Schweizer Register für Neuroendokrine Tumore
Le Registre Suisse des tumeurs neuroendocrines
Registro Svizzero per i Tumori Neuroendocrini

SwissNET

Präsident: Prof. Emanuel Christ
Registerleiter: Dr. Alexander Siebenhüner

Report of the president

During the past year, although the COVID-19 pandemic has forced the ENETS and SwissNET community to communicate almost through virtual platforms, the treatment as well as the patient care for NET patients in Switzerland stayed high and SwissNET has confirmed its leading role. The SwissNET registry includes now almost 2400 patients. Updates of the data set include systemic therapies and the new NEC G3, respectively NET G3 classification.

There were no changes within the committee of SwissNet. As mentioned above the annual meeting as well the meeting with the Sponsors were taken through virtual platforms, which was a big success for the community. During 2020 the data were moved from the old data platform (Webspirit no IT support anymore) to the new data system RedCap, which is supervised by the CTU in Berne. Within the calculated time all the data have been transferred without complication. This enables SwissNET for a broader data input for the upcoming years as well guarantees a stable data platform with IT support.

We are very happy that patients from new centers as Cantonal hospital Schaffhausen are now represent in our registry.

Finally yet importantly, we must highlight and thank the sponsoring who supports our activities and enables the future and the success of the database: Novartis, Pfizer Oncology and Ipsen. For sponsoring the SwissNET the support by AAA was installed by 2020 too, which gave us the needed financial support combined with the already active sponsors to keep the registry at this high quality level. Our now well-established annual sponsor meeting will be planned mid-autumn 2021 probably as a virtual platform again.

Prof. Emanuel Christ, Head of Interdisciplinary Endocrinology, University Hospital of Basel
President of SWISSNet

Database Report 2020

In total, 2393 patients are included in the SwissNET registry at end of 2020. Since the last statistical analysis of the SwissNET data 543 additional patients were registered and documented which represents a significant increase (29%) in patient number. Another situation to highlight here was the re-activation of the Cantonal Hospital Winterthur as well the new accrual by the Cantonal Hospital Schaffhausen. The 4 ENETS Centers (CHUV, Inselspital Bern, University Hospital Basel and University Hospital Zurich) could again represent a steady increase of new NET patients between 6-15% in 2020.

Patient and tumor characteristics

Patient characteristics and Follow up

The distribution of male and female patients (male: 53%, female: 47%) is relatively equal. The median follow up time increased to 3.0 years. There was no change in the mean age at diagnosis in comparison to data from 2013. (Table 1)

Table 1: Patient characteristics

Measurement	2014	2015	2016	2017	2018	2019	2020
Number of patients	835	1050	1245	1428	1586	1858	2393
Females (%)	46	46	47	47	47	47	47
Males (%)	54	54	53	53	53	53	53
Age at diagnosis (y)							
Mean	59.3	59.9	59.6	60.1	60.3	60	60
Follow-up							
Median (years)	2	2.1	2.23	2.38	2.61	3.0	3.0

Recruitment

Virtually all institutions, hospitals and cantons are recruiting NET patients. Most of the patients are recruited by the established major centers Berne, CHUV, St. Gallen, Zürich and HUG and Basel – here the 4 ENETS CoE are included. However, half of the included patients are from other hospitals or private practices. (Figure 1/2)

Figure 1: Recruitment of patients: dark grey: 2008-2019, grey: 2020

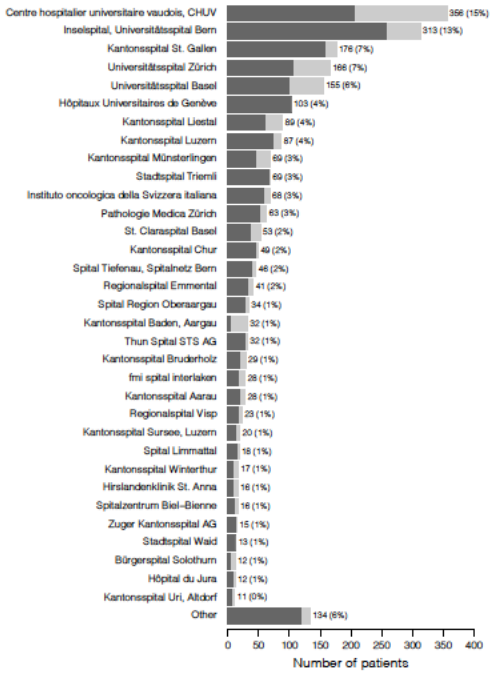
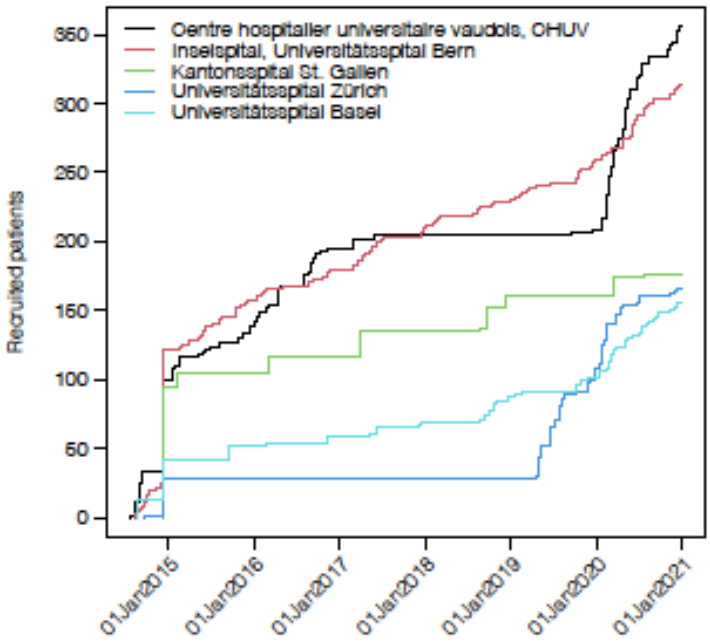


Figure 2: Number of patients recruited each year for the main centers



Distribution of primary sites and tumor grade

Most of the NET registered in the database are of pancreatic and ileal/jejunal origin. NET of the appendix, lung and of unknown origin are quite common, too. Of note the diagnosis p-NET and ileal NET increased by 21% each, as well a steady increase of appendix NET increased by 14% was noted. Compared to the former years rates of rare NET diagnoses were stable. In total 70% of NET were non-functional (Figure 3 and Table 2)

Figure 3: Distribution of primary sites of NET

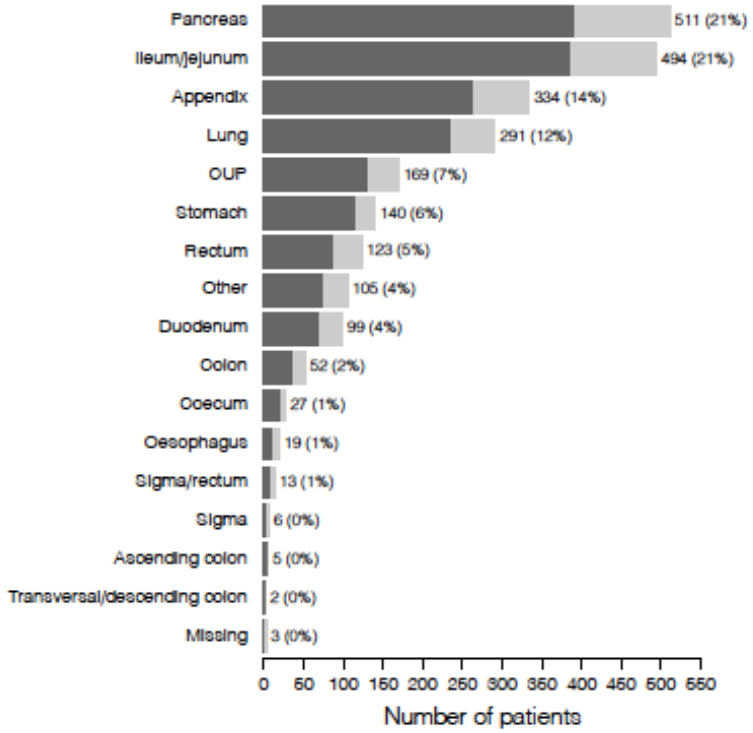
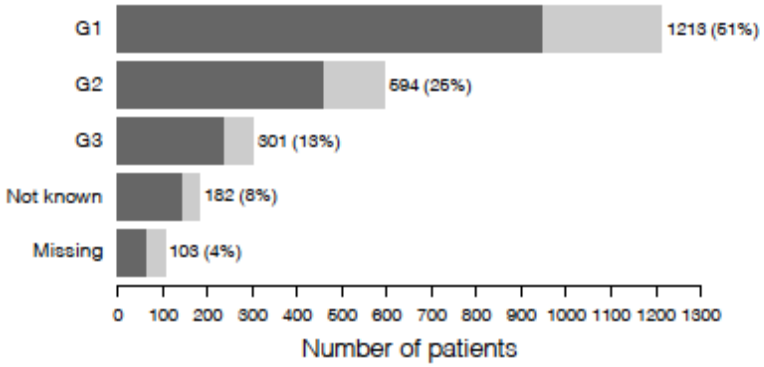


Table 2: Major diagnosis by sites and function vs non-functional tumors

Number of patients	2393
Primary Site - n (%)	
Lung	291 (12%)
Oesophagus	19 (1%)
Stomach	140 (6%)
Pancreas	511 (21%)
Duodenum	99 (4%)
Ileum/jejunum	494 (21%)
Coecum	27 (1%)
Appendix	334 (14%)
Colon	52 (2%)
Ascending colon	5 (0%)
Transversal/descending colon	2 (0%)
Sigma	6 (0%)
Sigma/rectum	13 (1%)
Rectum	123 (5%)
CUP	169 (7%)
Other	105 (4%)
missing	3 (0%)
Diagnosis - n (%)	
Neuroendocrine tumor	1862 (78%)
Neuroendocrine carcinoma	441 (18%)
MANEC	55 (2%)
Other	19 (1%)
Not known	10 (0%)
missing	6 (0%)
Functional tumor - n (%)	
No	1675 (70%)
Yes	271 (11%)
Not known	429 (18%)
missing	18 (1%)
Type - n (%)	
Carcinoid	150 (55%)
Cushing	6 (2%)
Gastrinoma	32 (12%)
Glucagonoma	8 (3%)
Insulinoma	63 (23%)
Somatostatinoma	2 (1%)
VIPoma	6 (2%)
missing	4 (1%)
Tumor incidentally found - n (%)	
No	1126 (47%)
Yes	983 (41%)
Not known	200 (8%)
missing	84 (4%)

The following differentiation is based on the WHO 2010 classification. Well differentiated neuroendocrine tumors (G1) are still the largest group of tumors. Neuroendocrine neoplasms G3 are much rarer. Of note there is not yet a sub-classification of G3 NEN in the registry. (Figure 4)

Figure 4: Tumor grading. Patient recruited in 2020 are highlighted in light grey



Treatment

Surgery

Surgery represents the most common treatment modality used (71.04% of patients). In median 1.3 surgery was performed per patient and 94% were curatively performed. 84% of the surgeries were R0 resection and 15% of the liver metastasis were resected. (Table 3).

Table 3: Surgery

	Surgeries	Patients*
Total	2196	1700
Center - n (%)		
University hospital	965 (44%)	758 (45%)
General hospital	1142 (52%)	911 (54%)
Private practise	67 (3%)	59 (3%)
Not known	20 (1%)	16 (1%)
missing	2 (0%)	2 (0%)
Surgery Type - n (%)		
Curative	1991 (91%)	1599 (94%)
Palliative	80 (4%)	70 (4%)
Not known	116 (5%)	87 (5%)
missing	9 (0%)	8 (0%)
Result Primary Tumor - n (%)		
R0 resection	1650 (75%)	1423 (84%)
R1 resection	102 (5%)	94 (6%)
R2 resection	8 (0%)	8 (0%)
Not applicable	177 (8%)	147 (9%)
Not known	231 (11%)	194 (11%)
missing	28 (1%)	23 (1%)
Result Metastases - n (%)		
R0 resection	173 (8%)	140 (8%)
R1 resection	42 (2%)	35 (2%)
R2 resection	4 (0%)	3 (0%)
Not applicable	1088 (50%)	959 (56%)
Not known	338 (15%)	276 (16%)
missing	551 (25%)	422 (25%)

Systemic treatment (Biotherapy)

The number of patients treated with different kinds of systemic therapies are limited, but steadily increasing (Table 4)

Table 4: overview of systemic treatments

modality	drug	Patient number
Biotherapy	Octreotid LAR	259
	Lanreotid	188
PRRT	Y-90-DOTATOC	39
	Lu- 77-DOTATATE	107
	Lu-177-DOTATOC	264
Molecular Tx	Sunitinib	29
	Everolimus	73
Chemotherapy	-	263

Somatostatin analogues

Octreotide and lanreotide were the most commonly prescribed somatostatin analogues. Both Lanreotide and Octreotide application have increased compared to 2019 and 2020. Reasons for this were the increase in NET patients by 2020 as well the inclusion of the total data of USZ and CHUV now by 2020. The promising results of the Clarinet-trial might explain this observation (Table 5).

Table 4: somatostatin analogues

Drug	year	Patient no.
Octreotid LAR	2014	65/87 (75%)
	2015	91/121 (75%)
	2016	108/149 (72%)
	2017	120/170 (71%)
	2018	136/206 (66%)
	2019	176/283 (62%)
	2020	336/625 (54%)
Lanreotid	2014	11/87 (13%)
	2015	22/121 (18%)
	2016	34/149 (23%)
	2017	47/170 (28%)
	2018	69/206 (33%)
	2019	111/283 (39%)
	2020	209/625 (33%)
Pasireotid	2018	5/206 (2%)
	2019	5/283 (1.7%)
	220	9/625 (1%)

Table 6: somatostatin analogues treatment according to primary NET site

	Octreotide LAR (N = 239)	Octreotide s.c. (N = 62)	Lanreotide (N = 188)	Pasireotide (N = 7)	Other Drug (N = 4)
Lung	12 (5%)	0 (0%)	5 (3%)	0 (0%)	0 (0%)
Stomach	4 (2%)	1 (2%)	3 (2%)	0 (0%)	0 (0%)
Pancreas	57 (24%)	28 (45%)	52 (28%)	2 (29%)	2 (50%)
Duodenum	4 (2%)	3 (5%)	4 (2%)	0 (0%)	0 (0%)
Ileum/jejunum	105 (44%)	17 (27%)	77 (41%)	2 (29%)	1 (25%)
Coecum	2 (1%)	0 (0%)	3 (2%)	0 (0%)	0 (0%)
Appendix	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Colon	2 (1%)	1 (2%)	2 (1%)	1 (14%)	0 (0%)
Sigma/rectum	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Rectum	2 (1%)	0 (0%)	6 (3%)	0 (0%)	0 (0%)
CUP	44 (18%)	12 (19%)	31 (16%)	1 (14%)	1 (25%)
Other	7 (3%)	0 (0%)	3 (2%)	1 (14%)	0 (0%)

Table 7: somatostatin analogues treatment according to NET differentiation

	Octreotide LAR (N = 239)	Octreotide s.c. (N = 62)	Lanreotide (N = 188)	Pasireotide (N = 7)	Other Drug (N = 4)
G1	79 (33%)	23 (37%)	70 (37%)	4 (57%)	1 (25%)
G2	108 (45%)	24 (39%)	91 (48%)	2 (29%)	2 (50%)
G3	20 (8%)	8 (13%)	13 (7%)	1 (14%)	0 (0%)
Not known	19 (8%)	3 (5%)	6 (3%)	0 (0%)	0 (0%)

Chemotherapy

In total, 327 patients were treated with classical chemotherapeutical agents. Carboplatin, cisplatin and etoposide were the drugs most commonly used in the metastatic setting. This is in contrast to the reported NET grading in our cohort. Based on the results of the NORDIC trial the efficacy of the agents mentioned above is mainly limited to poorly differentiated NET/NEC with a high (55% proliferation index). In addition and compared to former years the combination of Temodal plus Capecitabine (Xeloda) was used more often in 2020 with a total of 13%. (Table 8).

Table 8: chemotherapy agents

	Chemotherapies	Patients*
Total	1373	327
Scheme - n (%)		
Carboplatin+Etopophos	127 (9%)	89 (27%)
Cisplatin+Etopophos	78 (6%)	48 (15%)
Temodal+Xeloda	60 (4%)	43 (13%)
Temodal mono	10 (1%)	8 (2%)
Xeloda mono	7 (1%)	7 (2%)
STZ+5-FU+Doxo	25 (2%)	3 (1%)
STZ+Doxo	8 (1%)	1 (0%)
STZ+5-FU	4 (0%)	4 (1%)
5-FU mono	2 (0%)	2 (1%)
Cyclophosphamid	1 (0%)	1 (0%)
Oxaliplatin+5-FU+Bevacizumab	2 (0%)	2 (1%)
Other Drug	84 (6%)	55 (17%)
Not known	5 (0%)	2 (1%)
missing	960 (70%)	130 (40%)
Discontinuation - n (%)		
PD	103 (8%)	52 (16%)
Toxicity	75 (5%)	36 (11%)
Patient Wish	12 (1%)	9 (3%)
predefined	160 (12%)	107 (33%)
Other	299 (22%)	82 (25%)
Not known	200 (15%)	38 (12%)
missing	524 (38%)	111 (34%)

**Patients may not sum up as they can have several chemotherapies.*

Molecular therapies

As expected, everolimus and sunitinib were the most common used molecular therapy agents, in 73 and 29 patients, respectively (Table 9).

Table 9: molecular therapies

	Molecular therapies	Patients*
Total	142	97
Drug - n (%)		
Bevacizumab	1 (1%)	1 (1%)
RAD001/Everolimus	88 (62%)	73 (75%)
Sunitinib	36 (25%)	29 (30%)
Other Drug	17 (12%)	12 (12%)

**Patients may not sum up as they can have several molecular therapies.*

Sunitinib is commonly used in pancreatic NET which mirrors its approval. The use of molecular therapies according to primary NET site and NET differentiation is illustrated in table 10 and 11.

Table 10: molecular treatment according to primary NET site

	Bevacizumab (N = 1)	RAD001/Everolimus (N = 73)	Sunitinib (N = 29)	Other Drug (N = 12)
Lung	0 (0%)	9 (12%)	2 (7%)	4 (33%)
Stomach	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Pancreas	1 (100%)	28 (38%)	18 (62%)	3 (25%)
Duodenum	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Ileum/jejunum	0 (0%)	18 (25%)	3 (10%)	2 (17%)
Coecum	0 (0%)	0 (0%)	0 (0%)	1 (8%)
CUP	0 (0%)	12 (16%)	4 (14%)	0 (0%)
Other	0 (0%)	5 (7%)	1 (3%)	2 (17%)

Table 11: molecular treatment according to NET differentiation

	Bevacizumab (N = 1)	RAD001/Everolimus (N = 73)	Sunitinib (N = 29)	Other Drug (N = 12)
G1	0 (0%)	16 (22%)	3 (10%)	0 (0%)
G2	0 (0%)	34 (47%)	17 (59%)	6 (50%)
G3	0 (0%)	13 (18%)	6 (21%)	6 (50%)
Not known	1 (100%)	7 (10%)	3 (10%)	0 (0%)

Radiotherapy and targeted nuclear therapy

264 and 107 patients underwent a PRRT 90-Y-Dotatoc and 177-lutetium containing treatment, respectively. External radiation therapy seems to be an attractive treatment option in individual cases, as well (Table 13-15).

Table 13: radiotherapy and targeted nuclear therapy

	Irradiations	Patients*
Total	1287	420
Mode - n (%)		
External	182 (14%)	104 (25%)
PRRT Other	193 (15%)	107 (25%)
PRRT Lutetium Dotatoc	836 (65%)	264 (63%)
SIRT	52 (4%)	36 (9%)
Other	20 (2%)	19 (5%)
Not known	2 (0%)	1 (0%)
missing	2 (0%)	2 (0%)
Center - n (%)		
University hospital	1156 (90%)	365 (87%)
General hospital	116 (9%)	64 (15%)
Private practise	6 (0%)	4 (1%)
Not known	6 (0%)	5 (1%)
missing	3 (0%)	3 (1%)

**Patients may not sum up as they can have several irradiations.*

Table 14: radiotherapy and targeted nuclear therapy according to primary NET site

	External (N = 104)	PRRT Other (N = 107)	PRRT Lutetium Dotatoc (N = 264)	SIRT (N = 36)	Other (N = 19)	Not known (N = 1)
Lung	34 (33%)	5 (5%)	13 (5%)	2 (6%)	3 (16%)	1 (100%)
Oesophagus	4 (4%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)
Stomach	1 (1%)	1 (1%)	4 (2%)	0 (0%)	0 (0%)	0 (0%)
Pancreas	12 (12%)	42 (39%)	90 (34%)	15 (42%)	2 (11%)	0 (0%)
Duodenum	1 (1%)	2 (2%)	5 (2%)	0 (0%)	1 (5%)	0 (0%)
Ileum/jejunum	5 (5%)	30 (28%)	92 (35%)	12 (33%)	1 (5%)	0 (0%)
Coecum	0 (0%)	0 (0%)	1 (0%)	1 (3%)	1 (5%)	0 (0%)
Appendix	0 (0%)	1 (1%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Colon	3 (3%)	3 (3%)	5 (2%)	0 (0%)	0 (0%)	0 (0%)
Ascending colon	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sigma/rectum	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	0 (0%)
Rectum	4 (4%)	1 (1%)	6 (2%)	0 (0%)	2 (11%)	0 (0%)
CUP	13 (13%)	17 (16%)	39 (15%)	5 (14%)	3 (16%)	0 (0%)
Other	26 (25%)	5 (5%)	7 (3%)	0 (0%)	6 (32%)	0 (0%)

Table 15: radiotherapy and targeted nuclear therapy according to NET differentiation

	External (N = 104)	PRRT Other (N = 107)	PRRT Lutetium Dotatoc (N = 264)	SIRT (N = 36)	Other (N = 19)	Not known (N = 1)
G1	7 (7%)	29 (27%)	67 (25%)	7 (19%)	3 (16%)	0 (0%)
G2	18 (17%)	41 (38%)	123 (47%)	17 (47%)	7 (37%)	1 (100%)
G3	51 (49%)	16 (15%)	37 (14%)	8 (22%)	6 (32%)	0 (0%)
Not known	23 (22%)	10 (9%)	17 (6%)	3 (8%)	2 (11%)	0 (0%)

Outcome

No survival analysis has been performed in 2019 and 2020.

Research projects

a) published

- **Gouffon M**, Iff S, Ziegler K et al. Diagnosis and workup of 522 consecutive patients with neuroendocrine neoplasms in Switzerland. Swiss Med Wkly. 2014 Feb 19;144:w13924
- **Kollár A,** Blank A, Perren A et al. Additional malignancies in patients with neuroendocrine tumours: analysis of the SwissNET registry. Swiss Med Wkly. 2016 Nov 12;146:w14362
- **Sadowski SM**, Christ E, Bédat B et al. Nationwide multicenter study on the management of pulmonary neuroendocrine (carcinoid) tumors. Endocr Connect. 2018 Jan;7(1):8-15.
- **Kaderli R**, Spanjol M, Kollár A, Bütikofer L, Gloy V, Dumont RA, Seiler CA, Christ ER, Radojewski P, Briel M, Walter MA, Safety and efficacy of therapies for neuroendocrine tumors: Systematic review and network meta-analysis of randomized controlled trials; JAMA Oncol. 2019 Feb 14
- **Merola, Elettra**; Rinke, Anja; Partelli, Stefano; Gress, Thomas M; Andreasi, Valentina; Kollár, Attila; Perren, Aurel; Christ, Emanuel; Panzuto, Francesco; Pascher, Andreas; Jann, Henning; Arsenic, Ruza; Cremer, Birgit; Kaemmerer, Daniel; Kump, Patrizia; Lipp, Rainer W; Agaimy, Abbas; Wiedenmann, Bertram; Falconi, Massimo; Pavel, Marianne E. Surgery with Radical Intent: Is There an Indication for G3 Neuroendocrine Neoplasms? Annals of surgical oncology. , 2020, Vol.27(5), p.1348-1355
- **Attila Kollar,** Lukas Bütikofer, Adrian Ochsenbein, Christoph Stettler, Roman Trepp. Treatment sequence in patients with neuroendocrine tumours: a nationwide multicentre,

observational analysis of the Swiss neuroendocrine tumour registry. Swiss Med Wkly. 2020;150:w20176

- **Julie Refardt** , Zandee WT, Brabander T, Feelders RA, Franssen GJH, Hofland LJ, Christ E, de Herder WW, Hofland J. Inferior outcome of neuroendocrine tumor patients negative on somatostatin receptor imaging. Endocri Relat Cancer 2020 Nov;27(11):615-624. doi: 10.1530/ERC-20-0340.

b) Ongoing Projects

1. Analysis of Carcinoid Heart Disease in SWISSNet: ongoing (Lead: A. Siebenhüner)
2. The ENETS Registry: First results of a collaborative effort including >12'000 patients with NENs from 7 countries: ongoing (Lead: A. Kollar)

Financing

With regard to the finances, we received SRF 55'000.- from three sponsors (Novartis, Pfizer, AAA 15) and the membership fees added up to SFR 900.-. Compared to 2019 the membership fees were significantly lower.
The total income in 2020 was SFR 62'200.- , lower than expected because one sponsor provided no spnosorship in 2020. The main expenses include the salary for the research nurses working at the two sites (SFR Inselspital Bern; 40% and Universitätsspital Basel; 20%). Because the income was lower than anticipated (mainly by diminished sponsoring), the account closed with a negative balance sheet of 40'090.7.-. All the expenses were +/- within budget or lower.
The fortune of SWISSNet per 31. December 2020 add up to sFr. 80'119.02.-. It can, therefore, be stated that SWISSNet is financially still in a healthy situation. However, we have to consider the fact that to cover the current budget we need around SFR 80'000/year.

For 2021, the three sponsors have guaranteed to add the same amount as in 2020.

With the available finances and with the current state of our sponsors we can cover maximally two further years, which is required for a non-profit organisation. Whether we might be able to decrease the costs by collaborating with the national cancer registry has to be seen.