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

SwissNET

Präsident: PD Dr. Maurice Matter
Registerleiter: Dr. Attila Kollàr

Introduction to the 2015 annual SwissNET , report of the president

2015 was a fruitful year. SwissNET has been recognized as a partner with ENETS and our 4th pre-meeting SwissNET at ENETS was again a success. We are now able to use the database in order to produce scientific papers, that are already published or are in press. We must acknowledge that these data did not represent all NETs in Switzerland but our annual recruitment is growing and collaborations with different large hospitals will enable us to get the highest incidence so far. We estimated that more than two thirds of new cases are included: the only large review to date (1) with the best available estimations referred to an incidence rate of about 3-4 / 100'000 ten years ago. As mentioned below by Attila Kollar a major step for the exploitation of the data base was the possibility to reopen retrospectively the patients' identity in order to complete information for research purpose within the framework of the Ethics law.

A new partnership was created following contacts with the Groupe Français des Tumeurs Endocrines (GTE) and his president Prof Antoine Tabarin. We were invited to present our Society and to participate to the GTE itself. As a result, a "SwissNET session" will take place during the next GTE conference in 2016.

Finally, a partnership agreement was discussed with Victory NET foundation. Their purpose is mainly to improve patients' awareness, information and care but also to promote research in the field of NETs. For SwissNET this partnership will translate: first in facilities for patients' information in all languages and accessible through our website and second in the promotion of training dedicated NET nurses in our 6 main universities. This will start in 2016 as well.

While awaiting a Swiss policy for cancer registration, SwissNET stays the only available source for credible NETs data. All the above mentioned collaborations and future ones definitively strengthen our works. In this setting we must thank again the continuous support of our sponsoring: Novartis, Pfizer Oncology and Ipsen, ensuring the future of our association.

Dr. Maurice Matter, PD & MER
Médecin chef
Service de Chirurgie Viscérale, CHUV Lausanne.
Fellow of the European Society of Endocrine Surgery
President SwissNET

1. Fraenkel M, Kim M, Faggiano A, de Herder WW, Valk GD. Incidence of gastroenteropancreatic neuroendocrine tumours: a systematic review of the literature. Endocr Rel Cancer 2014, 21: R153–R163.

Database Report 2015

After the data transfer from an access-based database on a stand-alone computer to a web-based version in 2014 the inclusion and documentation of NET patients went on quite smoothly. Due to the increase in patient numbers recorded in the SwissNET registry the workload of the study nurses reaches a borderline level.

This year's highlight is represented by another renewal of the ethical approval. The major limitation of the SwissNET database was that only encoded/ pseudonymized data could be provided to researchers. This condition hampered potential research projects where additional data not included in the registry had to be collected for the endpoint analysis. To change this, we adapted the patient information sheet and the consent form asking the patients for allowance to provide researchers with patient names in order to answer scientific questions. The main precondition is that the research project has to be approved by the corresponding ethical committee with the aim of protecting patient data. The submitted changes were finally approved by the ethical committee in December 2015. This matter of facts opens the SwissNET registry for a broader and a more innovative research activity.

Currently, 4 research projects are running:

- Incidence and outcome of patients with neuroendocrine tumors and additional malignancies (Dr. A. Kollàr, Bern)
- Value of octreoscan and 18F-FDG PET for clinical prognosis of patients with neuroendocrine neoplasms (Prof. F. Pralong, Lausanne)
- Evidence-based medicine in neuroendocrine tumors: impact on long-term survival (eviNET study) (Dr. R. Kaderli, Bern/Vienna)
- Management of pulmonary carcinoids (typical and atypical): the Swiss experience (Dr. S. Sadikowski, Geneva)

The results are eagerly awaited.

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Analysis of data 2015

In total, 1050 patients are included in the SwissNET registry. Since the last statistical analysis of the SwissNET data 215 additional patients were registered and documented which represents an increase of 26%.

a) Patient characteristics and Follow up

The distribution of male and female patients (male: 54%, female: 46%) is relatively equal. The median follow up time increased to 2.1 years. There was no change in the mean age at diagnosis in comparison to data from 2013.

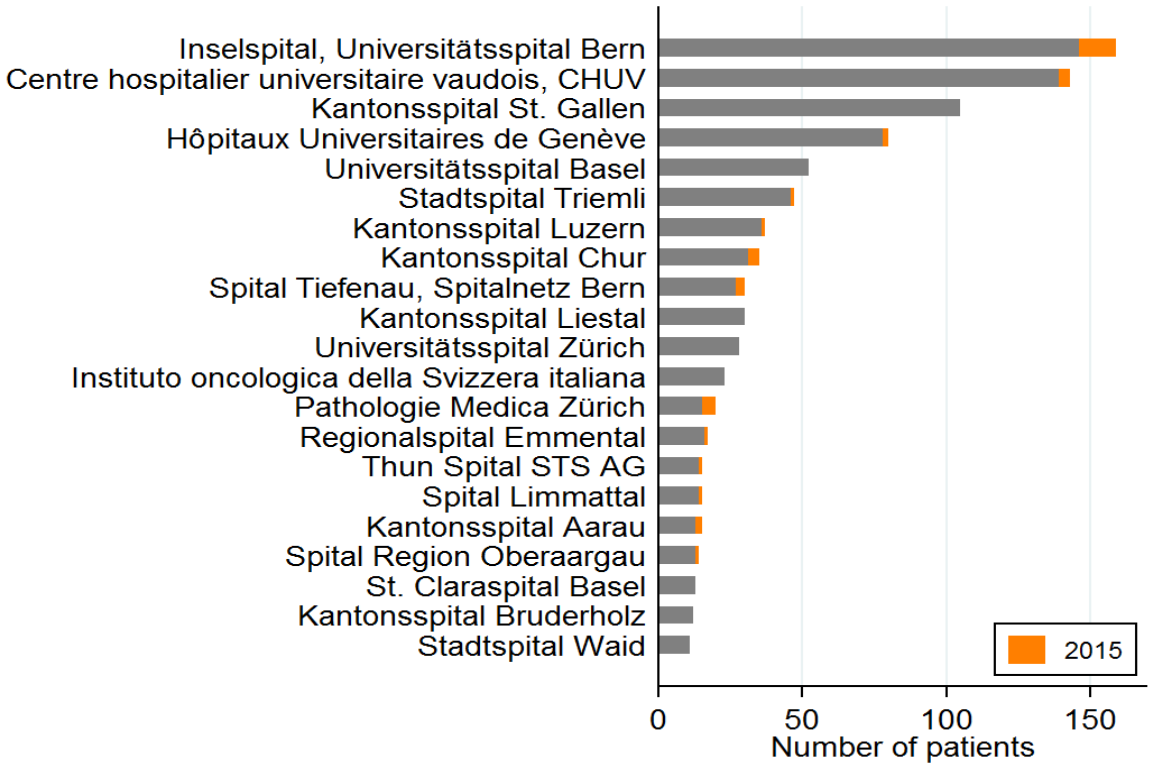
Table 1: Patient characteristics

Year	2013	2014	2015
Number of patients	**671**	**835**	**1050**
Females	47%	46%	46%
Males	53%	54%	54%
Age at diagnosis (y)			
Mean	59	59.3	59.9
Follow-up			
Median (years)	1.25	2	2.1

b) Recruitment

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

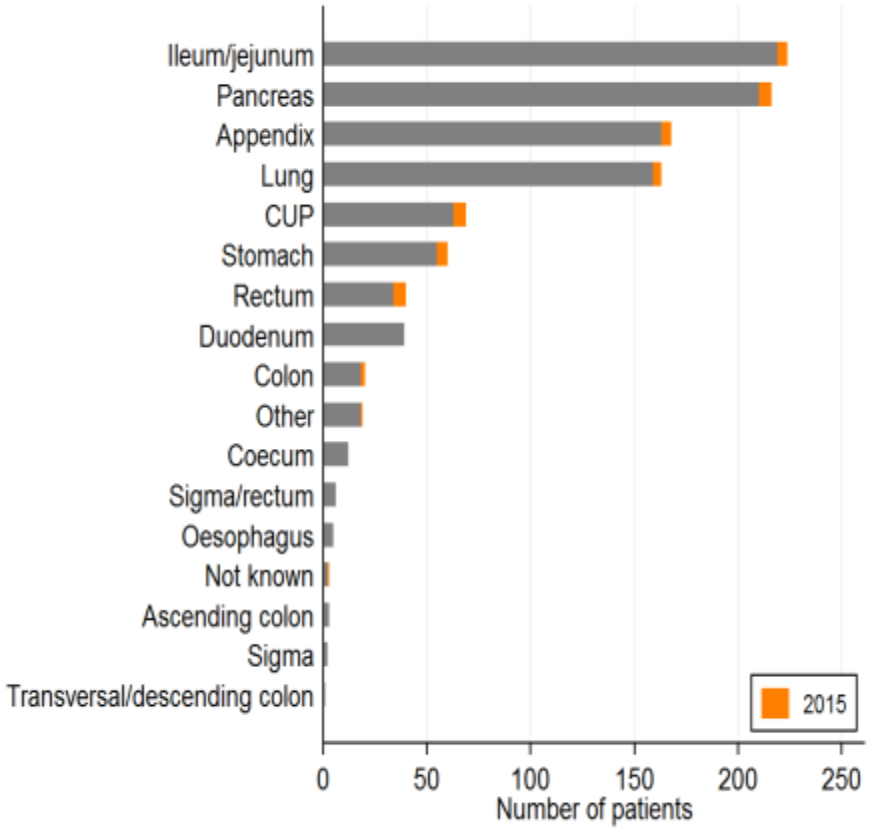
Figure 1: Recruitment of patients: grey: 2008-2014, orange: 2015



c) Distribution of primary sites and tumor grade

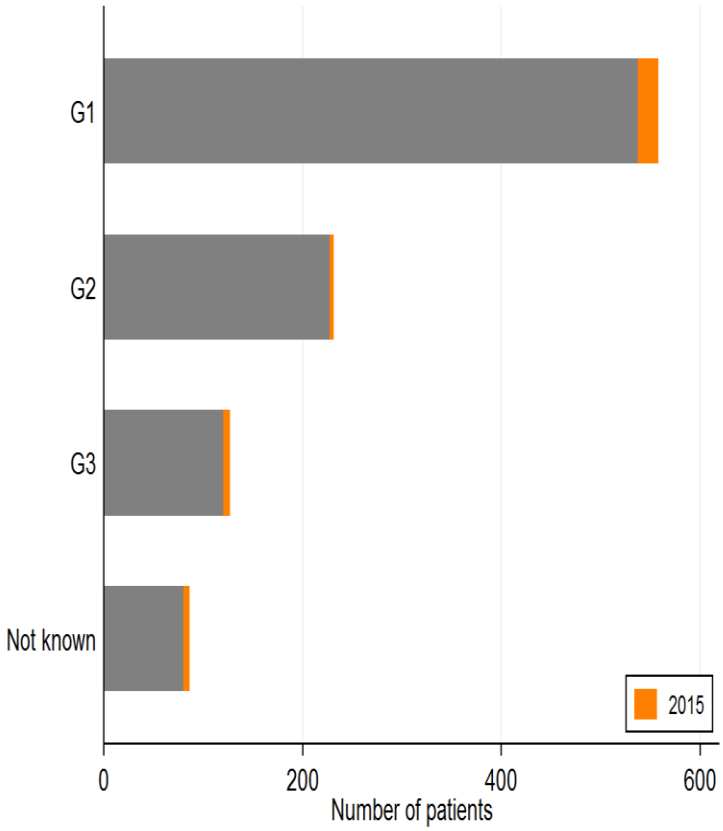
Most of the NET registered in the database are of ileal/jejunal and pancreatic origin. NET of the appendix, lung and of unknown origin are quite common, too. There's a slight, but steady increase in the incidence of NET at rarer primary sites.

Figure 2: 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 carcinomas are much rarer.

Figure 3: Tumor grading



d) Treatment

Surgery represents the most common treatment modality used (75% of patients). Tumor resection was performed in 43% and 55% in university hospitals and general hospitals, respectively (Table 2).

Octreotide and lanreotide were the most commonly prescribed somatostatin analogues. Whereas the use of octreotid was documented to be in the same range than the year before, the use of lanreotide has increased. The promising results of the Clarinet-trial might explain this observation (Table 3).

In total, 141 patients were treated with classical chemotherapeutical agents. Carboplatin, cisplatin and etoposide were the drugs most commonly used in the metatstatic setting. This is in contrast to the reported NET grading in our cohort. Based on the results of the NORDIC trial the efficacy of these agents is mainly limited to G1 and G2 differentiated neoplasms (Table 4).

As expected, everolimus and sunitinib were the most common used melocular therapy agent, in 27 and 16 patients, respectively (Table 5).

36% and 10% of the patients underwent a PRRT 90-Y-Dotatoc and 177-lutetium Dotatate treatment. External radiation therapy seems to be an attractive treatment option in individual cases, as well (Table 6).

Table 2: Surgery

	Surgeries	Patients*
Total	1096	791
per patient	1.4 ± 0.7	
Center	n = 1090,	n = 788,
University hospital	469 (43%)	348 (44%)
General hospital	603 (55%)	439 (56%)
Private practise	7 (1%)	7 (1%)
Not known	11 (1%)	7 (1%)

Table 3: somatostatin analogues

drug	year	Patient no.
Octreotid LAR	2014	65/87 (75%)
	2015	91/121 (75%)
Lanreotid	2014	11/87 (13%)
	2015	22/121 (18%)
Pasireotid	2014	2/87 (2%)
	2015	2/121 (2%)

Table 4: chemotherapy

	Chemotherapies	Patients*
Total	1041	141
per patient	7.4 ± 6.1	
Drug	n = 1041,	n = 141,
Carboplatin	193 (19%)	75 (53%)
Cisplatin	132 (13%)	50 (35%)
Cyclophosphamide	17 (2%)	11 (8%)
Dacarbazin	2 (0%)	1 (1%)
Doxorubicin	31 (3%)	14 (10%)
Etoposide	277 (27%)	95 (67%)
5-FU	69 (7%)	19 (13%)
Streptozotocin	41 (4%)	14 (10%)
Temozolomide	48 (5%)	17 (12%)
Capecitabine	21 (2%)	12 (9%)
Other Drug	210 (20%)	57 (40%)

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

Table 5: molecular therapies

	Molecular therapies	Patients*
Total	64	40
per patient	1.6 ± 0.9	
Drug	n = 64,	n = 40,
Bevacizumab	1 (2%)	1 (3%)
RAD001/Everolimus	35 (55%)	27 (68%)
Sunitinib	21 (33%)	16 (40%)
Other Drug	7 (11%)	6 (15%)

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

Table 6: radiotherapy and targeted nuclear therapy

	Irradiations	Patients*
Total	352	143
per patient	2.5 ± 1.4	
Mode	n = 352,	n = 143,
External	95 (27%)	42 (29%)
PRRT Y-90-Dotatoc	128 (36%)	69 (48%)
PRRT 177-lutetium Dotatate	34 (10%)	18 (13%)
PRRT 111-indium-Octreotide	1 (0%)	1 (1%)
PRRT Lutetium Dotatoc	74 (21%)	35 (24%)
SIRT	13 (4%)	9 (6%)
Other	7 (2%)	7 (5%)
Center	n = 351,	n = 142,
University hospital	333 (95%)	130 (92%)
General hospital	15 (4%)	12 (8%)
Private practise	1 (0%)	1 (1%)
Not known	2 (1%)	2 (1%)

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

e) outcome

In total, the remission status at last visit is recorded in 966 patients, 49% of patients are documented to be in complete remission. Partial remission, stable and progressive disease are recorded in 1%, 10%, and 6%, respectively. In 25% the remission status is not known (Table 7). Please find the mortality analysis performed in 2014 in the figures below (Figure 4 and 5). The survival analysis demonstrated a significant worse outcome for patients with poorly differentiated (G3) neuroendocrine neoplasms. Patients with well differentiated tumors, G1, had the best

prognosis. Female had a marginal, statistical not significant, better outcome in comparison to male gender.

Table 7: Remission status

Result, last visit	n = 966,
Complete remission	474 (49%)
Partial remission	9 (1%)
Stable disease	100 (10%)
Progressive disease	62 (6%)
Relapse	5 (1%)

Figure 4: Cumulative mortality of NET patients after major diagnosis by maximal histological grading.

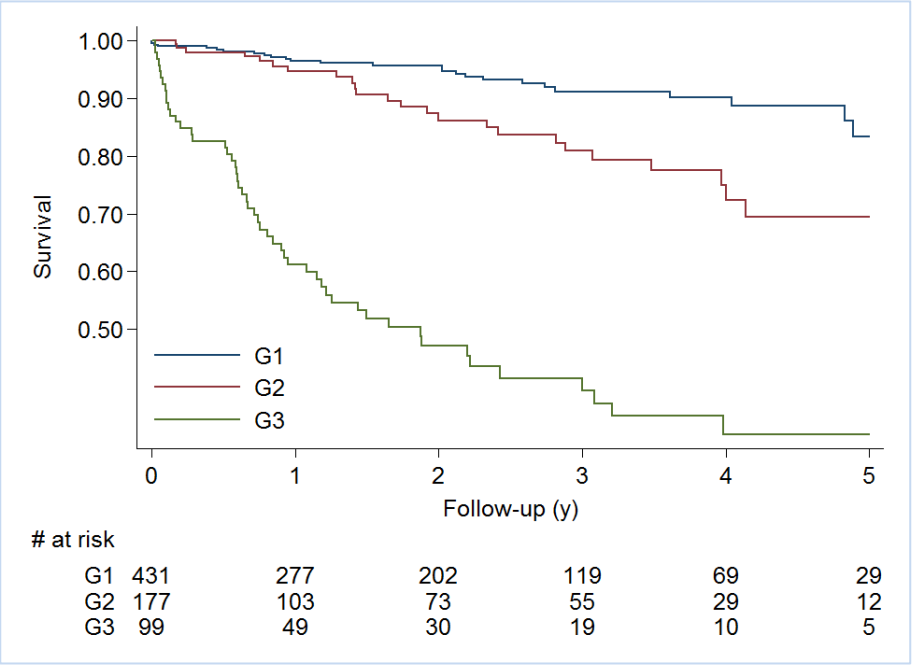
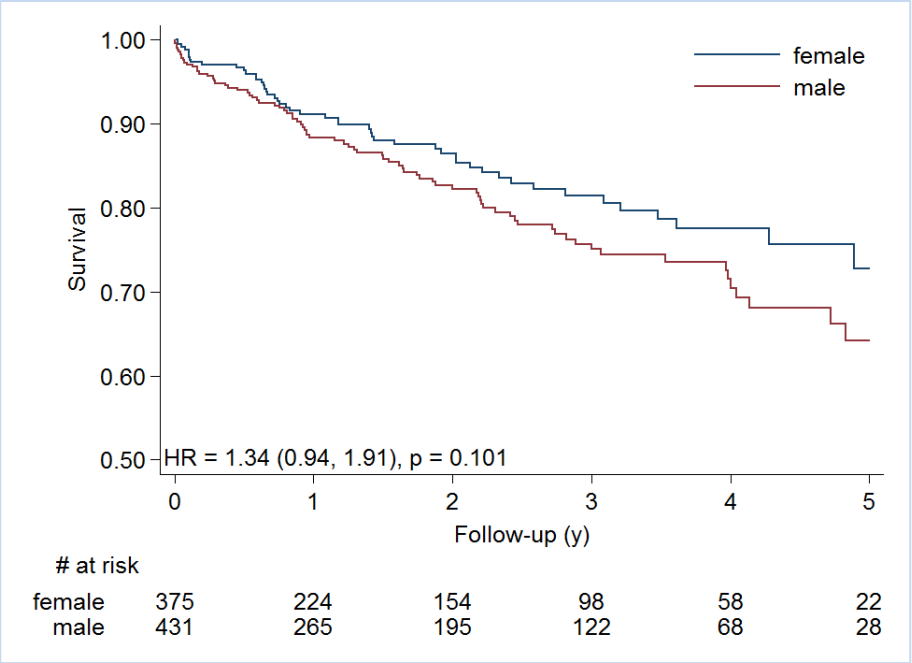


Figure 5: Cumulative mortality of NET patients after major diagnosis by gender. HR: hazard ratio from a Cox proportional hazard models with corresponding 95% confidence intervals.



Financing

With regard to the finances we received sFr. 64'980 from our three sponsors and the membership fees added up to 1'550.- (sFr. 400.- more than in 2014) . Together with the interest of the bank account the total income in 2014 was sFr. 66'536.- , comparable with 2014. The main expenses include the salary for the research nurses working at the two sites (sFr. Inselspital Bern; 20-30% and CHUV; 20%). Furthermore Dr. Annika Blank started to work 20% as a coordinator of SWISSNET in Bern (Institute of Pathology). Her main task was to give the necessary medical support to the research nurses and prepare and accomplish the move of the database to a web-based tool (in close collaboration with the CTU). This task was accomplished by the end of 2014, half of her annual salary had to booked in 2015 (24.212.-) . There were no additional costs for software or moving database. Due to the fact that all the other expenses (overheads for the research nurses, homepage) were considerably lower the balance closed with only a small negative balance sheet of sFr. -8'797.- (Budget: -19'800).

The fortune of SWISSNet per 31. December 2014 add up to sFr. 153'555.-. It, therefore, can 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 about sFr 70'000 – 75'000/year. With the available finances and without our sponsors we can cover maximally two further years. Furthermore, it is likely that we shall have to increase the activity level of our research nurses since there are more and more follow-up data to be put into the database. I, therefore, think that we have to aim for a budget of close to sFr. 100'000/year in order to fulfil all the tasks of SWISSNet in the near future. Consequently, we should aim to recruit additional sponsors for SWISSNet.