

RESEARCH

Nationwide multicenter study on the management of pulmonary neuroendocrine (carcinoid) tumors

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Abstract

Background and aim: To analyze the management and outcome of patients with primary typical (TC) and atypical lung carcinoids (AC) in Switzerland.

Methods: Retrospective analysis of patients selected from a neuroendocrine tumor (NET) registry. Patients were divided into TC and AC according to pathology reports, and surgical procedures were grouped as wedge/segmentectomy, lobectomy/bilobectomy and pneumectomy. Survival analysis was performed using the Kaplan–Meier method and log-rank test.

Results: Over 7 years, 113 pulmonary carcinoids (61.9% females, mean age 59.4 years) were included from 19 hospitals, with pathology data on Ki67 and necrosis incomplete in 16 cases. Eighty-three TC and 14 AC underwent surgical resection with a primary tumor size of median 14.5 (range 1–80) mm and diagnosis was established in 55.8% at surgery. Mean follow-up was 30.2 ± 23.1 months. Lobectomy was performed in 54.2% and wedge resection in 17.7% of cases. Six patients received additional systemic therapy. There was a trend for larger primary lesion size and a significantly higher rate of N2–N3 status in AC. Mean survival tended to be increased in patients with TC compared to AC (86.1 vs 48.4 months, $P=0.06$) and mean disease-free interval after surgical resection was 74.1 and 48.3 months for TC and AC, respectively ($P=0.74$).

Conclusion: AC of the lung has a more malignant behavior and a trend to a worse outcome. The results of this registry reinforce the need for standardized histological diagnosis and inter-disciplinary therapeutic decision making to improve the quality of care of patients with TC and AC.

Key Words

- ▶ pulmonary carcinoids
- ▶ surgery
- ▶ survival analysis
- ▶ registry

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Introduction

Neuroendocrine tumors of the lungs (LNET) represent approximately 30% of all NET (1, 2) and account for 1–2% of all lung tumors. Lung NETs are classified into typical carcinoid (TC, low-grade tumors) and atypical carcinoid (AC), which are considered intermediate-grade tumors. Small-cell lung cancer and large-cell neuroendocrine

carcinoma of the lung are considered high-grade neoplasms according to the WHO 2015 classification (3), with poor prognosis. Rindi and coworkers (4) have proposed a new prognostic classification based on mitotic count and presence of necrosis as the WHO adding Ki67 labeling index, but this is not universally accepted. Separation of TC

from AC requires a surgical specimen, as TC and AC cannot be reliably distinguished from each other in small biopsies or cytology due to sampling bias and is determined by the presence or absence of necrosis and increased mitotic count. Compared to TC of the lung, AC has a worse prognosis, more frequently metastasizes locally to hilar lymph nodes, and also distally to other organs (5).

Regarding the management of pulmonary carcinoids, Caplin and coworkers (6) have published a recent European Neuroendocrine Tumor Society expert consensus with recommendations for best practice: Patients are staged according to the UICC 7th TNM classification and surgery is the recommended therapy of choice in localized disease. Techniques are lobectomy or sleeve resection, with a complete anatomic resection and systematic nodal dissection recommended in patients with peripheral tumors. Lymphadenectomy and its extent are still debated but are recommended using the European Society of Thoracic Surgeons (ESTS) guidelines (7). Locoregional options include surgery (for primary and metastases) and endobronchial therapies, but trans-catheter embolization and radiofrequency therapy have been proposed for slowly progressive LNET. Following complete resection, the options are limited, as adjuvant chemotherapy or radiation therapy are not standard of care.

SwissNET is a prospective ongoing nationwide registry of patients with NET of all organs. Its goal is to collect data from NET cases in order to provide quality assessments, to advance knowledge and to establish standard of care for NET. Ultimately, this will enable to improve care and reduce the morbidity and mortality of patients with NET in Switzerland. The primary aim of the current study was to analyze the management and outcome of patients with TC and AC of the lung in Switzerland. The secondary aims included (i) the analysis of clinical and biomedical factors associated with surgical therapy and survival and (ii) the analysis of the current treatment strategies in Switzerland in relation to current guidelines.

Subjects and methods

SwissNET registry

Since 2009, clinical data on Swiss patients with NETs have been documented in a nationwide prospective database, the SwissNET registry (<http://www.swissnet.net/>). Currently, 45 participating hospitals across all of Switzerland are providing voluntarily SwissNET with data on their patients with NET. Data are collected by

professional research nurses directly from the pathologists and treating physicians at the respective hospitals or medical doctors report the diagnosis of NET to SwissNET directly. The patients are then contacted and written informed consent is obtained, in which the patients agree to the use of pseudonymised data for research purposes. In case of non-consent, the data are not registered.

The inclusion criteria for the SwissNET registry comprise all patients with well-differentiated NET of the aero-digestive tract irrespective of age, based on the revised WHO criteria 2010 (8). Patients with small-cell and large-cell neuroendocrine carcinomas of the lung are excluded from the analysis. All NETs, irrespective of sporadic or familial origin, are included. Follow-up is performed yearly by research nurses collecting the data at the respective hospitals.

Study design and population

For the current analysis, all patients diagnosed with TC and AC from the SwissNET registry were selected, from February 2009 to March 2016, with data acquired from 5 university hospitals and 14 community hospitals. The Ethics Review Board of the University Hospitals of Geneva approved this particular study (2016-00506), based on the multi-centric Ethics Review Board approval for the nationwide registry in Switzerland (395/14; NCT01039922).

Data from the registry were available for this study in coded form. Pathological grading was performed according to the WHO 2010 classification (8). Immunohistochemical analysis with chromogranin, synaptophysin and CD56 was documented to confirm neuroendocrine differentiation. In addition, Ki67 index and presence or absence of necrosis was recorded.

Patients and surgical outcomes were staged according to the UICC 7th TNM classification (9). Surgical procedures were recorded and grouped as wedge, segmentectomy, lobectomy and bilobectomy versus pneumectomy. The respective teams in each center decided the need and timing for additional chemo- or radiation therapy based on age, comorbidities, carcinoid syndrome, resection status and/or extent of disease.

Statistical analysis

Descriptive analyses were performed to determine the prevalence and current therapy modalities. Continuous data are presented as mean \pm standard deviation (s.d.) or median (range) and were analyzed using a two-tailed *t* test and the Mann–Whitney *U* test, as appropriate. A two-sided

P value <0.05 was considered statistically significant. Follow-up time was determined from the date of diagnosis to the date of death or last follow-up for survivors. Disease-free interval (DFI) represents the time in months following R0 resection, with no evidence of local recurrence or distant metastasis on imaging. Survival analyses using the Kaplan–Meier method were performed to determine outcomes, and log-rank test was performed for comparison. Statistical analyses were performed using SPSS, version 21 (IBM).

Results

Patient characteristics and diagnostics

Of 1050 patients with NET in the registry, 113 were classified as well-differentiated LNET and represent the study cohort. Patient demographics and clinical characteristics are shown in **Table 1**. The mean age at diagnosis was 59.4 ± 12.9 years, with 70 (61.9%) patients being female. The tumors were incidentally found in 19 (16.8%) cases and overall 18 (15.9%) patients had

Table 1 Patient demographics and clinical characteristics (N=113).

Variable	Value
Age at diagnosis (years, mean \pm s.d.)	59.4 \pm 12.9
Sex (female, <i>n</i> (%))	70 (61.9)
Functioning (yes, <i>n</i> (%))	18 (15.9)
Carcinoid/Cushing	16 (14.2)/1 (0.9)
MEN1	1 (0.9)
Tumors incidentally found (yes, <i>n</i> (%))	19 (16.8)
Follow-up time (months, mean \pm s.d.)	30.2 \pm 23.1 (1–88)
Center type (<i>n</i> (%))	
University/General Hospital	72 (63.7)/41 (36.3)
Surgical resection ^a (<i>n</i> (%))	
Wedge	17 (17.7)
Segmentectomy	9 (9.4)
Lobectomy	52 (54.2)
Bilobectomy	3 (3.1)
Pneumectomy	2 (2.1)
Bronchial resection	2 (2.1)
Lung Surgery (undefined)	11 (11.5)
Result primary tumor resection ^b (<i>n</i> (%))	
R0 resection	94 (94.9)
Size of primary lesion (mm, median (range))	14.5 (1–80)
Ki67 (% , median (range))	2 (0–80)
Histological type ^c (<i>n</i> (%))	
Typical/atypical	83 (73.5)/14 (12.4)
Necrosis ^d (no/yes, <i>n</i> (%))	41 (36.3)/2 (1.8)

Values are mean \pm s.d. for continuous and *n* (%) for categorical variables.

^a17 cases with missing surgical information, N=96; ^b14 cases with missing outcome information, N=99; ^c16 cases with missing histology information, N=97; ^d70 cases with missing information on the presence or absence of necrosis, N=43.

functioning tumors (one case presented with Cushing's syndrome and the others had TC syndrome), with an additional patient with multiple endocrine neoplasia type 1 (MEN1). The mean interval between symptoms and diagnosis was 6 ± 9.9 months. Overall, the follow-up time was 30.2 ± 23.1 months, ranging from 1 to 88 months, and leading to a median of 4 (1–16) visits per patient. Sixteen patients were lost to follow-up.

Imaging data at diagnosis were available in 108 of the 113 patients, showing that for axial imaging, 8 (7.4%) had a chest X-ray first, followed by 83 (73.5%) with a CT scan and 2 (1.9%) had additional abdominal MRI. Looking at functional imaging, 6 (5.3%) underwent somatostatin receptor scintigraphy, 5 (4.4%) ⁶⁸Gallium-DOTA-PET/CT and 26 (23.0%) patients underwent FDG-PET for oncological workup at diagnosis. Additionally, 1 patient underwent bone scintigraphy. Those studies resulted in the diagnosis of primary lesions in 72 (66.7%) of the 108 patients who underwent imaging studies. Furthermore, in 3 patients, lymph-nodes were suspected, and 3 patients were diagnosed with liver and 3 with bone metastases at diagnosis.

As for laboratory workup, data in the registry were incomplete. In 20 patients, median Chromogranin A was 60.8 (20–1773) μ g/L, for a normal upper limit of 85 μ g/L. In 9 patients, mean Neuron Specific Enolase (NSE) was 16.6 \pm 6.1 μ g/L, for a normal upper limit of 13 μ g/L. Laboratory values for 5-HIAA, Gastrin, Insulin, Glucagon and Serotonin were available in less than 4 patients.

Surgery and pathological staging

Overall, 63.7% of the cohort was treated in 5 University centers and 36.3% in 14 community hospitals. Of the 113 patients in the cohort, first diagnosis was established in 9 (8%) patients on cytology and in 41 (36.2%) with biopsy, however in 63 (55.8%) patients the diagnosis was established by surgical resection. As shown in **Table 1**, surgical resections in 96 patients were classified as: Wedge resection in 17 (17.7%), segmentectomy in 9 (9.4%), lobectomy in 52 (54.2), bilobectomy in 3 (3.1%), pneumectomy in 2 (2.1%) and bronchial resection in 2 (2.1%) patients. In 11 (11.5%) cases, the resection was classified as a general lung surgery procedure. Overall this resulted in a R0 primary tumor resection in 94.9% of cases.

Analyzing TNM pathological findings, primary tumor size was a median of 14.5 (1–80) mm. In 69 (61.1%) of the patients the information on surgical lymph-node sampling was available and in 4 (5.7%) of these cases no intraoperative sampling was performed. This resulted in N0 for 50 cases, N1 in 9, N2 in 5 and

N3 in 1 case. As for distant metastases, 27 were M0 and 2 were M1.

At histology, a cohort of 113 patients was labeled well-differentiated NET and details on Ki-67 labeling was available in 80 (70.8%) patients, with a median Ki67 of 2 (0–35)%. As for histological description of necrosis in the registry reports (present/absent), it was available in only 38.1% (43/113) of cases, with 41 (36.3%) without, and 2 (1.8%) with necrosis. Thus, based on the pathology reports in the registry, the overall cohort was classified into 83 (73.5%) TC cases and 14 (12.4%) AC cases, with information for classification missing in 16 cases. When comparing pathological data between TC and AC, results show an expected significant difference in Grade and Ki67 index, with higher values for AC, as shown in Table 2. There is a trend for a larger size of primary lesion in AC and a significant higher rate of N2–N3 status in AC cases. AC presented with significantly higher staging than TC.

Additional medical therapy

Overall, 6 patients in the cohort underwent chemotherapy and/or radiotherapy during their disease course. Two

patients had metastatic disease at diagnosis and received octreotide LAR treatment every 28 days at 30mg. One of them underwent sequentially a combination of carboplatin and etoposide therapy, external beam radiation and as alternative treatment modality two cycles of peptide receptor radionuclide therapy (PRRT; 177-Lutetium-DOTATOC) with stable disease at last follow-up. The other patient underwent first a combination chemotherapy with cisplatin and etoposide, followed by external radiation, with complete remission at last follow-up. Three recurred within 6 months of local treatment represented by a R0 resection, presenting liver and bone metastases. They all three underwent a combination chemotherapy of carboplatin and etoposide; one had radiofrequency ablation (RFA) to the liver and one had additional external radiation (66gy). One of them is in complete remission at the last follow-up, the two others progressed while on therapy. The last patient received systemic therapy after undergoing R1 resection in the presence of bone metastases. This patient progressed while on carboplatin and etoposide therapy and underwent additional treatments in form of RFA and external radiation.

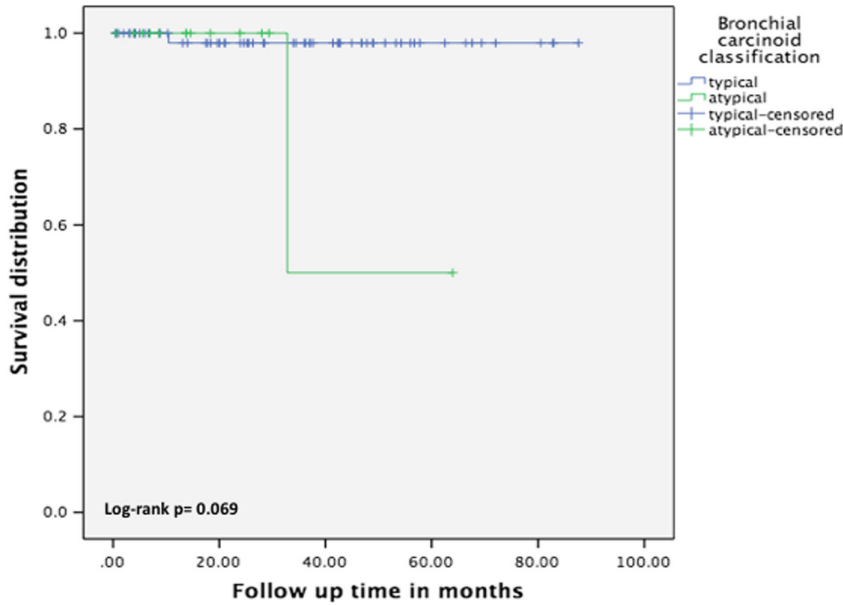
Table 2 Comparison between TC and atypical carcinoid ($N=97^a$).

Variable	TC	AC	P value
Grade, n (%)			
G1	77 (92.8)	2 (14.3)	<0.0001*
G2	6 (7.2)	12 (85.7)	
Ki 67, in %, mean \pm s.d.	4.05 \pm 11.8	9.22 \pm 9.99	<0.0001 [§]
Tumor size, in mm, mean \pm s.d.	18.6 \pm 14.8	36.2 \pm 26.1	0.053 [§]
Type of resection ^b , n (%)			
Wedge	14 (23.0)	0 (0)	0.36 [#]
Segmentectomy	7 (11.5)	1 (14.3)	
Lobectomy	40 (65.6)	6 (85.7%)	
Lymphadenectomy ^c , n (%)			
Yes	29 (87.9)	7 (100)	0.45 [#]
No	4 (12.1)	0 (0)	
Nodal status ^d s.d., n (%)			
N0	39 (81.3)	6 (60)	0.008 [#]
N1	7 (14.6)	0	
N2–N3	2 (4.2)	4 (40)	
Stage ^d , n (%)			
IA	33 (67.4)	3 (33.3)	0.009 [#]
IB	6 (12.2)	2 (22.3)	
IIA	7 (14.3)	0	
IIB	0	1 (11.1)	
IIIA	2 (4.1)	3 (33.3)	
IIIB	1 (2.0)	0	

Groups were compared using the Pearson Chi-square test* (or Fisher's exact test[#]) for categorical variables and the Wilcoxon Mann–Whitney test[§] for continuous variables; values are mean (s.d.) for continuous and n (%) for categorical variables.

^aCohort in this table represents the 97 patients who could be classified into TC and AC based on pathological criteria (16 missing data from total 113 WD LungNET); ^b96 cases underwent surgery, with 18 cases either surgical or pathology missing information, $N=78$; ^c57 cases with missing intraoperative information on lymphadenectomy, $N=40$; ^d39 cases with missing staging information, $N=58$.

AC, atypical carcinoid; n , number of patients in cohort; s.d., standard deviation; TC, typical carcinoid.



Patients at risk					
Typical	64	41	25	9	3
Atypical	14	5	1		

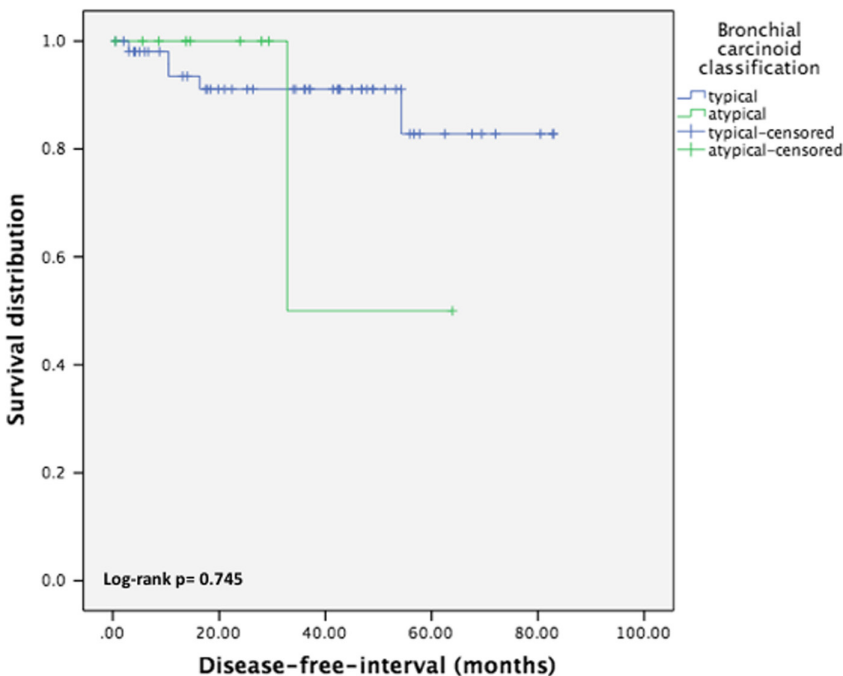
Figure 1

Kaplan–Meier survival distribution in months for the bronchial carcinoid classification. Cohort includes the 97 patients classified into TC and AC. Follow-up time was determined from the date of diagnosis to the date of death or last follow-up for survivors. Patients lost to follow-up and with unknown status (16 cases) were excluded.

Survival analysis

Overall, analysis shows that the mean survival for TC tended to be longer, at 86.1 months compared to 48.4 months for AC, $P=0.069$ (Fig. 1). The mean DFI was 73.9 months for the entire cohort, with TC at a mean DFI of 74.1 (range 66.8–81.5) months and 48.3

(range 26.8–69.9) months for AC, $P=0.745$ (Fig. 2). Looking at outcome, there was no difference in DFI with regards to the type of surgical resection, $P=0.98$, and a trend toward slightly better outcome was noted comparing lobar resection (mean DFI 72.4 months) to



Patients at risk					
Typical	53	34	24	7	3
Atypical	11	5	1	1	

Figure 2

Kaplan–Meier disease-free interval estimates in months for the bronchial carcinoid classification. Cohort includes the 97 patients classified into TC and AC who had R0 resection. Patients lost to follow-up and with unknown status at last follow-up were excluded. Disease-free interval (DFI) represents the time in months following R0 resection, with no evidence of local recurrence or distant metastasis on imaging.

sub-lobar resection (wedge or segmentectomy) (mean DFI 65.2 months). Of note, the number of patients was small in the different subgroups, as well as the numbers of events for DFI: 2 deaths, 2 relapses and 2 progressions. Furthermore, there was no difference in survival or DFI stratified for lymph-node status (log-rank test $P=0.31$, data not shown).

Discussion

The main findings of this study can be summarized as follows: (1) the workup, management and follow-up for pulmonary carcinoids were highly variable between centers and more than half of the cases were diagnosed at surgical resection; (2) patients with AC had larger primary lesions and a significantly higher rate of positive lymph-nodes and higher grading than TC.

For a long time, bronchial carcinoids were considered rare lesions with benign behavior, characterized by a better prognosis than other primary malignancies of the lung. Nowadays, they are considered malignant tumors because of their potential to locally invade, to develop lymph-node and distant metastases and to recur. This behavior is accounted for especially by AC (10, 11, 12, 13), shown in a recent study stratifying TC vs AC with statistically significant survival difference and thus confirming the validity of the WHO classification used in the present study (4). The more aggressive behavior of AC compared to TC documented in the present data, corroborates with other published studies. Like others, the results show that AC are characterized with a greater tendency to develop lymph-node metastases and have a higher recurrence rate (11, 14). The present study did not show a significant difference for lymph-node status (N0 vs N+) in terms of overall survival and DFI, suggesting nodal status might have a lower impact on survival of patients with bronchial carcinoids, despite the fact that AC had a higher rate of positive lymph-nodes. This might be due to small sample size and to the short follow-up time in this study. This finding differs from literature reports, such as the study by Cardillo and coworkers (14) showing that nodal status had more influence on prognosis than histological subtype. However, Garcia-Yuste and coworkers (15) have demonstrated in a multi-centric study that the atypical subtype was at high risk of recurrence, aligned with our results.

Regarding the type of recommended surgical resection, lobectomy with lymph-node sampling was the most frequently performed procedure in our cohort.

However, no significant difference in DFI was found with regards to the type of surgical resection, when comparing lobar resection to sub-lobar resection (wedge or segmentectomy). These results are to be taken with caution, as the term 'sub-lobar' includes both wedge resections and segmentectomies, with wedge resections representing oncologically incomplete resections and segmentectomies considered anatomical and oncological resections. In literature, Filosso and coworkers (11) found anatomical resections to be a protective factor against distant metastases, stating that wedge resections in their opinion are inappropriate for this type of tumors, even in the case of TC. However, a recent SEER database report suggested no difference in survival in univariate or multivariate analysis when comparing sub-lobar to lobectomy or greater surgeries (10), even when controlling for age and stage, thus corroborating our study's data. Other studies showed an increased rate in loco-regional recurrence in patients with AC undergoing sub-lobar resections, but found no significant difference in overall survival (16, 17). Furthermore, anatomical localization of lesions (central vs peripheral) might dictate the extent of resection needed, information that was not available in this registry. Therefore, prospective, randomized multi-centric studies are required to better understand the role of lung-sparing surgeries versus anatomical lobar or bronchial resections.

The European Neuroendocrine Tumor Society recently published an expert consensus and recommendations for best practice regarding the management of typical and atypical pulmonary carcinoids in 2015 (6). They state that pathology is the gold standard in the assessment of any pulmonary NET diagnosis, with problem cases benefiting from review by expert pathologists. They insist these pathology reports be shared by multidisciplinary teams along with oncologists, surgeons, radiologists, nuclear medicine physicians, pneumologists and endocrinologists, where pathologists contribute to the clinical decision-making process. All these specialists should have experience in treating NETs. In our study, description and reporting of pathology was highly variable and incomplete; however, the data were collected since 2009. Labeling with Ki-67 was not available in all patients (only in 71%), the classification into TC or AC was missing in 16 cases and as for histological description of necrosis in the reports, it was available in only 38.1% of cases. In our opinion, standardized pathological reporting is of utmost importance for the management of these patients, as outcome of disease and management differ between these two subgroups. Such reporting should

be requested by the multidisciplinary teams taking decisions for therapy. Furthermore, Caplin and coworkers recommend that patients be staged according to the UICC 7th TNM classification and that somatostatin scintigraphy SPECT/CT is useful to determine the N and M stage in the preoperative phase, especially in well-differentiated carcinoids; FDG-PET/CT might be useful in intermediate or poorly differentiated tumors. Additionally, whenever available, ⁶⁸Gallium-DOTA-PET should be preferentially performed, as it is more sensitive than scintigraphy when investigating possible metastases. In our study, less than 33% of the cohort had functional imaging at diagnosis, with only 5 patients undergoing ⁶⁸Gallium-DOTA-PET. The 'under'-utilization of functional images in this study might be due to the fact that in most cases, the diagnosis of TC or AC was made after surgical resection and/or because of the unawareness of the 'lung' NET community about the utility of these imaging modalities and lastly, because receptor-based imaging is currently not reimbursed in Switzerland. According to the consensus, surgery is the recommended therapy of choice for localized disease. Standard techniques are anatomical resections (segmentectomy, lobectomy, sleeve resection, pneumonectomy), with nodal dissection recommended in all patients. Also, lung-sparing surgery is preferred over pneumonectomy whenever possible. In our cohort, lymphadenectomy was performed in most AC cases, but the information was missing in more than 1/3 of the cohort, suggesting that the lymph-node status was not adequately evaluated in most of these patients. Lymphadenectomy and its extent is still debated but are recommended according to the ESTS guidelines and a recent European practice survey (18).

In further consensus recommendations, SSA may be considered as first-line systemic anti-proliferative treatment for patients with advanced unresectable LNET with loco-regional options including surgery (for primary and metastases), trans-catheter embolization or radiofrequency therapy. Chemotherapy has been the standard for aggressive metastatic LNET and PRRT is an option in patients with tumors that demonstrate strong expression of somatostatin receptors; however, the observed frequent use of cisplatin in Switzerland is not backed-up by clinical trials and might reflect the standard chemotherapy used by pulmonary oncologists. Additional systemic treatment was performed in 6 patients of the studied cohort, making analyses and recommendations based on our study impossible. Very recent evidence suggests that everolimus has a beneficial effect on progression-free survival in patients with lung

carcinoids (19). This therapeutic option was not reported in the SwissNET registry, probably due to the only recent approval and incompleteness of data. Finally, the general recommendation after primary surgery is that patients with TC and AC should be followed long-term.

Our study has limitations that are intrinsic to every registry. Essentially the data are observational and may, therefore, be prone to selection bias. Furthermore, due to the retrospective design of this study, diverse treatment strategies and non-standardized pathological analyses were reported, with essential data missing. In Switzerland, a new law on cancer registration will make reporting mandatory starting in 2019. Finally, the follow-up time of patients with lung carcinoids was short in order to draw firm conclusion. Thus, the results have to be interpreted with caution.

In conclusion, the quality of care of patients with TC and AC in Switzerland can be improved and standardized with regards to histological diagnosis, clinical decisions regarding imaging, surgery and medical treatments. Furthermore, the recent advances made in treatments of gastro-entero-pancreatic NET were not frequently applied to LNET, and overall, management was highly variable between centers with pathological and surgical information incomplete, either because of lack of standardized protocols or under-reporting. Thus, even though SwissNET is now an established and well-functioning registry, the quality of data reporting/collection could be improved and most importantly, multidisciplinary decision-making in the management of patients with TC and AC should be more standardized in Switzerland.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

Designed the study: S M S, E C, A P, F T; collected and analyzed data: S M S, B B, A T, W K; drafted manuscript: S M S, E C, A T; all authors reviewed and edited the manuscript.

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