients (34%) no surgical therapy was performed in the disease course. Surgery followed by biotherapy and biotherapy followed by surgery could be documented in 70 (44%) and 17 patients (11%), respectively. For functional NETs, biotherapy was given more often before surgery. There was no other obvious difference in patient and tumour characteristics ac-

cording to the biotherapy sequence groups (supplementary table S1, appendix 1).

Discussion

The main findings of this study can be summarised as follows:

1. Surgery is the treatment of choice in most NETs irrespective of tumour stage.

2. Only a small proportion of NET patients receive other treatment modalities in their disease course.

3. If patients treated with surgery only are excluded, there is a seemingly unlimited variety of treatment sequences used in NET patients.

Figure 1: Tree plot for small intestinal neuroendocrine tumours based on the secondary analysis set. Each row represents a therapy line. Stop indicates that no more treatments were documented. (n = 288 patients). PPRT = peptide receptor radionuclide therapy
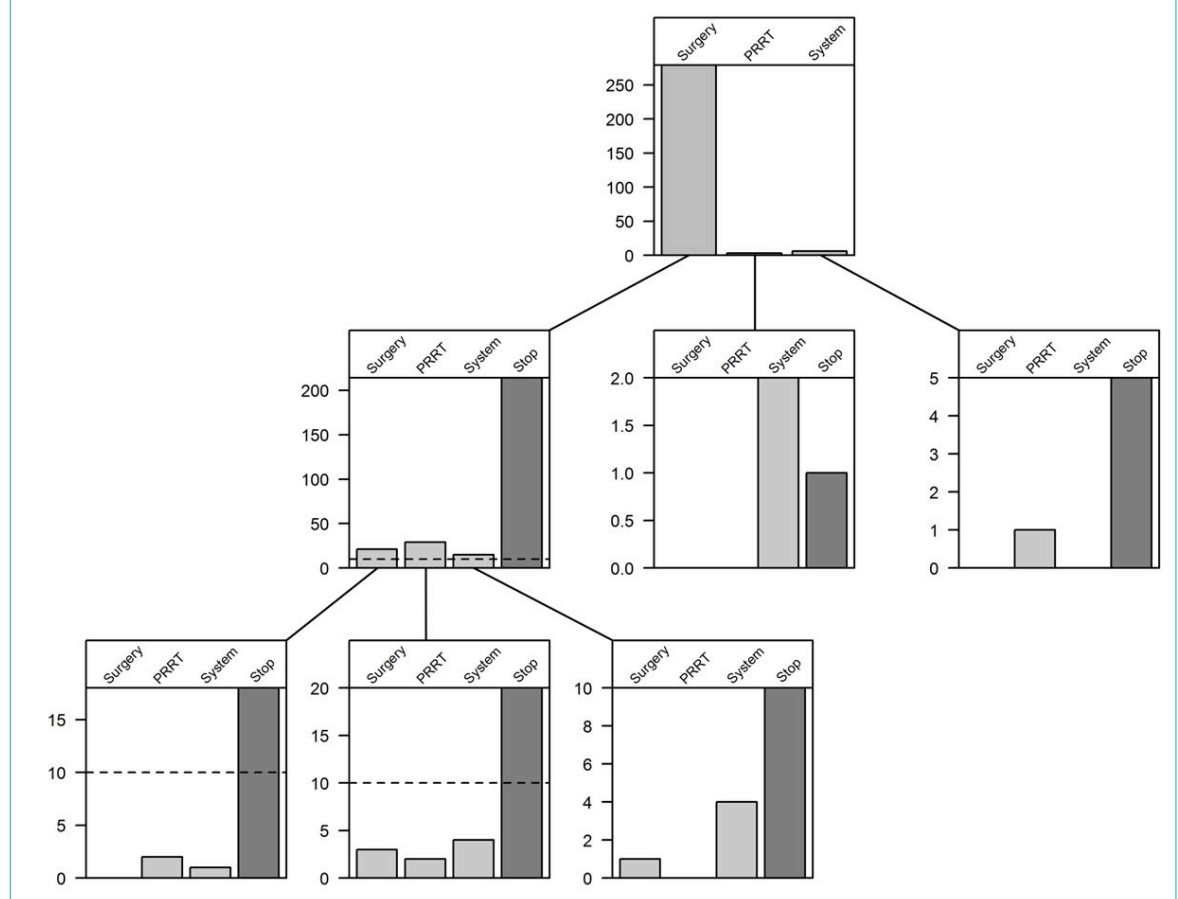
Table 5: Therapy sequence groups: peptide receptor radionuclide therapy (PRRT) versus systemic therapy (molecular or chemotherapy) and molecular versus chemotherapy.

	Small intestine	Pancreas	Lung
	n (%)		
PRRT vs systemic therapy	n = 56	n = 75	n = 41
PRRT but no systemic therapy	26 (46%)	19 (25%)	1 (2%)
Systemic therapy but no PRRT	21 (38%)	31 (41%)	35 (85%)
PRRT prior to systemic therapy	8 (14%)	11 (15%)	2 (5%)
Systemic therapy prior to PRRT	1 (2%)	14 (19%)	3 (7%)
Molecular vs chemotherapy	n = 30	n = 56	n = 40
Molecular but no chemotherapy	8 (27%)	6 (11%)	1 (3%)
Chemo- but no molecular therapy	19 (63%)	31 (55%)	35 (88%)
Molecular prior to chemotherapy	1 (3%)	6 (11%)	1 (3%)
Chemo- prior to molecular therapy	2 (7%)	13 (23%)	3 (8%)

4. PRRT seems to be preferred over systemic therapy in patients with small intestinal NETs, whereas the opposite is true in pancreatic and lung NETs.

5. Chemotherapy seems to be preferred over molecular therapy regardless of tumour site.

Our analysis confirms that tumour resection plays a major role for the treatment of NETs. The broad indication for surgical treatment explains this observation. Surgery is considered to be the treatment of choice for patients who have a localised well-differentiated NET, for predominantly hepatic disease in the metastatic setting with potentially curative intent and, importantly, to reduce tumour burden and thus symptoms of carcinoid syndrome [15].

In the case of multifocal tumour progression, evidence is limited with regard to which treatment option should be preferred in which situation. Therefore, studying the sequence of treatment modalities (e.g., PRRT, chemotherapy) and to a lesser extent local therapies is highly relevant to preventing disease progression and improving outcome [14, 16, 17]. Recently, treatment patterns in advanced NETs of the pancreas and potential differences between the treatment in an academic hospital and community oncology practices were reported. Patients treated within the academic tertiary cancer centre received more lines of therapy, were more likely to undergo surgery (47.8 vs 6.5%) including liver-directed therapy and were less often treated

with somatostatin analogues (23.8 vs 45.8%). However, the number of patients assessed (n = 44) was small [18].

The diversity of nonsurgical treatment sequences in our study is impressive and might reflect firstly the complexity of the disease and secondly the lack of guidance from clinical studies. Nevertheless, we were able to find some commonalities in the use of different treatment approaches. Note, sunitinib and everolimus gained approval by the European Medical Agency for the treatment of pancreatic NETs in 2010 and 2011, respectively. In 2016, everolimus received approval for treatment of non-pancreatic types of NET, too. PRRT was available in Switzerland during the whole registry period.

Small intestinal neuroendocrine tumours

Tumours treated with surgery followed by biotherapy or followed by PRRT were mostly well-differentiated (G1) NETs of the small intestine. These findings are completely in line with the recently published tumour site-specific guidelines of the European Neuroendocrine Tumor Society (ENETS) [12, 19, 20]. Chemotherapy is not recommended in non-pancreatic NETs unless for tumours with a high proliferation index indicating aggressive biological behaviour or those with somatostatin receptor negativity. Somatostatin analogues may be used in stable or progressive disease for antiproliferative purposes and are mainly recommended as a first-line therapy in midgut NETs.

Assessment of the treatment sequence for PRRT and systemic therapy showed that most patients received PRRT

Figure 2: Tree plot for pancreatic neuroendocrine tumours based on the secondary analysis set. Each row represents a therapy line. Stop indicates that no more treatments were documented. (n = 251 patients). PPRT = peptide receptor radionuclide therapy
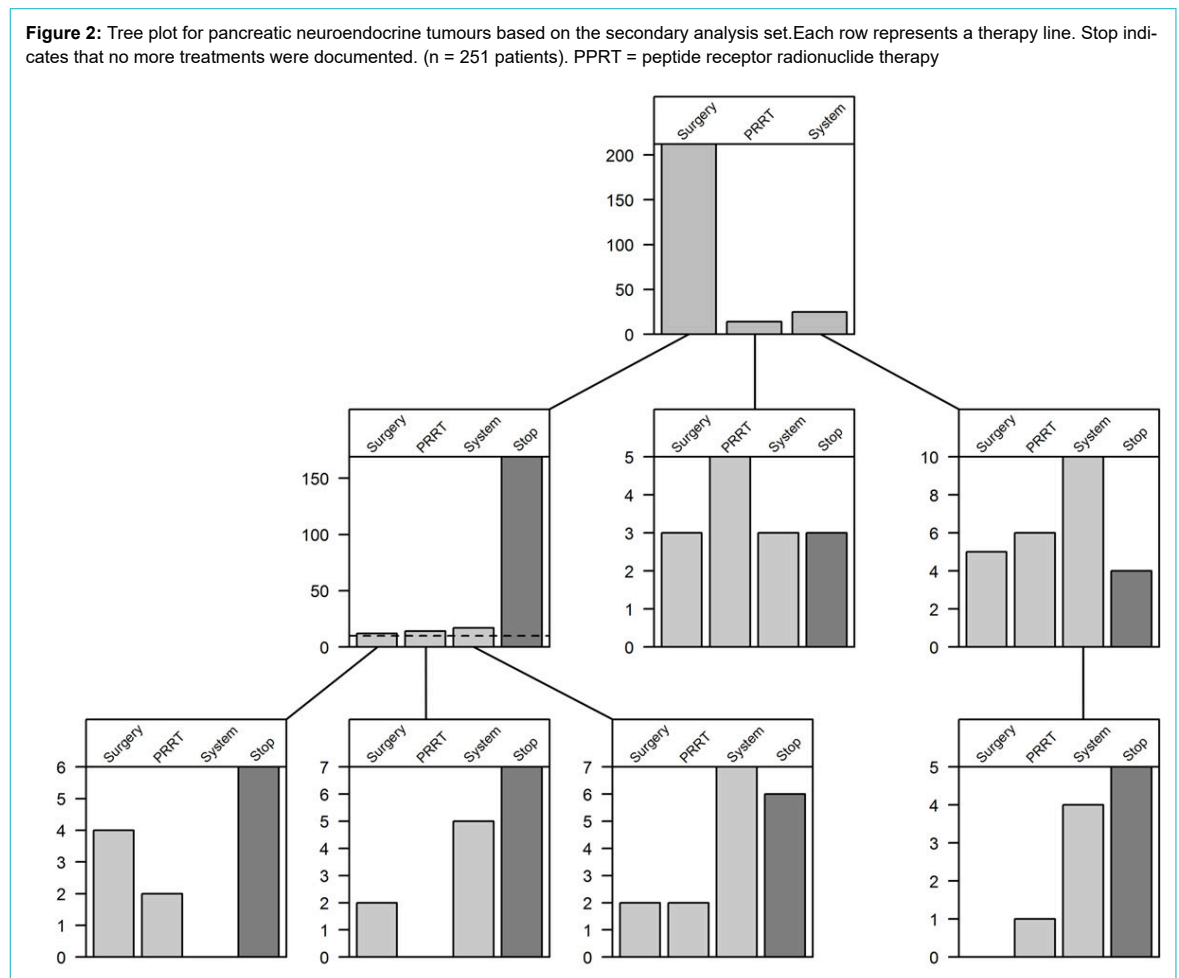
first. There are mainly two reasons for this observation. Firstly, most studies in midgut NETs report on an only modest response rate of streptozocin- and temozolomide-containing chemotherapy in this specific NET subtype [21, 22]. Additionally, the evidence for the use of molecular therapies such as sunitinib or everolimus in small intestinal NETs, was limited until recently when the results of the RADIANT-4 trial were published [10]. Further evidence for the use of PRRT was provided by the phase III randomised controlled NETTER-1 trial, which assessed the efficacy and safety of ^{177}Lu-DOTATATE in patients with advanced, somatostatin receptor-positive, G1/G2 midgut NETs that were progressing on long-acting octreotide. Objective tumour responses were reported in 18% of patients who received PRRT compared with 3% in those who did not. At the time of primary endpoint analysis, the median progression-free survival had not been reached for the patients who received PRRT and was 8.4 months in the control group [11]. Owing to the limited patient numbers no conclusion can be drawn regarding the sequence of chemo- and molecular therapy.

Pancreatic neuroendocrine tumours

Based on the current evidence there are rather more accepted treatment options for patients with pancreatic NETs compared with NETs of other primary sites [12]. The sequence of surgery followed by chemotherapy was most frequently documented in poorly differentiated (G3) and pancreatic NETs. These findings correlate with the current literature. Streptocotozin- and temozolomide-containing chemotherapy combinations are associated with a high tumour response rate (up to 70%) in NETs of pancreatic origin [6, 7]. In contrast, the chemo-responsiveness of gas-trointestinal NETs seems to be very limited [23]. Additionally, Sorbye et al. reported a significant benefit of platinum-based chemotherapy in poorly differentiated NETs with a proliferation fraction of >55% [24].

Nevertheless, in patients receiving both PRRT and systemic therapies, no clear pattern in treatment sequences could be observed in our analysis. Given the different established and approved therapeutic options in pancreatic NETs and the lack of a prospective trial with PRRT in pancreatic NETs, PRRT is generally recommended in G1/G2 NETs after failure of medical therapy including a somatostatin analogue, chemotherapy or novel targeted drugs [12]. There are several prospective and retrospective studies looking at tumour response to PRRT and survival outcomes for patients with a pancreatic NET, [25, 26]. Ramage et al. reported a median disease control rate and objective response rate of 83% (range 50–94%) and 58% (range 13–73%), respectively [27]. Notably, chemotherapy in pancreatic NETs was more commonly used first followed by molecular therapy than vice versa. This might be explained by the higher response rate with chemotherapy in pancreatic NETs when compared with molecular therapies, sunitinib and everolimus rather leading to disease stabilisation [9, 10].

Lung neuroendocrine tumours

When compared with PRRT, systemic drug treatment modalities, and in particular chemotherapy, were more commonly used in lung NET patients. This is surprising as the evidence for the use of chemotherapy for pulmonary NETs is very low. Platinum-based chemotherapy and temozolomide were studied in rather small retrospective

Figure 3: Tree plot for lung neuroendocrine tumours based on the secondary analysis set. Each row represents a therapy line. Stop indicates that no more treatments were documented. (n = 170 patients). PPRT = peptide receptor radionuclide therapy
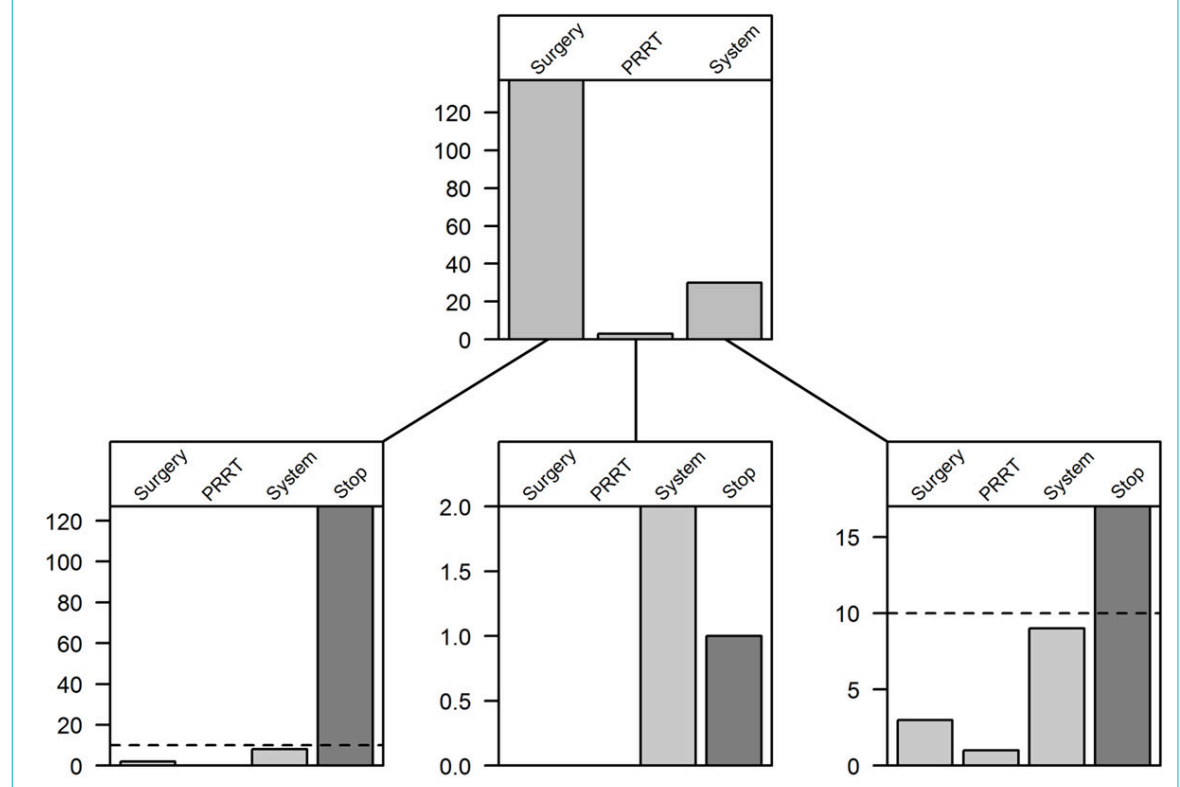
cohorts with a reported response rate in thoracic NETs of 0–67% and progression-free survival in the range of 10 months [28, 29]. Only a few phase II trials assessed the potential efficacy of cytotoxic drugs. Oxaliplatin-based chemotherapy was associated with a response rate of 14% [30]. Notably, Imhof et al. investigated in a phase II trial the efficacy of PRRT in NETs and reported a response rate of 29% in the lung NET subgroup [31]. The rarity of lung NETs has precluded further prospective trials in the past. Again, the small cohorts in our study hampered a meaningful sequence analysis of nonsurgical therapies and therefore further interpretation.

Strengths and limitations

The strength of our study is based on the large cohort, the high quality and completeness of data assessment within the SwissNET database. The prospective nature of the registry and data collection by highly dedicated, specialised study nurses ensures high data quality. Despite the rarity and heterogeneity of this disease, data on the treatment of NETs of the main primary sites are provided in this analysis. There are several limitations of our analysis. The nature of the data is observational and the follow-up time relatively short. Although the total number of intestinal, pancreatic and lung NET patients analysed is high, the small sample size in several treatment cohorts hampers drawing consequences.

Future prospects

Ongoing and future research should improve knowledge around the molecular biology of NET and efficacy of different sequencing or combination strategies. An ongoing Phase III clinical trial, the SEQTOR trial, studies the right treatment sequence for patients with NET of pancreatic origin assessing the best treatment strategy comparing the efficacy of everolimus followed by streptozotocin/fluorouracil or vice versa (NCT02246127). Additionally, the results of the COMPETE trial assessing prospectively the optimal first-line therapy (PRRT with 177Lu-Edotreotide compared to everolimus) in patients with an inoperable NET of gastroenteric or pancreatic origin are eagerly awaited (NCT03049189). A randomised phase III trial of lanreotide autogel versus placebo in advanced, unresectable lung NETS is ongoing (NCT02683941).

Conclusion

We present the largest cohort reporting on the treatment sequence in patients suffering from NETs of any primary site. Our report illustrates the omnium gatherum of used treatment modalities and sequences. Surgery is clearly the treatment option of choice when feasible. If additional therapies are required, PRRT seems to be preferred to systemic therapy in patients with small intestinal NETs, whereas systemic therapy is favourably used in pancreatic and lung NETs.

References

1   van der Zwan JM, Trama A, Otter R, Larrañaga N, Tavilla A, Marcos-Gragera R, et al.; RARECARE WG. Rare neuroendocrine tumours: results of the surveillance of rare cancers in Europe project. Eur J Cancer. 2013;49(11):2565–78. doi: http://dx.doi.org/10.1016/j.ejca.2013.02.029. PubMed.

2   Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26(18):3063–72. doi: http://dx.doi.org/10.1200/JCO.2007.15.4377. PubMed.

3   Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3(10):1335–42. doi: http://dx.doi.org/10.1001/jamaoncol.2017.0589. PubMed.

4   Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al.; PROMID Study Group. 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. J Clin Oncol. 2009;27(28):4656–63. doi: http://dx.doi.org/10.1200/JCO.2009.22.8510. PubMed.

5   Caplin ME, Pavel M, Ćwikła JB, Phan AT, Raderer M, Sedláčková E, et al.; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33. doi: http://dx.doi.org/10.1056/NEJMoa1316158. PubMed.

6   Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin-fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med. 1992;326(8):519–23. doi: http://dx.doi.org/10.1056/NEJM199202203260804. PubMed.

7   Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117(2):268–75. doi: http://dx.doi.org/10.1002/cncr.25425. PubMed.

8   Hadoux J, Malka D, Planchard D, Scoazec JY, Caramella C, Guigay J, et al. Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. Endocr Relat Cancer. 2015;22(3):289–98. doi: http://dx.doi.org/10.1530/ERC-15-0075. PubMed.

9   Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364(6):501–13. doi: http://dx.doi.org/10.1056/NEJMoa1003825. PubMed.

10   Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al.; RAD001 in Advanced Neuroendocrine Tumours, Fourth Trial (RADIANT-4) Study Group. Everolimus for the treatment of advanced, nonfunctional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet. 2016;387(10022):968–77. doi: http://dx.doi.org/10.1016/S0140-6736(15)00817-X. PubMed.

11   Strosberg J, El-Haddad G, Wolin E, Hendifar A, Yao J, Chasen B, et al.; NETTER-1 Trial Investigators. Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. N Engl J Med. 2017;376(2):125–35. doi: http://dx.doi.org/10.1056/NEJMoa1607427. PubMed.

12   Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, et al., Vienna Consensus Conference participants. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. Neuroendocrinology. 2016;103(2):172–85. doi: http://dx.doi.org/10.1159/000443167. PubMed.

13   Kollár A, Blank A, Perren A, Bütikofer L, Stettler C, Christ E. Additional malignancies in patients with neuroendocrine tumours: analysis of the SwissNET registry. Swiss Med Wkly. 2016;146:. doi: http://dx.doi.org/10.4414/smw.2016.14362. PubMed.

14   Pavel M, Valle JW, Eriksson B, Rinke A, Caplin M, Chen J, et al.; Antibes Consensus Conference Participants; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Systemic Therapy - Biotherapy and Novel Targeted Agents. Neuroendocrinology. 2017;105(3):266–80. doi: http://dx.doi.org/10.1159/000471880. PubMed.

15 Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003;197(1):29–37. doi: http://dx.doi.org/10.1016/S1072-7515(03)00230-8. PubMed.

16 Garcia-Carbonero R, Rinke A, Valle JW, Fazio N, Caplin M, Gorbounova V, et al.; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms. Systemic Therapy 2: Chemotherapy. Neuroendocrinology. 2017;105(3):281–94. doi: http://dx.doi.org/10.1159/000473892. PubMed.

17 Hicks RJ, Kwekkeboom DJ, Krenning E, Bodei L, Grozinsky-Glasberg S, Arnold R, et al.; Antibes Consensus Conference participants. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasia: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogues. Neuroendocrinology. 2017;105(3):295–309. doi: http://dx.doi.org/10.1159/000475526. PubMed.

18 Herring M, Huynh L, Duh MS, Vekeman F, Tiew A, Neary M, et al. Real-world treatment patterns in advanced pancreatic neuroendocrine tumors in the era of targeted therapy: perspectives from an academic tertiary center and community oncology practices. Med Oncol. 2017;34(5):88. doi: http://dx.doi.org/10.1007/s12032-017-0927-0. PubMed.

19 Pape UF, Niederle B, Costa F, Gross D, Kelestimur F, Kianmanesh R, et al., Vienna Consensus Conference participants. ENETS Consensus Guidelines for Neuroendocrine Neoplasms of the Appendix (Excluding Goblet Cell Carcinomas). Neuroendocrinology. 2016;103(2):144–52. doi: http://dx.doi.org/10.1159/000443165. PubMed.

20 Caplin ME, Baudin E, Ferolla P, Filosso P, Garcia-Yuste M, Lim E, et al.; ENETS consensus conference participants. Pulmonary neuroendocrine (carcinoid) tumors: European Neuroendocrine Tumor Society expert consensus and recommendations for best practice for typical and atypical pulmonary carcinoids. Ann Oncol. 2015;26(8):1604–20. doi: http://dx.doi.org/10.1093/annonc/mdv041. PubMed.

21 Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO, Jr. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol. 1984;2(11):1255–9. doi: http://dx.doi.org/10.1200/JCO.1984.2.11.1255. PubMed.

22 Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. Clin Cancer Res. 2009;15(1):338–45. doi: http://dx.doi.org/10.1158/1078-0432.CCR-08-1476. PubMed.

23 Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG; Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol. 2005;23(22):4897–904. doi: http://dx.doi.org/10.1200/JCO.2005.03.616. PubMed.

24 Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013;24(1):152–60. doi: http://dx.doi.org/10.1093/annonc/mds276. PubMed.

25 Sansovini M, Severi S, Ambrosetti A, Monti M, Nanni O, Sarnelli A, et al. Treatment with the radiolabelled somatostatin analog Lu-DOTATATE for advanced pancreatic neuroendocrine tumors. Neuroendocrinology. 2013;97(4):347–54. doi: http://dx.doi.org/10.1159/000348394. PubMed.

26 Brabander T, van der Zwan WA, Teunissen JJM, Kam BLR, Feelders RA, de Herder WW, et al. Long-Term Efficacy, Survival, and Safety of [^{177}Lu-DOTA^0,Tyr^3]octreotate in Patients with Gastroenteropancreatic and Bronchial Neuroendocrine Tumors. Clin Cancer Res. 2017;23(16):4617–24. doi: http://dx.doi.org/10.1158/1078-0432.CCR-16-2743. PubMed.

27 Ramage J, Naraev BG, Halfdanarson TR. Peptide receptor radionuclide therapy for patients with advanced pancreatic neuroendocrine tumors. Semin Oncol. 2018;45(4):236–48. doi: http://dx.doi.org/10.1053/j.seminoncol.2018.08.004. PubMed.

28 Granberg D, Eriksson B, Wilander E, Grimfjärd P, Fjällskog ML, Oberg K, et al. Experience in treatment of metastatic pulmonary carcinoid tumors. Ann Oncol. 2001;12(10):1383–91. doi: http://dx.doi.org/10.1023/A:1012569909313. PubMed.

29 Saranga-Perry V, Morse B, Centeno B, Kvols L, Strosberg J. Treatment of metastatic neuroendocrine tumors of the thymus with capecitabine and temozolomide: a case series. Neuroendocrinology. 2013;97(4):318–21. doi: http://dx.doi.org/10.1159/000345938. PubMed.

30 Kunz PL, Balise RR, Fehrenbacher L, Pan M, Venook AP, Fisher GA, et al. Oxaliplatin-Fluoropyrimidine Chemotherapy Plus Bevacizumab in Advanced Neuroendocrine Tumors: An Analysis of 2 Phase II Trials. Pancreas. 2016;45(10):1394–400. doi: http://dx.doi.org/10.1097/MPA.0000000000000659. PubMed.

31 Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol. 2011;29(17):2416–23. doi: http://dx.doi.org/10.1200/JCO.2010.33.7873. PubMed.

Appendix 1   **Supplementary data**

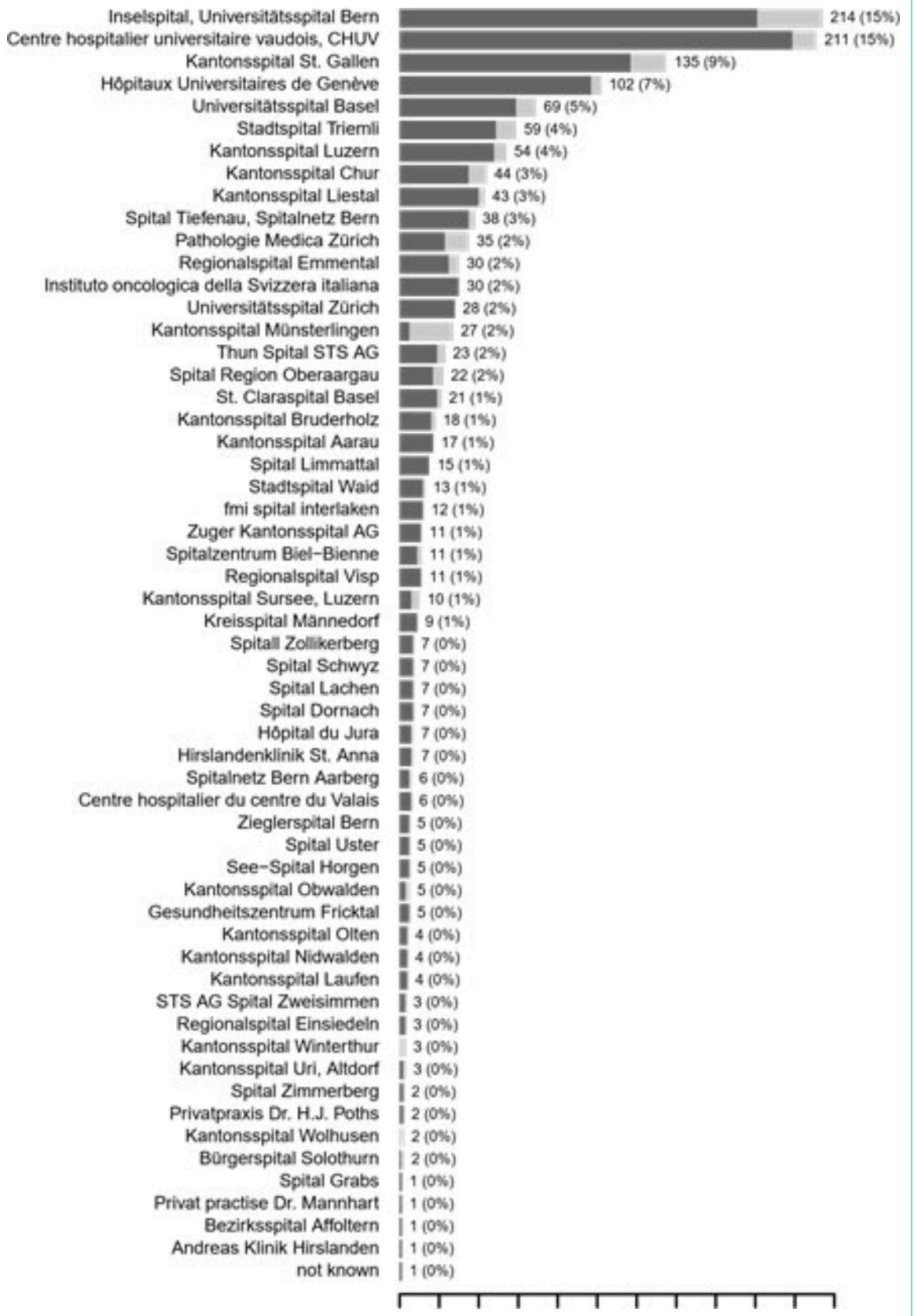**Figure S1:** Accrual sites in the SwissNET registry.

Table S1: Patient characteristics according to biotherapy sequence groups.

		Total (n = 158)	Biotherapy prior to surgery (n = 17)	Surgery prior to bio-therapy (n = 70)	Both (n = 18)	No surgery (n = 53)
		n (%) or median (IQR)				
Age at diagnosis (years)		62.0 (49.0–71.0)	65.0 (50.0–69.0)	58.5 (47.0–70.0)	58.0 (48.0–72.0)	65.0 (57.0–71.0)
Sex	Female	65 (41%)	7 (41%)	28 (40%)	7 (39%)	23 (43%)
	Male	93 (59%)	10 (59%)	42 (60%)	11 (61%)	30 (57%)
Primary site	Lung	6 (4%)	0 (0%)	3 (4%)	0 (0%)	3 (6%)
	Pancreas	52 (33%)	6 (35%)	24 (34%)	3 (17%)	19 (36%)
	Small intestine	59 (37%)	6 (35%)	35 (50%)	11 (61%)	7 (13%)
	Colorectal	4 (3%)	1 (6%)	3 (4%)	0 (0%)	0 (0%)
	CUP	33 (21%)	4 (24%)	3 (4%)	4 (22%)	22 (42%)
	Other	3 (2%)	0 (0%)	2 (3%)	0 (0%)	1 (2%)
	Not known	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Diagnosis	Neuroendocrine tumour	91 (58%)	12 (71%)	41 (59%)	13 (72%)	25 (47%)
	Neuroendocrine carcinoma	67 (42%)	5 (29%)	29 (41%)	5 (28%)	28 (53%)
Functioning	No	77 (49%)	5 (29%)	45 (64%)	5 (28%)	22 (42%)
	Yes	51 (32%)	8 (47%)	13 (19%)	9 (50%)	21 (40%)
	Not known	30 (19%)	4 (24%)	12 (17%)	4 (22%)	10 (19%)
Tumor grade at baseline	G1	58 (37%)	5 (29%)	30 (43%)	7 (39%)	16 (30%)
	G2	61 (39%)	6 (35%)	29 (41%)	9 (50%)	17 (32%)
	G3	7 (4%)	0 (0%)	4 (6%)	0 (0%)	3 (6%)
Tumor stage at baseline	I	3 (2%)	1 (6%)	2 (3%)	0 (0%)	0 (0%)
	II	5 (3%)	0 (0%)	5 (7%)	0 (0%)	0 (0%)
	III	15 (9%)	2 (12%)	9 (13%)	2 (11%)	2 (4%)
	IV	33 (21%)	4 (24%)	19 (27%)	8 (44%)	2 (4%)
Follow-up time after major diagnosis (years)		2.87 (1.40–4.39)	3.39 (0.87–4.52)	3.41 (1.61–5.45)	3.38 (1.40–4.88)	2.30 (1.39–3.48)

CUP = cancer of unknown primary origin; IQR = interquartile range