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## Additional malignancies in patients with neuroendocrine tumours: analysis of the SwissNET registry

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### Summary

**PRINCIPLES:** Neuroendocrine neoplasms (NENs) are believed to be associated with an increased risk for additional malignancies (AMs). We aimed to (1) assess the occurrence of AM in NEN patients (2) investigate the characteristics and temporal relationship of NEN patients with and without AM.

**METHODS:** The SwissNET registry has prospectively documented patients with NEN since 2008, covering the entire area of Switzerland. Clinical characteristics, functionality, location and histology of NEN as well as survival of all consecutive patients were retrieved. The characteristics of the AM (location, histology, time point of diagnosis in relation to diagnosis of NEN) were extracted.

**RESULTS:** Out of 934 patients, 193 patients (21%) presented with AMs. There was no statistically significant difference with regard to location, functionality and grading (G1–G3) between the NEN patients with and without AM. AMs were diagnosed synchronously ( $\pm 3$  months), before ( $>-3$  months) and after ( $>+3$  months) diagnosis of NEN in 82 (42%), 96 (50%) and 13 (7%) patients, respectively. Location of NEN correlated with the anatomical origin of the AM. Age- and gender- corrected survival was not significantly different between NEN patients with and without AM.

**CONCLUSION:** The prevalence of AM in NEN is high. The comparable characteristics with regard to functionality and grading in the NEN cohorts with and without AM and the similar location of AM and NEN suggest a selection bias towards frequent imaging procedures in NEN patients with AM.

**Key words:** NET; neuroendocrine tumour; secondary malignancy; screening; survival

### Introduction

Neuroendocrine neoplasms (NENs) are rare tumours with an estimated annual incidence of 1–5 per 100 000, equally affecting males and females [1, 2]. The median age at diagnosis is approximately 63 years [2]. NENs represent a highly heterogeneous group of tumours. Since neuroendocrine cells are distributed widely throughout the body, NENs can be diagnosed in various organs, but are predominantly found in the aerodigestive tract [3]. The most recent nomenclature for neuroendocrine neoplasms of the digestive system from the World Health Organization (WHO) distinguishes two broad subgroups, according to the histological grade and differentiation: well-differentiated neuroendocrine tumours and poorly-differentiated neuroendocrine carcinomas [4].

NENs are believed to be associated with an increased risk for additional malignancies (AMs). Previous studies reported incidence rates between 7.1% and 46% for associated tumours [5, 6]. The wide range of incidence rates of AM in different studies suggests a possible selection bias. However, genetic predisposition, i.e. multiple endocrine neoplasia (MEN) types 1 and 2 and von Hippel-Lindau syndrome, endocrine effects of NEN, environmental influences or therapy modalities of NEN may also play a role [7, 8].

We therefore aimed at assessing the clinical, functional and histological characteristics of NEN patients with and without AM. The primary site of the NEN and AM, and the temporal relationship with NEN diagnosis were retrieved in order to explore a potential relationship between the occurrence of NEN and AM. Furthermore, we investigated the prevalence of AM in our cohort and the survival of NEN patients with and without AM.

## Materials and methods

### Study design and population

Since 2008, clinical data on Swiss patients with NENs has been documented in a nation-wide prospective database, the SwissNET registry [9]. Ethical approval was obtained from the lead ethics committee in Bern and from all the other cantonal ethics committees according to the Swiss human research law of 2015 [10]. Currently, 45 participating hospitals across the whole of Switzerland are providing SwissNET with the data of their consenting patients with NEN, including about 50–60% of the expected incidence/year in Switzerland.

Gatekeepers for the SwissNET registry are pathologists or any medical doctors who report the diagnosis of NEN to SwissNET. The patients are then contacted and written informed consent is obtained, in which the patients agree to the use of the encoded data for research purposes.

The inclusion criteria for the SwissNET registry comprises all patients with NEN of the aerodigestive tract irrespective of age based on the revised WHO criteria 2010 [11]. Patients with small cell neuroendocrine carcinoma of the lung are excluded from the registry. All NENs, irrespective of sporadic or genetic origin, are included.

Data of all consecutive patients recruited into the prospective SwissNET registry between 2008 and 2015 were included. AM was defined as at least one additional malignant neoplasm. Clinical characteristics, functionality, location and histology of NEN, as well as survival of all patients were retrieved. The characteristics of AMs (location, histology, time-point of diagnosis in relation to diagnosis of NEN) were extracted. Synchronous AM was defined as occurrence of an AM within the range of 3 months before until 3 months after the diagnosis of NEN. Metachronous diagnoses of AM before and after NEN diagnosis were defined as >3 months before or after NEN diagnosis, respectively. The characteristics of NEN patients with AM were compared with NEN patients without AM.

### Statistical analysis

Categorical variables are reported as number and percentage in each category and compared between groups with Fisher's exact tests. Continuous data are reported as median and interquartile range (IQR) and compared with Wilcoxon rank-sum tests.

Survival analysis was performed with Kaplan-Meier curves and Cox proportional hazard models. Patients became at risk at the date of NEN diagnosis and death was considered as an event. Follow-up time was restricted to three years. Cox models were fitted with additional malignancies as the only covariate and adjusted for sex and age (the latter with a linear time-dependent effect). The proportional hazard as-

sumption was checked by log-log plots and the analysis of Schoenfeld residuals. All analyses were done in Stata Release 13 (Ref: StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

## Results

### SwissNET cohort

The Swiss Neuroendocrine Tumour registry comprised 934 patients between 2008 and 2015. Patients were followed up for a median time of 1.49 years (IQR 0.28 to 3.13) (table 1). Patient's and tumour characteristics are summarised in tables 1 and 2. A total of 113 patients (12%) suffered from secreting NENs. Carcinoid syndrome was the most common registered syndrome (40 patients; 4%). The most common primary site was the ileum (205 tumours; 22%) followed by the pancreas (201 tumours, 22%), the appendix/caecum (165 tumours; 18%) and lung (138 tumours; 15%). In 57 patients (6%), the anatomical origin of the NEN could not be established (cancer of unknown primary; CUP). In total, in 14 patients a syndromic disease was documented, seven patients with MEN syndrome, one patient with tuberous sclerosis, one patient with neurofibromatosis type 1 and five patients with von Hippel-Lindau disease.

### NEN patients without AM

A total of 741 patients (79%) experienced no AM during the observation period. The median follow-up time was 1.49 years (IQR 0.27 to 3.14) (table 1). Patient and tumour characteristics are provided in tables 1 and 2. In total, 92 cases (12%) were recorded to be hormonally active. Carcinoid syndrome represented the most common secretory NENs (33 patients; 4%). The most common primary NEN sites were the pancreas and small intestine (157 cases; 21% each), followed by appendix/caecum (128 cases; 17%) and lung tumours (117 cases, 16%).

### NEN patients with AM

One hundred and ninety-three patients (21%) were diagnosed with at least one AM. The median age at diagnosis was 67 years. The median follow up time was 1.49 years (IQR 0.27 to 3.14) (table 1). Patient and tumour characteristics are presented in tables 1 and 2. A secreting NEN was documented in 21 patients (11%). Carcinoid syndrome was the most prevalent syndrome (7 patients; 4%). The most common primary site of NEN was the ileum (48 tumours, 25%). NEN of pancreatic, appendicular/caecal and pulmonary origin occurred less often: 44 tumours, 23%; 35 tumours, 18%; 21 tumours, 11%, respectively (table 2)

**Table 1:** Demographics for patients with and without additional malignancies.

	All patients in registry n = 934	Patients with AM n = 193	Patients without AM n = 741	p value
Age at diagnosis (yr), median (IQR)	62.2 (49.8–71.6)	67.0 (60.1–73.7)	60.2 (47.9–70.5)	<0.001
Sex – male, n (%)	501 (54%)	101 (52%)	400 (54%)	0.686
Follow-up (yr), median (IQR)	1.49 (0.28–3.13)	1.49 (0.29–3.12)	1.49 (0.27–3.14)	0.990
Deceased, n (%)	173 (19%)	53 (27%)	120 (16%)	<0.001

AM = additional malignancy; IQR = interquartile range

### Comparison between the cohorts of NEN patients without and with AM

The quality of data with regard to grading and functionality was not significantly different between the cohorts with and without AM. Primary site, NEN grading, functionality and the median follow-up time were not statistically different between the patients with and without AM (tables 1 and 2). The median age of the patients with AM at diagnosis of NEN was 67 years, significantly older than the cohort without AM ( $p < 0.001$ ).

### Location of AM in relation to primary site of NEN

Patients with an AM of the gastrointestinal tract (67 patients) had their NEN mainly located in the gastrointestinal tract (49 patients, 73%), whereas patients with an AM of the lung (14 patients) had primarily a NEN of the lung (6 patients, 43%). AM of the urogenital tract was often associated with pancreatic and ileal NEN (33 patients, 69%) (table 3).

### Time-point of diagnosis of AM in relation to the diagnosis of NEN

A synchronous diagnosis of the AM and the NEN could be documented in almost half of the AM cohort (82 patients; 42%) (table 4). Appendicular NEN accounted for the highest proportion of synchronously detected NENs (28

out of 82 patients, 34%). Small bowel and pancreatic NEN represented 20% (16 patients) and 18% (15 patients), respectively of all simultaneously diagnosed NENs. In contrast, diagnosis of NEN of the appendix was associated in 76% with synchronous diagnosis of an AM (table 5).

The remaining AMs were diagnosed metachronously. Most of the AMs were detected before the onset of the NEN (50%) and a minority of cases afterwards (7%). The time intervals for a diagnosis of AM prior and after the NEN diagnosis were -4.7 (IQR -8.5 to -1.1) and +1.8 (IQR 0.9 to 4.4) years, respectively (table 4).

Patients with metachronously diagnosed AM before the diagnoses of the NEN had their NEN most often in the small bowel and in the pancreas (27 out of 96 patients; 28% each) and in the lung (12 patients, 13%). In contrast, a NEN of pancreatic origin was often diagnosed during follow-up of urogenital AMs, and lung NENs after lung and breast carcinomas.

Patients with an AM diagnosed after the onset of the NEN had their primary tumour located in the small bowel (4 out of 13; 31%), stomach (3; 23%), or pancreas (2; 15%) (table 5).

### Prevalence data

The prevalence for all AM sites including all patients of the SwissNET registry was 21.2% and 20.2% for women

**Table 2:** Clinical characteristics of neuroendocrine neoplasms for patients with and without additional malignancies.

	All patients in registry n = 934	Patients with AM n = 193	Patients without AM n = 741	p value
<b>Site of NEN</b>				
Foregut	429 (46%)	86 (45%)	343 (46%)	
Lung	138 (15%)	21 (11%)	117 (16%)	
Pancreas	201 (22%)	44 (23%)	157 (21%)	
Others	90 (10%)	21 (11%)	69 (9%)	
Midgut	373 (40%)	85 (44%)	288 (39%)	
Ileum	205 (22%)	48 (25%)	157 (21%)	
Appendix/caecum	165 (18%)	37 (19%)	128 (17%)	
Others	3 (0%)	0 (0%)	3 (0%)	
Hindgut	56 (6%)	6 (3%)	50 (7%)	
CUP	57 (6%)	11 (6%)	46 (6%)	
Others	16 (2%)	4 (2%)	12 (2%)	
Unknown	3 (0%)	1 (1%)	2 (0%)	
<b>Histological grading*</b>				
G1	506 (54%)	108 (56%)	398 (54%)	0.419
G2	205 (22%)	37 (19%)	168 (23%)	
G3	108 (12%)	18 (9%)	90 (12%)	
Unknown	115 (12%)	30 (16%)	85 (11%)	
<b>Functional tumour</b>				
No	575 (62%)	129 (67%)	446 (60%)	0.454
Yes	113 (12%)	21 (11%)	92 (12%)	
Carcinoid	40 (4%)	7 (4%)	33 (4%)	
Cushing	2 (0%)	1 (1%)	1 (0%)	
Gastrinoma	14 (1%)	3 (2%)	11 (1%)	
Glucagonoma	5 (1%)	3 (2%)	2 (0%)	
Insulinoma	32 (3%)	4 (2%)	28 (4%)	
Somatostatinoma	3 (0%)	1 (1%)	2 (0%)	
VIPoma	4 (0%)	0 (0%)	4 (1%)	
Unknown	13 (1%)	2 (1%)	11 (1%)	
Unknown	246 (26%)	43 (22%)	203 (27%)	

AM = additional malignancy; CUP = cancer of unknown primary; NEN = neuroendocrine neoplasm; VIP = vasoactive intestinal peptide

\* According to WHO classification criteria 2010

and men, respectively (supplementary table S1 in the appendix). The prevalences for the assessed subtypes are also documented in table S1.

### Survival analysis

Follow-up data for survival analysis was available for 844 of 934 patients (90%). The cumulative overall risk for death of NEN patients was significantly increased in the cohort with AM in the crude model (hazard ratio [HR] 1.63, 95% confidence interval [CI] 1.13 to 2.35,  $p = 0.009$ ). Forty-six patients (26%) and 110 patients (16%) died in the patient cohorts with and without AM, respectively. When adjusted for age and gender, however, statistical significance was lost (HR = 1.18, 95% CI 0.81 to 1.70,  $p = 0.389$ ) (data not shown).

### Discussion

The main findings of this study can be summarised as follows: (1) AMs were diagnosed in 21% of the patients with NEN; (2) the location of the primary site, grading and functionality were not significantly different in NEN patients with or without AM; (3) the type of AM covered a broad spectrum of neoplasms, but were mainly associated with NEN in a similar anatomical context and were primarily diagnosed before or synchronously with the diagnosis of NEN.

In our cohort 21% of the NEN patients suffered from an AM consistent with previously reported data in the literature [12, 13]. The characteristics of the AM in NEN patients covered a broad spectrum of neoplasms without any predilections consistent with previous data [5, 14].

**Table 3:** Relation between the primary site of neuroendocrine malignancy and first additional malignancy.

	Site of AM					
	Gastrointestinal tract	Urogenital tract	Breast	Lung	Lymphoma	Others
<b>Site of NEN</b>	n = 67	n = 48	n = 22	n = 14	n = 6	n = 36
Foregut	25 (37%)	19 (40%)	11 (50%)	11 (79%)	2 (33%)	18 (50%)
Lung	1 (1%)	—	6 (27%)	6 (43%)	1 (17%)	7 (19%)
Pancreas	14 (21%)	18 (38%)	3 (14%)	2 (14%)	1 (17%)	6 (17%)
Others	10 (15%)	1 (2%)	2 (9%)	3 (21%)	—	5 (14%)
Midgut	37 (55%)	23 (48%)	7 (32%)	3 (21%)	3 (50%)	12 (33%)
Ileum	14 (21%)	15 (31%)	5 (23%)	3 (21%)	3 (50%)	8 (22%)
Appendix/caecum	23 (34%)	8 (17%)	2 (9%)	—	—	4 (11%)
Hindgut	2 (3%)	2 (4%)	1 (5%)	—	—	1 (3%)
CUP	1 (1%)	3 (6%)	2 (9%)	—	1 (17%)	4 (11%)
Others	2 (3%)	1 (2%)	—	—	—	1 (3%)
Unknown	—	—	1 (5%)	—	—	—

AM = additional malignancy; CUP = cancer of unknown primary; NEN = neuroendocrine neoplasm

**Table 4:** Temporal relation between neuroendocrine neoplasm and the first additional malignancy.

Temporal relationship of NEN and AM	n = 193
Metachronous, before NEN	96 (50%)
Synchronous	82 (42%)
Metachronous, after NEN	13 (7%)
Unknown	2 (1%)
Time between NEN and AM, synchronous (yr)	n = 81, 0.0 (−0.0 to 0.0)
Time between NEN and AM, before (yr)	n = 94, −4.7 (−8.5 to −1.1)
Time between NEN and AM, after (yr)	n = 13, 1.8 (0.9 to 4.4)

AM = additional malignancy; NEN = neuroendocrine neoplasm

Time interval was not registered for 5 patients (1 with synchronous, 2 with metachronous and 2 with unknown relation).

**Table 5:** Site of neuroendocrine neoplasm and timing of first additional malignancy.

Site of NEN	Timing of first AM		
	Metachronous, before NEN	Synchronous	Metachronous, after NEN
Foregut (n = 86)	47 (55%)	31 (36%)	8 (9%)
Lung (n = 21)	12 (57%)	8 (38%)	1 (5%)
Pancreas (n = 44)	27 (61%)	15 (34%)	2 (5%)
Others (n = 21)	8 (38%)	8 (38%)	5 (24%)
Midgut (n = 84)	36 (43%)	44 (52%)	4 (5%)
Ileum (n = 47)	27 (57%)	16 (34%)	4 (9%)
Appendix/caecum (n = 37)	9 (24%)	28 (76%)	—
Hindgut (n = 6)	5 (83%)	1 (17%)	—
CUP (n = 10)	6 (60%)	4 (40%)	—
Others (n = 4)	1 (25%)	2 (50%)	1 (25%)
Unknown (n = 1)	1 (100%)	—	—

AM = additional malignancy; CUP = cancer of unknown primary; NEN = neuroendocrine neoplasm

Location of primary site and grading of NEN were not significantly different in patients with and without AM. This indicates that the association is related rather to chance than to a specific – possibly biologically explained – pattern. Additionally, the characteristics of functional NEN were similar in the cohort with AM compared with the cohort without AM. Although this suggests that the metabolites secreted by the NEN probably do not play an important biological role in the context of the occurrence of AM, no definitive conclusion can be drawn owing to the limited patient numbers and highly heterogeneous patient population. Interestingly, NEN of the gastrointestinal tract were mainly associated with AM of the gastrointestinal tract, and patients with lung NEN had mainly an AM of the lung. This finding is consistent with the hypothesis that the investigation of a possible neoplasm in a given clinical context may have resulted in the detection of two different tumour entities in the similar anatomical context using the corresponding diagnostic modalities (imaging, endoscopies) [15, 16]. Most of the AMs were diagnosed before or simultaneously with the NEN. The rate of AM diagnosis is approximately the same in the two time periods “metachronously before” and “synchronously”. Our results may, firstly, indicate that the investigations for a neoplasm (other than NEN) resulted in the additional diagnosis of NEN and, therefore, questions the sequence of diagnosis between NEN and AM. The awareness that more than 50% of the NEN in our cohort are well differentiated (NEN G1) and, therefore, characterised by a slow growth rate and long asymptomatic period supports the hypothesis of screening bias. Secondly, detection bias could explain the increased occurrence of synchronously diagnosed AM and NEN. Notably, the screening methods and their frequency were in accordance with local practice and are not documented in the registry. The occurrence of AM after NEN diagnosis was significantly less. Most likely, the short follow-up explains this finding. The association of NEN and AM in the same anatomical context – as mentioned before – is in line with this hypothesis. However, the numbers are small. In the biggest reported cohort from the Netherlands 67 AM (13.7%) in 459 NEN patients have been diagnosed, 13 (19%), 25 (37%) and 29 (44%), synchronously, metachronously before and after NEN diagnosis, respectively [15]. In the publication of Krausch et al., notable for a much longer follow-up time but with a small sample size ( $n = 143$ ), similar data were presented, reporting mostly metachronous AMs before NEN diagnosis (8/11 patients) [17].

Whether there is a true rise in incidence of additional malignancies when compared with the corresponding malignancy in the general population is still an unanswered issue. In a retrospective analysis from Krausch et al., secondary malignancies, especially with gastroenteropancreatic NENs, are reported to be more frequent than in the general population [17]. Since only in a few patients ( $n = 13$ ) an AM was diagnosed after the diagnosis of NEN, and because of the relatively short follow-up, the calculation of a valid incidence rate is not possible. However, the prevalence of AM in our study with regard to all cancer sites was approximately 20%, which appears to be increased compared with the reported prevalence of 3.6% for all cancer sites in Switzerland (National Institute for Cancer Epidemi-

ology and Registration; NICER) [18]. Splitting the AM according to their specific origin left only a small number of patients per group, thereby hampering a meaningful comparison with the NICER data (table S1).

Although the crude analysis of survival suggested a significant increase in all-cause mortality in the cohort with AM, adjustment for age and gender did not confirm this. Thus, it is probably rather age (and possibly gender) that relevantly impact on the increased mortality rate than the AM *per se*. The fact that the cohort of patients with NEN and AM is significantly older is consistent with this hypothesis. This result is consistent with previous data in two small series of patients with NEN. Krausch and colleagues reported a subtle separation of the survival curves without statistical significance ( $p = 0.349$ ) [17]. The findings of Prommegger et al. indicate that there was no survival difference between patients with and without AM [19].

The strength of our study is based on the high patient numbers included in the analysis and the high quality of data assessment within the prospective SwissNET registry. The observational nature of the data and the relatively short follow-up time may influence and limit the interpretation of the results.

In conclusion, the current data indicate that the suggested increase in AM in NEN patients is related rather to the increased rate of investigational procedures in a given clinical context than to a true biological association. Based on the present results, specific investigations aimed at diagnosing AM are probably not mandatory, but clearly more evidence with regard to this issue is needed.

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## References

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- Modlin IM, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer*. 2003;97(4):934–59.
- 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.
- Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. *Lancet Oncol*. 2008;9(1):61–72.
- Rindi G. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. WHO Classification of Tumours of the Digestive System 2010.
- Pape UF, Berndt U, Muller-Nordhorn J, Bohmig M, Roll S, Koch M, et al. Prognostic factors of long-term outcome in gastroenteropancreatic neuroendocrine tumours. *Endocr Relat Cancer*. 2008;15(4):1083–97.
- Habal N, Sims C, Bilchik AJ. Gastrointestinal carcinoid tumors and second primary malignancies. *J Surg Oncol*. 2000;75(4):310–6.

- 7 Zucker KA, Longo WE, Modlin IM, Bilchik AJ, Adrian TE. Malignant diathesis from jejunal-ileal carcinoids. *Am J Gastroenterol.* 1989;84(2):182–6.
- 8 Perez EA, Koniaris LG, Snell SE, Gutierrez JC, Sumner WE, 3rd, Lee DJ, Hodgson NC, et al. 7201 carcinoids: increasing incidence overall and disproportionate mortality in the elderly. *World J Surg.* 2007;31(5):1022–30.
- 9 Swiss NET registry. <http://www.swissnet.net>
- 10 <http://www.bag.admin.ch/themen/medizin/00701/00702/07558/index.html?lang=de>
- 11 Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO Classification of Tumours of the Digestive System, vol. 3, 4 edn: WHO; 2010.
- 12 Brune M, Gerdes B, Koller M, Rothmund M. Neuroendocrine tumors of the gastrointestinal tract (NETGI) and second primary malignancies – which is dominant? *Dtsch Med Wochenschr.* 2003;128(46):2413–7.
- 13 Niederle MB, Niederle B. Diagnosis and treatment of gastroenteropancreatic neuroendocrine tumors: current data on a prospectively collected, retrospectively analyzed clinical multicenter investigation. *Oncologist.* 2011;16(5):602–13.
- 14 Kauffmann RM, Wang L, Phillips S, Idrees K, Merchant NB, Parikh AA. Incidence of additional primary malignancies in patients with pancreatic and gastrointestinal neuroendocrine tumors. *Ann Surg Oncol.* 2014;21(11):3422–8.
- 15 Kamp K, Damhuis RA, Feeders RA, de Herder WW. Occurrence of second primary malignancies in patients with neuroendocrine tumors of the digestive tract and pancreas. *Endocr Relat Cancer.* 2012;19(1):95–9.
- 16 Clift AK, Drymousis P, Al-Nahhas A, Wasan H, Martin J, Holm S, Frilling A. Incidence of Second Primary Malignancies in Patients with Neuroendocrine Tumours. *Neuroendocrinology.* 2015;102(1-2):26–32.
- 17 Krausch M, Raffel A, Anlauf M, Schott M, Lehwald N, Krieg A, et al. Secondary malignancy in patients with sporadic neuroendocrine neoplasia. *Endocrine.* 2013;44(2):510–6.
- 18 NICER Nifcear: Prevalence of all cancer sites combined in Switzerland. Internet: [www.nicer.org](http://www.nicer.org).
- 19 Prommegger R, Ensinger C, Steiner P, Sauper T, Profanter C, Margreiter R. Neuroendocrine tumors and second primary malignancy – a relationship with clinical impact? *Anticancer Res.* 2004;24(2C):1049–51.

## Appendix: Supplementary table

**Table S1:** Prevalence of additional malignancies in all patients in the SwissNET registry.

	<b>Women (n = 433)</b>	<b>Men (n = 501)</b>
	n (%)	
All sites	92 (21.2%)	101 (20.2%)
Gastrointestinal	28 (6.5%)	39 (7.8%)
Male genital tract	0 (0.0%)	24 (4.8%)
Breast	22 (5.1%)	0 (0.0%)
Female genital tract	8 (1.8%)	0 (0.0%)
Lung	6 (1.4%)	8 (1.6%)
Lymphoma	4 (0.9%)	2 (0.4%)
Kidney	1 (0.2%)	7 (1.4%)
Bladder	1 (0.2%)	7 (1.4%)
Other	22 (5.1%)	14 (2.8%)