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

SwissNET

Präsident: Prof. Emanuel Christ
Registerleiter: Dr. Attila Kollàr

Report of the president

During the last months, SwissNET has confirmed its leading role as a network in the management of NET patients in Switzerland and at an international level. The SwissNET registry includes now about 1600 patients. Updates of the data set include systemic therapies and the new NEC G3, respectively NET G3 classification.

There were significant changes within the committee of SWISSNet. Maurice Matter stepped down in 2018, Samira Sadowski resigned as secretary because she left Switzerland to pursue her career as an endocrine surgeon in Washington (NIH) and Attila Kollar will step down as head of the registry at the general assembly in 2019. A very warm thank you for your dedication and effort towards our association.

Luckily, the committee is now again complete with several motivated and well-known experts in the NET field: the new secretary is Reto Kaderli, endocrine surgeon in Bern (Inselspital), Alexander Siebenhüner (oncologist, USZ) will take on the task of Attila Kollar as head of the registry and myself, I was elected president last year. The financial responsibility (which was my responsibility since the beginning of the registry) will be taken over by Ralph Winterhalder, oncologist in Lucerne. Furthermore, we are happy to welcome Martin Walter (Head of Nuclear Medicine at the University Hospital of Geneva) as Vice-President and Guillaume Nicolas (nuclear medicine physician, University Hospital of Basel), Roman Trepp (endocrinologist, Inselspital) and Niklaus Schäfer, (Nuclear Medicine and Oncology, CHUV). Aurel Perren, pathologist, Bern, remains in the committee and provides important international inputs as a member of the ENETS committee.

Developments of ENETS Centres of Excellence) in Switzerland is an ongoing process: The University Hospital of Zurich is a re-certified ENETS centre of excellence, the University Hospital of Lausanne (CHUV) has been accepted as a new ENETS centre of excellence in April 2019 and the University Hospital of Basel will submit its application in 2019.

Thanks to the hard work undertaken by Attila Kollar and our fruitful collaboration with ENETS and the Registry meetings, Switzerland belongs to the core of the multinational ENETS registry who was launched in 2015. In 2018, data from seven countries (Belgium, Czech Republic, Germany, Greece, Poland, Spain and Switzerland) were presented at ASCO. Eleven percent of the data of the ENETS registry were provided by SWISSNet. The ENETS NET registry is to date the largest multinational dataset of NEN patients.

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. Our now well-established annual sponsor meeting and the SWISSNet evening in Barcelona (ENETS congress) promotes our achievements and upcoming projects.

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

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Database Report 2018

In total, 1586 patients are included in the SwissNET registry. Since the last statistical analysis of the SwissNET data 162 additional patients were registered and documented which represents a significant increase (11%) in patient number.

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 2.6 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
Number of patients	**835**	**1050**	**1245**	**1428**	**1586**
Females (%)	46	46	47	47	47
Males (%)	54	54	53	53	53
Age at diagnosis (y)					
Mean	59.3	59.9	59.6	60.1	60.3
Follow-up					
Median (years)	2	2.1	2.23	2.38	2.61

Recruitment

Virtually all institutions, hospitals and cantons are recruiting NET patients. Most of the patients are recruited by the established major centers in Lausanne, Berne, St. Gallen, Geneve and Basel. However, half of the included patients are from other hospitals or private practices. (Figure 1/2)

Figure 1: Recruitment of patients: dark grey: 2008-2017, grey: 2018

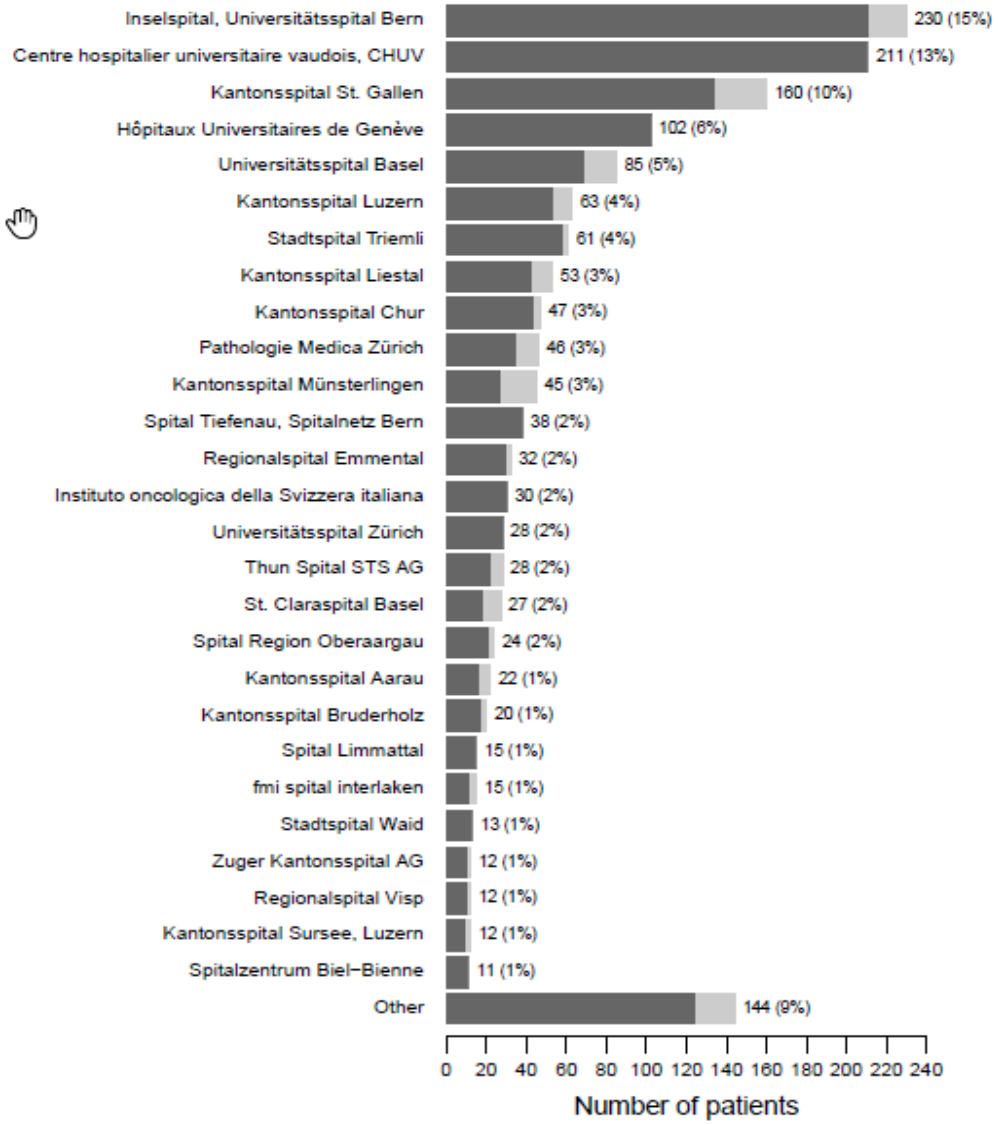
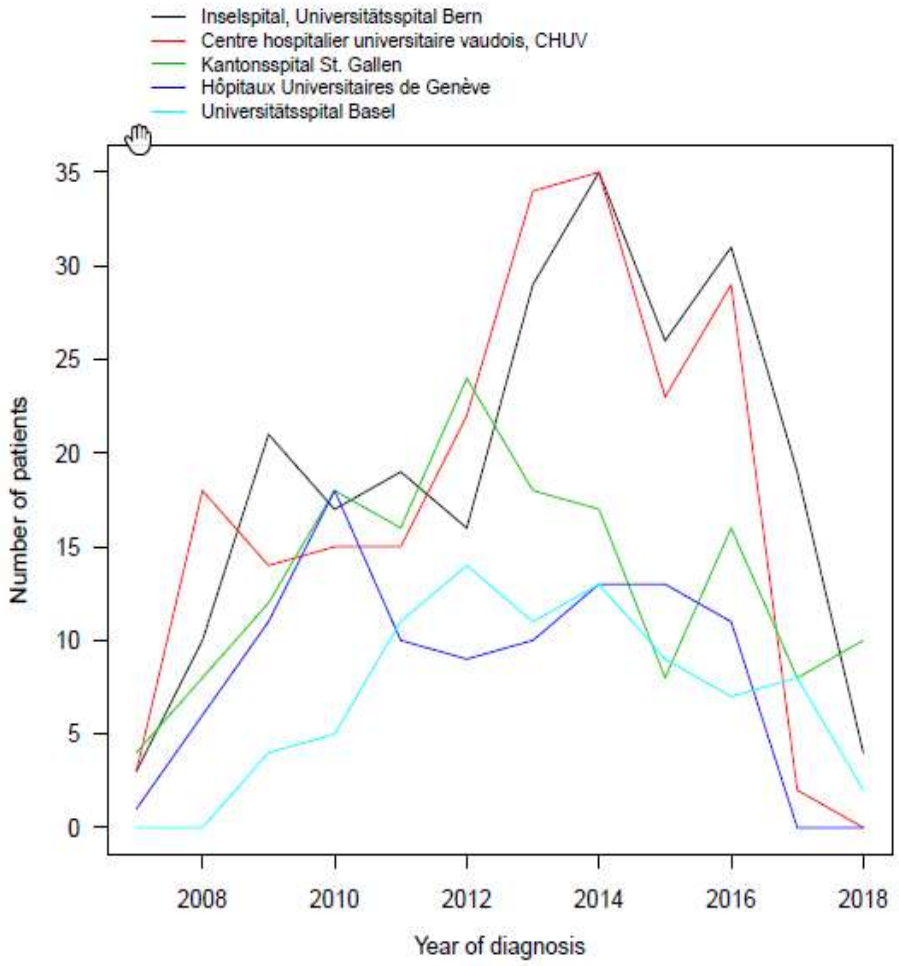


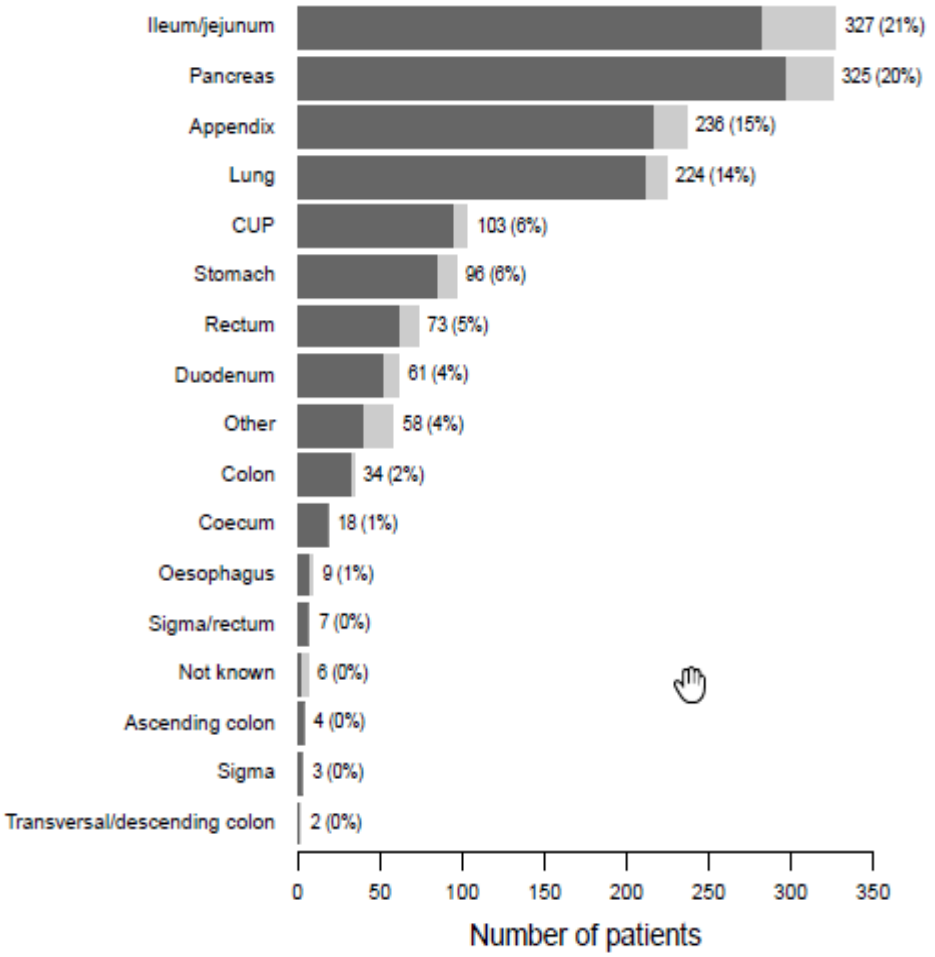
Figure 2: Number of patients recruited each year for the main centers



Distribution of primary sites and tumor grade

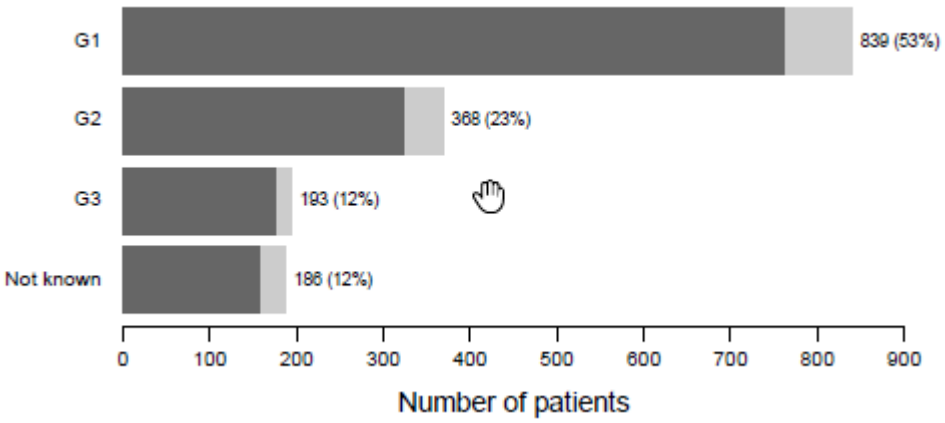
Most of the NET registered in the database are of pancreatic and ileal/jejunal origin. NET of the appendix, lung and of unknown origin are quite common, too. There's a slight, but steady increase in the number of NET at rarer primary sites. (Figure 3)

Figure 3: Distribution of primary sites of NET



The following differentiation is based on the WHO 2010 classification. Well differentiated neuroendocrine tumors are still the largest group of tumors. Neuroendocrine neoplasms G3 are much rarer. (Figure 4)

Figure 4: Tumor grading



Treatment

Surgery

Surgery represents the most common treatment modality used (74% of patients). Tumor resection was performed in 44% and 55% in university hospitals and general hospitals, respectively (Table 2).

Table 2: Surgery

	no. of surgeries	n (%)	no. of patients	n (%)*
Total	1584 (1.3 per patient)		1180	
Center	1582		1179	
University hospital		651 (41%)		496 (42%)
General hospital		877 (55%)		666 (56%)
Private practise		39 (2%)		36 (3%)

Systemic treatment

The number of patients treated with different kinds of systemic therapies are limited, but steadily increasing (table 3)

Table 3: overview of systemic treatments

modality	drug	Patient number
biotherapy	Octreotid LAR	136
	Lanreotid	69
PRRT	Y-90-DOTATOC	82
	Lu- 77-DOTATATE	40
	Lu-177-DOTATOC	77
Molecular Tx	Sunitinib	21
	Everolimus	46
Chemotherapy	-	154

Somatostatin analogues

Octreotide and lanreotide were the most commonly prescribed somatostatin analogues. Whereas the use of octreotid was slightly below the percentage of last year, the use of lanreotide has increased. The promising results of the Clarinet-trial might explain this observation (Table 4).

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%)
Lanreotid	2014	11/87 (13%)
	2015	22/121 (18%)
	2016	34/149 (23%)
	2017	47/170 (28%)
	2018	69/206 (33%)
Pasireotid	2018	5/206 (2%)

Table 5: somatostatin analogues treatment according to primary NET site

	Octreotide LAR (N = 136)	Octreotide s.c. (N = 46)	Lanreotide (N = 69)
Lung	8 (100%)	0 (100%)	2 (100%)
Stomach	1 (100%)	0 (100%)	1 (100%)
Pancreas	36 (100%)	21 (100%)	22 (100%)
Duodenum	2 (100%)	1 (100%)	2 (100%)
Ileum/jejunum	55 (100%)	14 (100%)	25 (100%)
Coecum	1 (100%)	0 (100%)	1 (100%)
Appendix	0 (100%)	0 (100%)	1 (100%)
Colon	1 (100%)	1 (100%)	0 (100%)
Rectum	1 (100%)	0 (100%)	1 (100%)
CUP	27 (100%)	9 (100%)	12 (100%)
Other	4 (100%)	0 (100%)	1 (100%)
Not known	0 (100%)	0 (100%)	1 (100%)

Table 6: somatostatin analogues treatment according to NET differentiation

	Octreotide LAR (N = 136)	Octreotide s.c. (N = 46)	Lanreotide (N = 69)
G1	46 (100%)	18 (100%)	27 (100%)
G2	63 (100%)	20 (100%)	31 (100%)
G3	13 (100%)	4 (100%)	5 (100%)
Not known	9 (100%)	1 (100%)	1 (100%)

Chemotherapy

In total, 188 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) (Table 7).

Table 7: chemotherapy agents

	no. of chemotherapies	n (%)	no. of patients	n (%)*
Total	1222 (5.8 per patient)		211	
Drug	1111		154	
Carboplatin		199 (18%)		80 (52%)
Cisplatin		144 (13%)		54 (35%)
Cyclophosphamide		18 (2%)		12 (8%)
Dacarbazin		2 (0%)		1 (1%)
Doxorubicin		33 (3%)		16 (10%)
Etoposide		294 (26%)		104 (68%)
5-FU		70 (6%)		20 (13%)
Streptozotocin		42 (4%)		15 (10%)
Temozolomide		58 (5%)		24 (16%)
Capecitabine		32 (3%)		19 (12%)
Other Drug		219 (20%)		60 (39%)

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

Molecular therapies

As expected, everolimus and sunitinib were the most common used melocular therapy agent, in 46 and 21 patients, respectively (Table 8).

Table 8: molecular therapies

	no. of molecular therapies	n (%)	no. of patients	n (%)*
Total	99 (1.6 per patient)		63	
Drug	99		63	
Bevacizumab		1 (1%)		1 (2%)
RAD001/Everolimus		58 (59%)		46 (73%)
Sunitinib		28 (28%)		21 (33%)
Other Drug		12 (12%)		10 (16%)

**Patients do 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 9 and 10.

Table 9: molecular treatment according to primary NET site

	Bevacizumab (N = 1)	RAD001/Everolimus (N = 46)	Sunitinib (N = 21)	Other Drug (N = 10)
Lung	0 (100%)	4 (100%)	1 (100%)	4 (100%)
Stomach	0 (100%)	0 (100%)	1 (100%)	0 (100%)
Pancreas	1 (100%)	18 (100%)	13 (100%)	4 (100%)
Duodenum	0 (100%)	1 (100%)	0 (100%)	0 (100%)
Ileum/jejunum	0 (100%)	12 (100%)	2 (100%)	2 (100%)
CUP	0 (100%)	8 (100%)	3 (100%)	0 (100%)
Other	0 (100%)	3 (100%)	1 (100%)	0 (100%)

Table 10: molecular treatment according to NET differentiation

	Bevacizumab (N = 1)	RAD001/Everolimus (N = 46)	Sunitinib (N = 21)
G1	0 (100%)	8 (100%)	1 (100%)
G2	0 (100%)	21 (100%)	13 (100%)
G3	0 (100%)	10 (100%)	5 (100%)
Not known	1 (100%)	5 (100%)	2 (100%)

Radiotherapy and targeted nuclear therapy

81 and 89 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 12-14).

Table 12: radiotherapy and targeted nuclear therapy

	no. of irradiations	n (%)	no. of patients	n (%)*
Total	608 (2.7 per patient)		226	
Mode	606		225	
External		120 (20%)		64 (28%)
PRRT Y-90-Dotatoc		148 (24%)		82 (36%)
PRRT 177-lutetium Dotatate		100 (17%)		40 (18%)
PRRT Lutetium Dotatoc		195 (32%)		77 (34%)
SIRT		26 (4%)		19 (8%)
Other		15 (2%)		15 (7%)
Not known		2 (0%)		1 (0%)
Center	605		225	
University hospital		533 (88%)		193 (86%)
General hospital		62 (10%)		36 (16%)
Private practise		6 (1%)		4 (2%)
Not known		4 (1%)		3 (1%)

Patients do not sum up as they can have several irradiations.

Table 13: radiotherapy and targeted nuclear therapy according to primary NET site

	External (N = 64)	PRRT Y-90-Dotatoc (N = 82)	PRRT 177-lutetium Dotatate (N = 40)	PRRT Lutetium Dotatoc (N = 77)	SIRT (N = 19)	Other (N = 15)	Not known (N = 1)
Lung	30 (100%)	5 (100%)	3 (100%)	4 (100%)	0 (100%)	2 (100%)	1 (100%)
Oesophagus	3 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Stomach	0 (100%)	1 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (100%)	0 (100%)
Pancreas	7 (100%)	36 (100%)	15 (100%)	24 (100%)	10 (100%)	2 (100%)	0 (100%)
Duodenum	1 (100%)	2 (100%)	2 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Ileum/jejunum	4 (100%)	20 (100%)	13 (100%)	27 (100%)	5 (100%)	0 (100%)	0 (100%)
Coecum	0 (100%)	0 (100%)	0 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (100%)
Appendix	0 (100%)	1 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (100%)	0 (100%)
Colon	1 (100%)	1 (100%)	2 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Ascending colon	1 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Rectum	1 (100%)	1 (100%)	0 (100%)	1 (100%)	0 (100%)	2 (100%)	0 (100%)
CUP	4 (100%)	12 (100%)	5 (100%)	14 (100%)	2 (100%)	2 (100%)	0 (100%)
Other	12 (100%)	3 (100%)	0 (100%)	3 (100%)	1 (100%)	6 (100%)	0 (100%)
Not known	0 (100%)	0 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (100%)	0 (100%)

Table 14: radiotherapy and targeted nuclear therapy according to NET differentiation

	External (N = 64)	PRRT Y-90-Dotatoc (N = 82)	PRRT 177-lutetium Dotatate (N = 40)	PRRT Lutetium Dotatoc (N = 77)	SIRT (N = 19)	Other (N = 15)	Not known (N = 1)
Lung	30 (100%)	5 (100%)	3 (100%)	4 (100%)	0 (100%)	2 (100%)	1 (100%)
Oesophagus	3 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Stomach	0 (100%)	1 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (100%)	0 (100%)
Pancreas	7 (100%)	36 (100%)	15 (100%)	24 (100%)	10 (100%)	2 (100%)	0 (100%)
Duodenum	1 (100%)	2 (100%)	2 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Ileum/jejunum	4 (100%)	20 (100%)	13 (100%)	27 (100%)	5 (100%)	0 (100%)	0 (100%)
Coecum	0 (100%)	0 (100%)	0 (100%)	1 (100%)	1 (100%)	1 (100%)	0 (100%)
Appendix	0 (100%)	1 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (100%)	0 (100%)
Colon	1 (100%)	1 (100%)	2 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Ascending colon	1 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)	0 (100%)
Rectum	1 (100%)	1 (100%)	0 (100%)	1 (100%)	0 (100%)	2 (100%)	0 (100%)
CUP	4 (100%)	12 (100%)	5 (100%)	14 (100%)	2 (100%)	2 (100%)	0 (100%)
Other	12 (100%)	3 (100%)	0 (100%)	3 (100%)	1 (100%)	6 (100%)	0 (100%)
Not known	0 (100%)	0 (100%)	0 (100%)	1 (100%)	0 (100%)	0 (100%)	0 (100%)

Outcome

No survival analysis has been performed in 2018.

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

b) Ongoing

Title	Collaboration	Author(s)
Value of octreoscan and 18F-FDG PET for clinical prognosis of patients with neuroendocrine neoplasms	national	Pralong F. et al
eviNET - A network meta-analysis of therapeutic options for the treatment of neuroendocrine tumors	national	Kaderli R, Walter M et al.
Treatment pattern in neuroendocrine tumors: Analysis of the SwissNET Database	national	Kollár A, Trepp R et al.
Analysis of CHD among the SwissNET registry	national	Siebenhüner A. et al.
The ENETS Registry: First Results of a Collaborative Effort Including Over 12.000 Patients with Neuroendocrine Neoplasms (NENs) from 7 European Countries	international	Borbath Y, Kollár A. et al
Surgery is there an indication for G3 neuroendocrine neoplasms	international	Merola E, Christ E, Perren A, Kollár A

Financing

With regard to the finances, we received sFr.65'000 from three sponsors (IPSEN 25k, Novartis 25k, Pfizer 15k) and the membership fees added up to sFR 1'100.-. Compared to 2017 the member fees were significantly lower by sFR 750, reason are unclear as no official dropout was noticed.

The total income in 2018 was sFr. 66'150. - , but sFR 24'150 higher than 2016 as the third sponsoring party added an important sFR 15'000- . The main expenses include the salary for the research nurses working at the two sites (sFr. Inselspital Bern; 40% and CHUV; 20%). Because the income was lower than anticipated (mainly by unclear missing payment of membership), the account closed with a negative balance sheet of 8'411.15.-. With the exception of the expenses for the CTU (<5000.- instead of the budget of 1'100.-), all the other expenses were +/- within budget or lower.

The fortune of SWISSNet per 31. December 2018 add up to sFr. 133'659.-. 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 2019, two out of three sponsors have guaranteed to add the same amount as in 2018. The negotiations with third Sponsor are ongoing but we are optimistic that we shall finally receive the funding as anticipated.

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. Furthermore, it is likely that we shall have to increase the activity level of our research nurses since there are more and follow-up data to put into the database. Consequently, we should aim to recruit additional sponsors for SWISSNet. This will be a priority task for the committee of SWISSNet next year.