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

Gastroenteropancreatic Neuroendocrine tumors (NETs) have a low incidence: overall more than 5/100'000. The significant growing incidence has been attributed to diagnostic tools (endoscopy, radiology) (1) and possibly other environmental factors. Small bowel (mainly ileum) NETs are the most frequently encountered followed by large bowel NETs including appendix. Pancreatic NETs have an incidence of about 1/100'000 person accounting for 3-5% of all pancreatic malignancies (2). It is no mystery why patients with pNETs represent the larger group in the SwissNET database presented below. Patients are included mainly form University centers and are overrepresented. However, it is in patients with pNETs where important advances have been observed regarding treatments options. Fortunately the recruitment of patients from many other centers parallels the arrival of new SwissNET members. Lung NETs are also included and are well represented in the data base. NETs are regarded and registered as orphan disease and SwissNET is now included as a registry in the Orphanet website (3).

2014 is the year for migration of the data base to a web base system facilitating data registration and access. With a growing database and nearly 700 patients registered, it is time now to start analysis and research. To this end a scientific committee has been reinforced. Dr. Attila Kollar is running the data base with Dr. Annika Blank as scientific advisor and coordinator for the registry and Dr. Samuel Iff as statistical advisor. The bylaws presented and accepted at the last general assembly of SwissNET are on the website. One of the main conditions for submitting a research protocol is to be member of SwissNET. The informed consent has been adapted accordingly. A first paper has been published in Swiss Medical Weekly (4) showing that western part and eastern part of Switzerland do not differ regarding epidemiology and treatments. It showed also that the first line therapy was surgery in 87% of patients and medical therapy in 9% only.

The purpose of the cohort study is to approach as far as possible the incidence of NET in the Swiss population in order to make serious advances in the understanding of the NETs diseases and their treatments options. It should be also possible in the near future to include data at a European level when ENETS database will be operational. There is an obvious necessity of new prospective studies as treatment options are growing. Finally SwissNET works is made possible thank to the continuous support of our sponsoring: Novartis, Pfizer Oncology and Ipsen.

Dr. Maurice Matter, PD & MER
Médecin adjoint. President SwissNET 2013-2014

Reference:

1. Turaga KK, Kvols LK. **Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors.** *CA Cancer J Clin* 2011, 61;113-132.
2. Krampitz GW, Norton JA. Pancreatic neuroendocrine tumors. Current Probl Surg 2013, 50: 509–545.
3. http://www.orpha.net/consor/cgi-bin/index.php
4. Gouffon M, Iff S, Ziegler K, Larche M, Schwarzenbach C, Prior JO, Matter M, Stettler C, Pralong FP. Diagnosis and workup of 522 consecutive patients with neuroendocrine neoplasms in Switzerland. Swiss Med Wkly. 2014;144:w13924.

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

Database – brief historic review and current state

In 2008, SwissNET received official permission from the Swiss authorities to collect data on neuroendocrine tumors (NET) within a registry. Therefore, an electronic, access-based database was established being located on two stand-alone-computers without access to the internet. Provided that a signed patient informed consent was present, patient data was entered into the registry by two skilled study nurses.

Currently, 45 participating hospitals are providing SwissNET with patient data. Collecting all this patient information is associated with a high workload. Hence, data collection can be ensured for most of the institutes only once a year, but twice a year for major centers. These circumstances may cause time periods in which up-to-dateness of registry data is limited leading to a loss of information regarding ongoing studies and analysis.

Recently, increasing requirements necessitated a move towards a web-connected database. Taking advantage of current technology progress different database systems have been evaluated. The decision has been made to implement the WebSpirit Clinical Trial Management System (CTMS). This new database is thought to simplify the process of entering data and ensures a pervasive access to the latest data for research projects.

The data transfer from the old database into the new one is a challenging task and is due to start in June 2014. It should be fully transferred by autumn of this year.

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

Analysis of data 2012/13

As a consequence of discontinuous updates and restructuring of data entry, data transfer for 2013 has not been completely performed, yet. Therefore, data from 2012 and 2013 has been combined for the following statistical analysis.

a) Patient characteristics

Between 2008 and 2013, a total of 671 patients were included. The absolute number of included patients per year was more or less constant over the last five years, ranging from 115 to 142 patients a year. The low number of enclosed patients in 2013 is solely due to the current migration of database and the associated data locking. As soon as migration is completed, patient data will be updated and will likely result in similar numbers than in previous years.
A relatively even distribution of male (354; 53%) and female (317; 47%) patients was documented. The median age at diagnosis was 61 years, with a range from 14 to 95 years.

Measurement	Statistics
Number of patients	**671**
Females	317 (47%)
Males	354 (53%)
Age at diagnosis in years	
Mean	59
Standard deviation	15.9
Median	61
Minimum – Maximum	14 – 95
Number of patients diagnosed per year (first diagnosis)	
Unknown year	26 (4%)
<2007	3 (0%)
2007	15 (2%)
2008	90 (13%)
2009	115 (17%)
2010	141 (21%)
2011	117 (17%)
2012	142 (21%)
2013	22 (3%)

Table 1: Patient characteristics

b) Recruitment

Patient recruitment is excellent in many hospitals. Most of the recently included patients from 2012 and 2013 were understandably recruited in the major centers, Berne, St. Gallen, Lausanne, Geneva and Basel. There is only one single university center (Zurich) which is currently not providing data for SwissNET. Discussions are ongoing to find a solution for this situation.

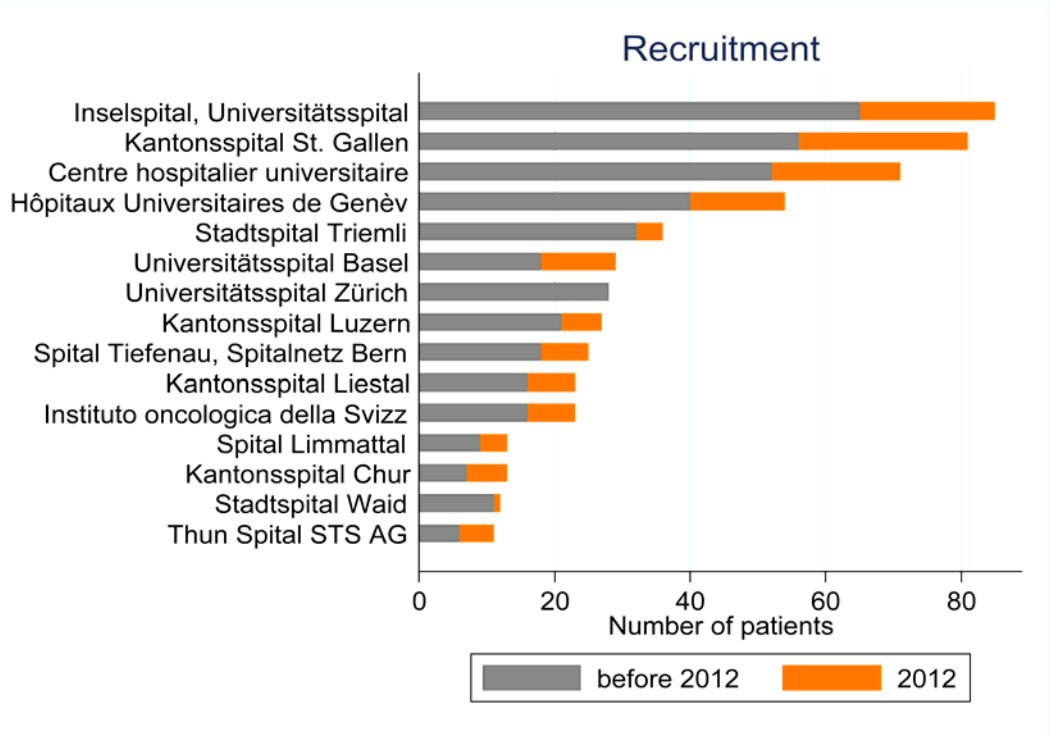

Figure 1: Recruitment of patients: *grey: 2008-2011, orange: 2012-2013*

c) Follow-up

The median follow-up was 455 days (ranged from 77 to 1036 days). The median time span between onset of first symptoms and diagnosis was 2.0 years.

Measurement	Statistics
Follow-up (days)	
Median	455
Interquartile Range	77 - 1036
Time from first symptoms to diagnosis (years)	
Mean	2.1
Standard deviation	1.5
Median	2.0

Table 2: Follow-up time and time span between first symptoms and diagnosis

d) Distribution of primary sites and tumor grade

Up to 2012, the ileum was the most common primary site of involvement. Including data from 2012 and partly 2013, an increasing number of patients with primary pancreatic NET were documented resulting in pancreas to be the most common primary site of disease. Appendical NET, ranked third, might be underrepresented in the database due to unreported incidental findings after performing appendectomy. A relatively high number of neuroendocrine “cancers of unknown primary” (CUP) were determined.

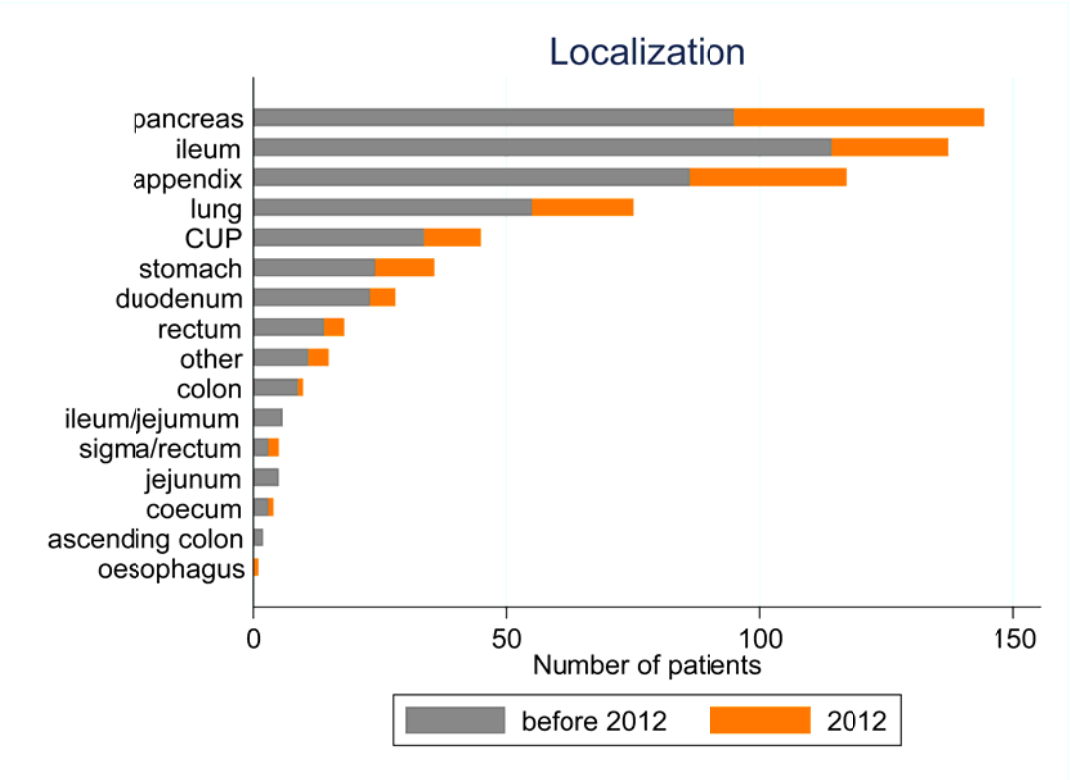

Figure 2: Distribution of primary sites of NET

In most of the reported cases pathology examination revealed a well-differentiated tumor (G1). G3 NET's represented a much rarer event.

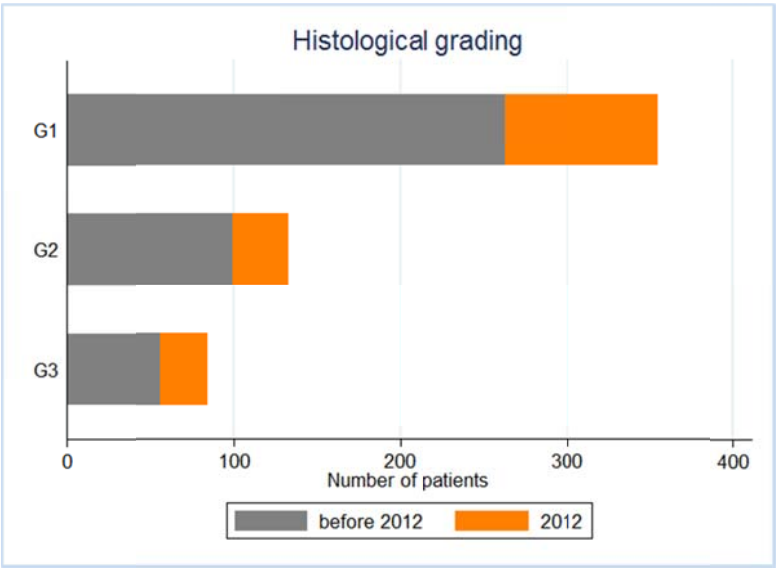

Figure 3: Tumor grading

e) Treatment

The majority of patients (507; 87%) received surgery as first line of treatment. Medical therapy (59, 10%), irradiation or ablative therapy (20; 4%) were considered only in a small proportion of patients as a first therapeutic option.

In slightly more than half of the patients one surgical intervention was performed (305; 57%). Over time, a relevant part of population underwent at least two (145; 27%) or more surgical procedures (88; 16%).

In total, 133 patients were treated with systemic treatment options, either as first line intervention or at some point after primary surgery. 44% of those patients received chemotherapy, 40% biotherapy, 16% both, respectively. Biotherapy was defined as “targeted” treatment in form of somatostatin analogue drugs, tyrosine kinase inhibitors and/or mTOR-inhibitors.

Octreotide was the most common used biotherapeutic agent (95 patients; 69%), second most common used was RAD001/Everolimus (21 patients; 15%).

Measurement	Statistics
First therapy	
Ablative	5 (1%)
Irradiation	15 (3%)
Medical	59 (10%)
Surgery	507 (87%)
Surgical therapy (number of patients)	
Once	305 (57%)
Twice	145 (27%)
Three times	51 (9%)
Four times	16 (3%)
≥ Five	21 (4%)
Medical therapy (number of patients)	**133**
Biotherapy	53 (40%)
Chemotherapy	59 (44%)
Both	21 (16%)
Biotherapy (number of therapies)	**137**
Octreotide LAR	66 (48%)
Octreotide s.c.	29 (21%)
RAD001/Everolimus	21 (15%)
Lanreotide Autogel	5 (4%)
Sunitinib	5 (4%)
SOM 230 LAR	4 (3%)
Lanreotide LAR	3 (2%)
other	3 (2%)
Lanreotide s.c.	1 (1%)

Table 3: Distribution of performed therapeutic procedures

f) outcome

The remission status of the disease is labelled at each recorded visit according to the below mentioned definitions/terms. Notably, only 39% of patients have been in complete remission at their last follow-up. Progressive disease is recorded in 17% of patients and stable disease in 7%, respectively. Death of any cause has occurred in 15%.
The relatively low number of patients being in complete remission could be explained by a selection bias. A considerable amount of NET are treated surgically in peripheral centers, which are not participating in the accrual process for SwissNET.

Measurement	Statistics
Remission status (last visit)	
Complete remission	260 (39%)
Partial remission	7 (1%)
Progressive disease	17 (17%)
Stable disease	46 (7%)
Not known	242 (36)
Relapse	1 (0%)
Dead	98 (15%)

Table 4: Remission status

Survival analyses according to the primary site show a high mortality for rare primary sites, such as the gallbladder or liver as well as for metastasized NET with unknown primary site (CUP). The observed mortality rate for small and large intestinal, pancreatic and pulmonary NET were in the expected range. The mortality rate for gastric and appendiceal NET was, not surprisingly, low due to a considerable amount of incidentally found appendiceal NET and a high amount of atrophic gastritis-related gastric NET.

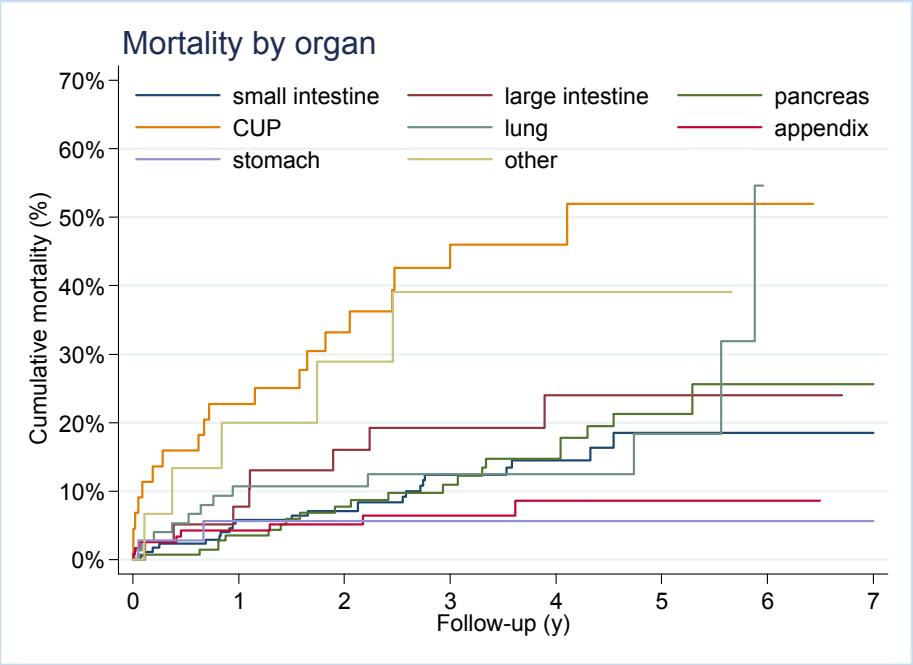

Figure 5: Mortality by primary tumor site

Additionally, our results confirm the prognostic impact of tumor grading on the mortality rate. Grade 1 tumors are associated with a significantly better outcome than grade 3 tumors. In the first 4 to 5 years of follow-up grade 2 NET's show a similar survival as G1 tumors, but curves divide afterwards in favor of grade 1 tumors. Note that the interpretation of these results may be influenced by the lower incidence of G2 and G3 neoplasms.

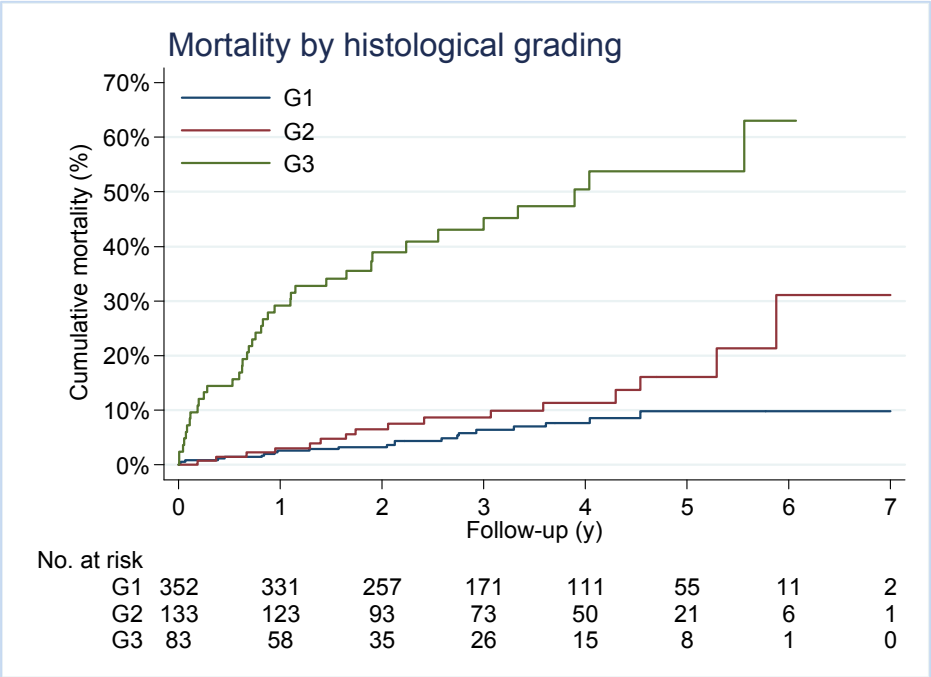

Figure 6: Survival according to histological grading

g) secondary neoplasms

NET are believed to be associated with an increased risk for secondary neoplasia. Previous studies suggest incidence rates between 7% and 46%. Patients included in the SwissNET database were found to have an overall incidence of 20% for secondary neoplasms.
50% of them were diagnosed synchronously, 41% before and 8% after the onset of NET, respectively.

Secondary neoplasms were associated most frequently with small intestinal (34%), appendiceal (20%) and pancreatic (19%) NET. In particular, adenocarcinoma localized in the GI-tract, breast or prostate were among the most frequent ones.

The mortality curves presented below (Figure 6) show a higher mortality in the population with diagnosis of a secondary neoplasm. Crude mortality was 88/1000 patient-years, compared to 43/1000 patient-years in those without secondary tumours. Unadjusted HR (cox model) was 2.00 (95% CI 1.19 to 3.34, p=0.008). When adjusted for age, significance was lost (figure 7).

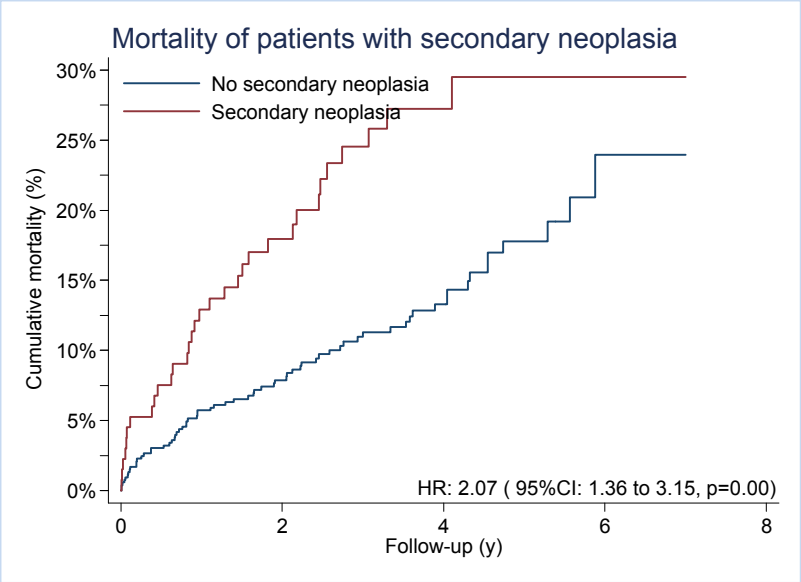

Figure 6: Survival of patients with secondary neoplasm; unadjusted for age

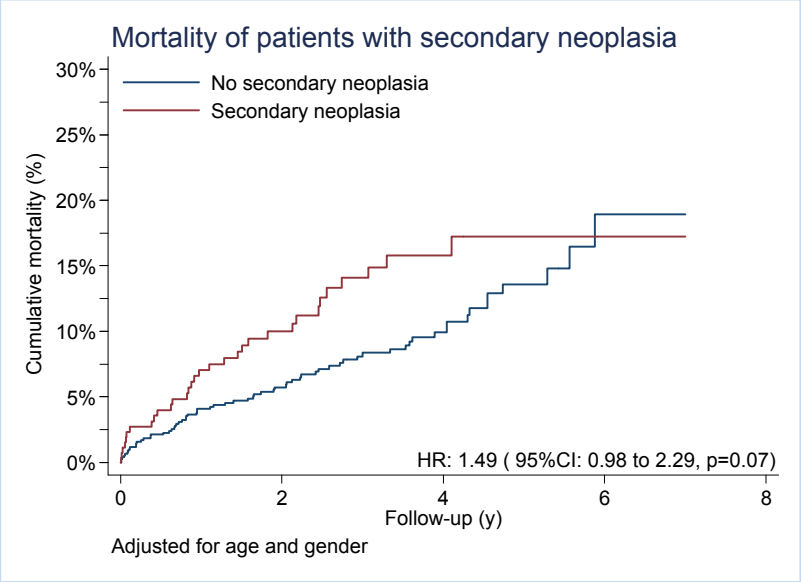

Figure 7: Survival of patients with secondary neoplasm; adjusted for age

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

Financing

With regard to the finances we received SFr. 75'000 from our three sponsors. The main expenses include the salary for the research nurses working now at the two sites (Inselspital Bern; 30% and CHUV; 20%). Cost of the database and the projects with the database exceeded the budget by approximately SFr. 8'000. Due to the fact that all the other expenses (overheads for the research nurses, homepage, cost for the general assembly) were considerably lower the balance closed with a positive balance sheet of sFr. 2'645.
The fortune of SwissNET amounts to SFr. 165'239 at the end of 2013. It, therefore, can be stated that SwissNET is financially healthy for the time being.