European Journal of Cardio-Thoracic Surgery 48 (2015) 55–64
doi:10.1093/ejcts/ezu404 Advance Access publication 18 November 2014

ORIGINAL ARTICLE

Cite this article as: Filosso PL, Rena O, Guerrera F, Moreno Casado P, Sagan D, Raveglia F *et al*. Clinical management of atypical carcinoid and large-cell neuroendocrine carcinoma: a multicentre study on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours of the Lung Working Group. Eur J Cardiothorac Surg 2015;48:55–64.

Clinical management of atypical carcinoid and large-cell neuroendocrine carcinoma: a multicentre study on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours of the Lung Working Group†

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Received 14 May 2014; received in revised form 28 August 2014; accepted 2 September 2014

Abstract

OBJECTIVES: In 2012, the European Society of Thoracic Surgeons (ESTS) created the Lung Neuroendocrine Tumors Working Group (NETs-WG) with the aim to develop scientific knowledge on clinical management of such rare neoplasms. This paper outlines the outcome and prognostic factors of two aggressive NETs: atypical carcinoids (ACs) and large-cell neuroendocrine carcinomas (LCNCs).

METHODS: Using the ESTS NETs-WG database, we retrospectively collected data on 261 patients in seven institutions in Europe, between 1994 and 2011. We used a Cox regression model to evaluate variables affecting patient survival and disease-free survival. Univariate and multivariate analysis were also carried out.

RESULTS: Five-year overall survival rates for ACs and LCNCs were 77 vs 28% ($P < 0.001$), respectively. We found that for ACs, age ($P < 0.001$), tumour size ($P = 0.015$) and sub-lobar surgical resection ($P = 0.005$) were independent negative prognostic factors; for LCNCs, only pTNM stage III tumours ($P = 0.016$) negatively affected outcome in the multivariate analysis. Local recurrences and distant metastases developed in 93 patients and were statistically more frequent in LCNCs ($P = 0.02$).

CONCLUSIONS: The biological aggressiveness of ACs and LCNCs has been demonstrated with this study. Our aim is to confirm these results with enhanced data collection through the ESTS NETs database.

Keywords: Lung • Neuroendocrine tumour • Atypical carcinoid • Large-cell neuroendocrine carcinoma • Surgery • Survival • Recurrence • Metastasis

INTRODUCTION

Neuroendocrine tumours (NETs) typically arise in the gastrointestinal tract, pancreas, lung and thymus. Endocrine glands (parathyroid, pituitary, thyroid and adrenal) may host them as well. Pulmonary NETs

†Presented at the 21st European Conference on General Thoracic Surgery, Birmingham, UK, 26–29 May 2013.
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are a distinct subset of tumours accounting for approximately 20% of all primary lung cancers [1].

The 2004 World Health Organization (WHO) Lung Tumors Classification combined architectural patterns (cell size, organoid palisading rosettes, distinct nuclear/cytoplasm ratio) with other parameters (different mitotic index, presence of necrosis), aiming at classifying pure pulmonary NETs in four different groups: typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNC) and small-cell lung carcinoma (SCLC). Additionally, a very small percentage of NETs exhibit histological heterogeneity, and are classified as mixed NE carcinomas (small-cell and large-cell types with adenocarcinoma or squamous cell carcinoma, or, less frequently, with sarcomatous tumours).

The incidence of NETs has grown during the last decades due to the utilization of recent lung cancer screening programmes and the improvement of available diagnostic tools. Actually, the incidence of NETs has been reported to be 1.35/100 000/year, with a median age at diagnosis of 64 years. These tumours account for about 3% of all primary lung cancers, with approximately 6000 new cases per annum in the USA [2, 3].

In 2012, the European Society of Thoracic Surgeons (ESTS) launched the NETs Working Group (NETs-WG), gathering a group of experts worldwide and accumulating knowledge of such rare neoplasms within the scientific community. A specific dedicated database has been rapidly designed, approved by the ESTS NETs-WG Steering Committee and sent to all Thoracic Units that noted their interest in this project, collecting data retrospectively.

By 31 May 2013, a series of 935 patients operated for NETs was collected among eight European Centres.

Using the retrospective database, we intentionally focused on two uncommon NETs subtypes, belonging to the so-called NETs grey zone, AC and LCNC, with the purpose to evaluate their clinical management and long-term outcome. To our knowledge, this study represents one of the largest series ever collected on such rare tumours.

MATERIALS AND METHODS

A retrospective, multicentre study of patients operated for ACs and LCNCs between 1994 and 2011 at eight different high-volume European Thoracic Surgery Institutions. Data were taken from the ESTS NETs-WG retrospective database.

During the cited period, 935 patients affected by pulmonary NETs were treated in the above-mentioned European Institutions. Among these, 261 patients (27.9%) had histologically confirmed AC or LCNC.

Demographic and clinico-pathological characteristics included age, gender, smoking habit, previous malignancies and symptoms at the time of diagnosis, with emphasis on paraneoplastic syndromes (acromegaly, Cushing's syndrome, encephalitis, carcinoid syndrome and other rare associated syndromes).

According to the 'tumour location' definition, previously reported by Detterbeck *et al.* [4], all those tumours directly visualized at bronchoscopy or in association with lung atelectasis and/or obstructive pneumonia were classified as 'central', whereas those absent at bronchoscopy were classified as 'peripheral' lesions. All diagnostic procedures used to achieve preoperative cytological or histological confirmation [either carcinoid/carcinoma with neuroendocrine features or common non-small-cell lung cancer (NSCLC)] were recorded, including preoperative bronchoscopy and tissue sampling or CT-guided fine-needle aspiration.

Surgical approaches were defined as 'open' (posterolateral or anterolateral thoracotomy, sternotomy) or 'minimally invasive' (video-assisted thoracoscopic surgery or robotic); the extent of the surgical resections were classified as 'anatomical' (segmentectomy, lobectomy or pneumonectomy) and 'non-anatomical' (wedge resection). Bronchoplastic procedures (i.e. sleeve lobectomy) were identified within the lobectomy group; there was specific interest in recording data on the management and confirmation of complete bronchial margins intraoperatively.

Lymph-nodal dissection data were also collected: lymphadenectomy was classified as 'sampling' or 'systematic hilar and mediastinal'.

All the histological samples were reviewed by local pathologists and the definitive histological diagnosis of AC or LCNC was in conformance with the 2004 WHO Lung Tumors Classification [5] and even according to the Travis' histological guidelines for the diagnosis of NETs [6].

The mitotic index obtained by immunohistochemical staining using anti-Ki67 antibody (DAKO, Glostrup, Denmark) and the Ki-67 labelling index (expressed as a percentage of positive cells) were captured when available.

Completeness of surgical resection was classified as R0 (absence of residual disease either micro- or macroscopic), R1 (microscopic residual disease) and R2 (macroscopic residual disease).

Tumour staging was reviewed by the local pathologists and classified according to the 7th edition of TNM classification for malignant lung tumours [7, 8].

Additional treatments complementing surgery such as induction or adjuvant radio- or chemotherapy were also recorded.

STATISTICAL ANALYSIS

Continuous data are presented as median (interquartile range, IQR) and categorical data as a number (percentage, %).

The primary outcome was the overall survival (OS), the secondary the disease-free survival (DFS).

OS was calculated from the date of surgical resection to the date of death or last recorded follow-up. DFS was calculated from the date of surgical resection to the date of local recurrence (LR) or metastasis development or death, only in case of complete (R0) resections. In both OS and DFS, dates of the last follow-up for living patients were recorded.

Survival curves and DFS curves were estimated by the Kaplan–Meier method. Cox regression models were used to identify variables influencing OS and DFS. Univariate and multivariate analyses were also carried out.

The association between histological subtypes, demographic and clinico-pathological characteristics was evaluated with χ^2 test and Fisher's exact test, when appropriate.

We considered the following variables: age, gender, smoking habit, previous malignancies, symptoms at presentation, tumour location, tumour size, Ki67 percentage, type of surgery, completeness of resection, T and N status, administration of induction or adjuvant therapy, development of local or distant metastases (MTS).

In all regression models fitted in this study, missing data were multiple-imputed. Combined estimates were obtained from 10 imputed data sets.

All statistical analyses were performed using STATA (version 12.1, StataCorp LP, TX, USA).

Table 1: General patients' characteristics

	AC		LCNC		*P*-value[a]
	Median	IQR	Median	IQR	
Age (as continuous years)	59	20	65	12	
Size (as continuous cm)	2.5	2.1	2.9	4	
	n	%	*n*	%	
Gender (male, *n* = 261 patients)	68	54	96	71	0.005
Smoking (yes, *n* = 241 patients)	67	59	114	90	<0.001
Symptoms (yes, *n* = 212 patients)	69	59	59	62	0.67
Paraneoplastic syndrome (yes, *n* = 174 patients)	5	6	4	4	0.51
Acromegaly	1		1		
Cushing's syndrome	1		0		
Encephalitis	1		0		
Carcinoid syndrome	0		1		
Other syndrome	2		2		
Previous malignancy (yes, *n* = 224 patients)	15	12	17	17	0.25
Tumour location (peripheral, *n* = 254 patients)	57	48	92	69	0.001
Side (right, *n* = 108 patients)	27	60	29	46	0.18
pT (*n* = 253 patients)					
T1	69	57	38	29	<0.001
T2	38	32	61	46	
T3	9	8	27	20	
T4	4	3	7	5	
pN (*n* = 255 patients)					
N0	78	64	75	56.2	0.15
Nx	4	3	1	0.8	
N1	24	20	40	30	
N2	16	13	17	13	
Stage (*n* = 254 patients)					
I	69	57	50	37	0.002
II	29	24	46	35	
III	20	17	30	23	
IV	3	2	7	5	
Chemotherapy (yes, *n* = 82 patients)					
Adjuvant	14	16	51	41	<0.001
Induction	1	1	6	5	0.26
Adjuvant + induction	1	1	3	2	
Palliative	0		6	5	
Radiotherapy (yes, *n* = 198 patients)					
Adjuvant	4	5	7	6	0.56
Induction	2	2	6	5	0.47
Palliative	0		2	2	
Surgical approach (*n* = 260 patients)					
Thoracotomy (as reference)	122	97	134	99	0.11
VATS	2	2	1	1	
Sternotomy	1	1	0		
Type of intervention (*n* = 257 patients)					
Lobectomy (as reference)	89	72	81	61	
Wedge resection	5	4	13	10	
Segmental resection	7	5	11	8	
Sleeve resection	2	2	3	2	
Bilobectomy	8	6	2	2	
Extended	1	1	6	4	
Pneumonectomy	12	10	17	13	
Pathological resection (*n* = 181 patients)					
R0 (as reference)	85	99	90	95	0.21
R1	1	1	1	1	
R2	0		4	4	
Ki 67% (*n* = 78 patients)					
<5% per HPF (as reference)	12	24	0		
≥5% per HPF	39	76	27	100	
Local recurrence (yes, *n* = 195 patients)	7	6	15	18	0.021
Distant MTS (yes, *n* = 158 patients)	26	34	45	55	0.011

AC: atypical carcinoid; LCNC: large-cell neuroendocrine carcinoma; IQR: interquartile; MTS: metastases.
[a]χ^2 test or Fisher's exact test, when appropriate.

RESULTS

Patients' clinical characteristics

Between 1994 and 2011, 261 patients were identified: 126 (48%) were affected by AC and 135 (52%) by LCNC. Patients' characteristics are summarized in Table 1.

Those affected by LCNC were more frequently males (68/126 AC vs 92/135 LCNC, $P = 0.005$) and smokers (67/114 AC vs 114/127 LCNC, $P < 0.001$); LCNC also more commonly presented as a peripheral lesion (57/120 AC vs 92/134 LCNC, $P = 0.001$) compared with AC.

Patients affected by LCNC had bigger tumours, less frequently referred clinical symptoms at the time of diagnosis and most often had a previous history of malignancy; however, these data did not reach statistical significance.

Nine cases of paraneoplastic syndromes (2 acromegaly, 1 Cushing's syndrome, 1 carcinoid syndrome, 1 encephalitis and 4 classified as other) were observed, 5 of them in AC patients.

Surgery and multimodality treatment

Data concerning the surgical approach were available in all but one case: 'open' surgery was administered in the majority of cases (257/260, 99%), with thoracotomy (posterolateral or anterolateral) being the commonest approach (99%).

A radical resection (R0) was accomplished in 255 patients (98%); microscopic residual disease (R1) was demonstrated in 2 cases (1 LCNC), while macroscopic residual disease was observed in 4 LCNCs.

Data concerning the type of surgical resections were available for 257 patients (99%); details of interventions according to the histological subtypes are reported in Fig. 1. There was a trend towards a higher number of lobectomy/bilobectomy performed in the AC group, whereas pneumonectomy/extended resection were more frequently performed in LCNC patients, even if these data did not reach a statistical significance.

Data about T status were available in 255 cases (98%): ACs were more frequently T1 at the time of surgical resection than LCNCs (69/120 ACs vs 38/133 LCNCs, $P < 0.001$). Pathological N status data were also available in 255 cases because in 6 patients (2%; 4 AC) lymphadenectomy was not performed. A trend towards higher N1/N2 tumours in LCNC was observed, even if these data did not reach a statistical significance ($P = 0.15$). Consequently, while Stage I was more frequently observed in ACs, LCNCs were more commonly operated at Stage II and Stage III ($P = 0.004$).

Data concerning mitotic index by anti-Ki-67 immuno-staining were available for 78 patients (30%; 27 LCNCs).

Induction chemotherapy was offered to 1/126 AC (0.8%) and to 6/135 LCNC (4.4%). Adjuvant treatment was most commonly administered to LCNC (51/135 LCNC vs 14/126 AC, $P = 0.001$). Platinum plus etoposide represented the preferred chemotherapeutic regimen.

Survival and tumour recurrences

The median recorded follow-up was 59 months (range: 1–304 months) for AC and 28 months (range: 1–122 months) for LCNC. Thirty-eight of 126 AC (30%) patients died, 25/38 because of recurrent cancer or cancer-related treatment; 52 of 135 LCNC (39%)

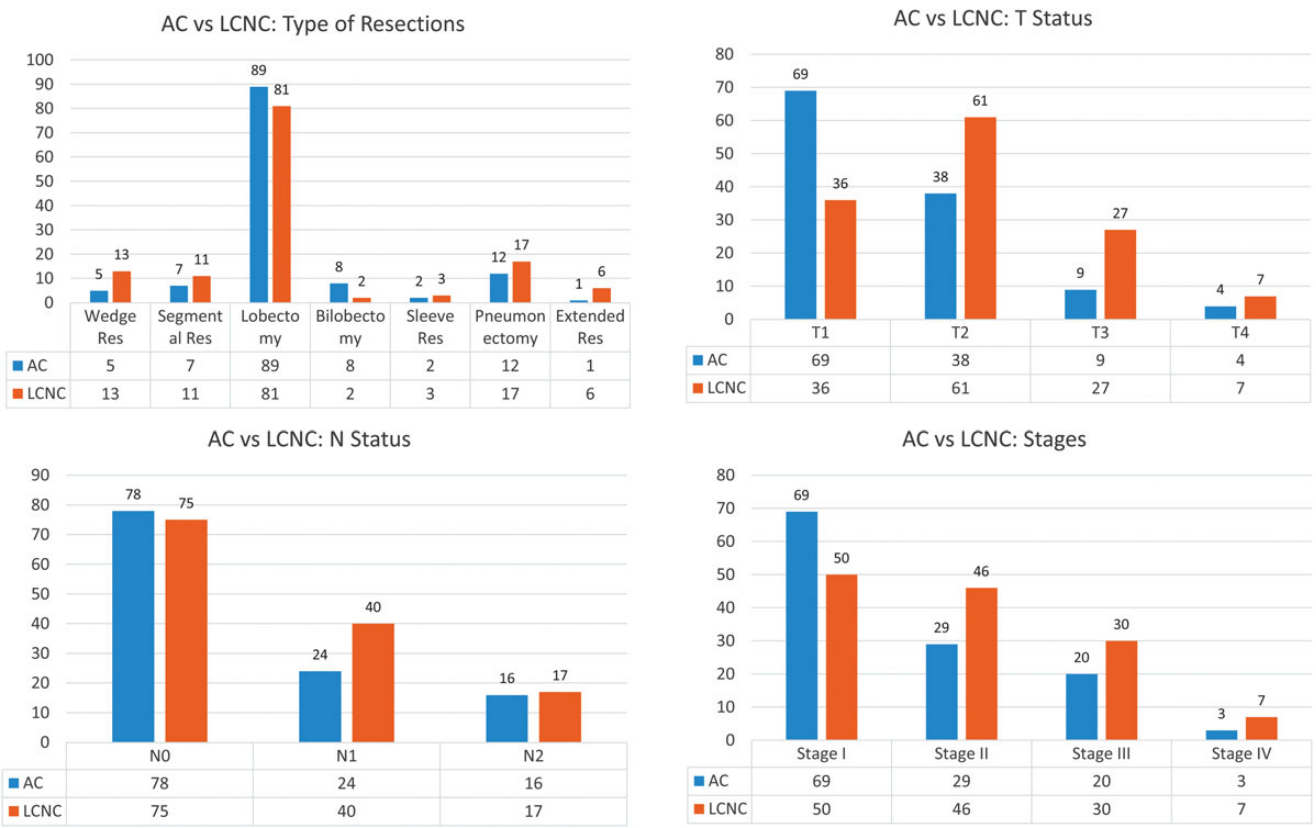

Figure 1: Atypical carcinoid (AC) versus large-cell neuroendocrine carcinoma (LCNC): surgical procedures, T and N status and stages.

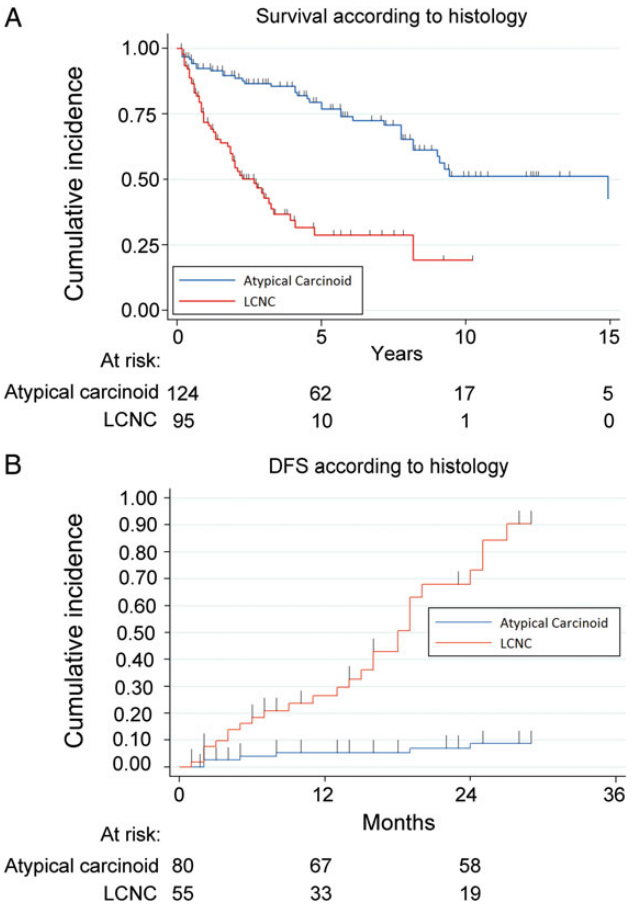

Figure 2: Atypical carcinoid (AC) versus large-cell neuroendocrine carcinoma (LCNC): survival curves (**A**, $P < 0.001$) and disease-free survival (DFS) curves (**B**, $P < 0.001$).

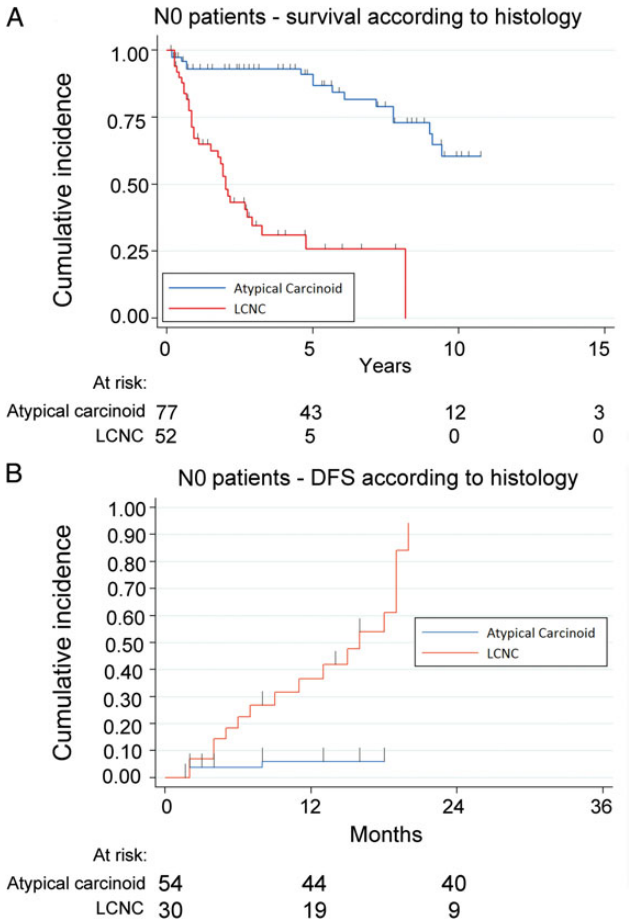

Figure 3: N0 Atypical carcinoid (AC) versus large-cell neuroendocrine carcinoma (LCNC): survival curves (**A**, $P < 0.001$) and disease-free survival (DFS) curves (**B**, $P < 0.001$).

patients died, 26/52 because of recurrent disease or cancer-related treatment.

OS curves for AC and LCNC are shown in Fig. 2A. LCNC showed a worse survival [hazard ratio (HR) 3.32; 95% confidence interval (CI): 2.69–4.10, $P < 0.001$] when compared with AC (5-year OS 77 vs 28%, respectively). A significant difference in survival between AC and LCNC was also observed when the OS for N0 patients and Stage I tumours was analysed (Figs 3A and 4A).

Factors negatively affecting long-term OS for AC at 'univariate analysis' were as follows: age (HR 1.08; 95% CI: 1.04–1.12, $P < 0.001$), tumour size (HR 1.15; 95% CI: 0.99–1.35, $P = 0.073$), T4 tumours (HR 5.87; 95% CI: 1.15–15.29, $P = 0.032$), Stage III (HR 2.63; 95% CI: 1.16–5.97, $P = 0.021$) and presence of distant MTS (HR 4.28; 95% CI: 1.75–10.45, $P = 0.002$). At the 'multivariate analysis', the following variables strongly influenced the long-term OS of AC patients: age (HR 1.08; 95% CI: 1.04–1.12, $P < 0.001$), tumour size (HR 1.56; 95% CI: 1.09–2.22, $P = 0.015$) and sub-lobar resections (HR 8.42; 95% CI: 1.89–37.57, $P = 0.005$) (Table 2) .

When LCNC was considered, in 'univariate analyses' the following clinical variables were demonstrated to influence OS: tumour size (HR 1.16; 95% CI: 1.04–1.30, $P = 0.01$), T3 tumours (HR 2.03; 95% CI: 0.93–4.32, $P = .076$), Stage III (HR 2.06; 95% CI: 0.98–4.32, $P = .057$) and the presence of distant MTS (HR 3.05; 95% CI: 1.55–5.98, $P = 0.001$). At the 'multivariate analysis', Stage III (HR 7.24; 95% CI: 1.44–36.39, $P = 0.016$) was a predictor of worse OS (Table 3).

Data concerning the development of LRs and MTS were available in 195 and 158 cases, respectively. LCNC showed a worse DFS ($P < 0.001$) (Fig. 2B). Variables influencing DFS at 'univariate analyses' were: male gender (HR 3.03; 95% CI: 1.08–8.54, $P = 0.036$), age (HR 1.04; 95% CI: 1.00–1.09, $P = 0.048$) and pT4 tumour (HR 5.21; 95% CI: 1.11–24.48, $P = 0.037$) (Table 3). When considering LCNCs, in 'univariate models' smoking history (HR 0.39; 95% CI: 0.14–1.07, $P = 0.068$) demonstrated a protective effect on LR/MTS development, while increase in tumour size (HR 1.15; 95% CI: 1.00–1.34, $P = 0.06$) was associated with worse DFS (Table 3).

DISCUSSION

Neuroendocrine tumours of the lung exhibit a spectrum of histology, clinical profiles and biological behaviours, which range from low-grade and relatively indolent TCs to histologically high-grade and biologically aggressive tumours (LCNC and SCLC).

One of the aims of the ESTS NETs-WG was to collect the largest series of neuroendocrine lung tumours from the greatest possible number of Thoracic Surgery Institutions worldwide, together with knowledge on the biology and behaviour of such rare neoplasms.

In this paper, which represents the first NETs-WG scientific activity result, we intentionally focused on AC and LCNC because they represent the so-called 'NETs grey zone', since treatment of advanced stages is still controversial. While several articles on lung NETs have been published in recent years [9–12], to our

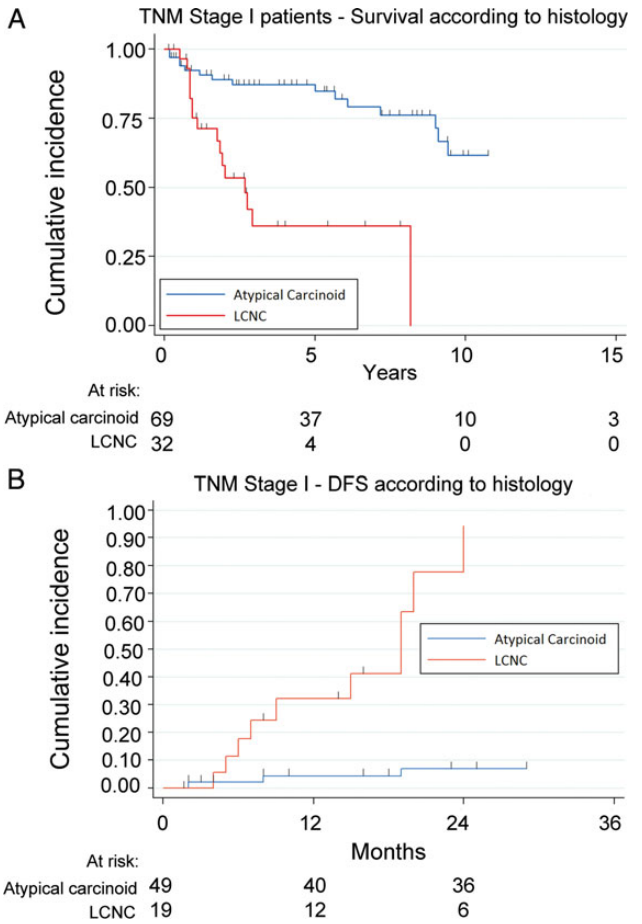

Figure 4: Stage I Atypical carcinoid (AC) versus large-cell neuroendocrine carcinoma (LCNC): survival curves (**A**, $P = 0.001$) and disease-free survival (DFS) curves (**B**, $P < 0.001$).

knowledge, the present paper is the only one dedicated to such rare neuroendocrine tumours.

The gradual and steady increase in the diagnosis of lung NETs during the last decades might be explained with the evolution of the radiological techniques and the recent advent of new lung cancer screening programmes.

The first significant clinico-pathological implication of this study is the confirmation, through a large-scale, multi-institutional series, of the relatively high grade of malignancy of each histological tumour type. Moreover, several other interesting clinical and therapeutic messages emerged from this study.

Clinical characteristics

In agreement with other reported series [13, 14], we observed that LCNC affects more predominantly males and smokers, and occurs in patients older than those with AC. These findings suggest that LCNCs, such as small-cell lung cancer, are the result of cigarette smoking, whereas ACs may be related to other causes.

To avoid confusion regarding tumour mapping, we followed reported criteria in the literature: all tumours directly visualized at bronchoscopy or in association with lung atelectasis and/or obstructive pneumonia were classified as 'central', whereas 'peripheral' lesions were those not observed at bronchoscopy.

As previously reported, a statistically significant predominance of peripheral lesions was observed among LCNC patients [13–15]; in contrast [16], the majority of ACs proved to be centrally located. Interestingly, LCNCs are more frequently found in the peripheral lung, suggesting this histotype to be the peripheral form of high-grade neuroendocrine tumour of the lung in contrast with the SCLC, which is the central form of the disease, but such arguments have not had any histo-pathological confirmation. The clinical presentation of these tumours, such as for the majority of lung cancers, is principally related both to the extension/location of the disease; other symptomatic aspects are related to the associated paraneoplastic syndromes.

Radiologically, NETs are not distinguishable from other subtypes of NSCLC; even in 'central' lesions the challenge remains in correctly identifying preoperatively the neuroendocrine differentiation and classifying them as AC/LCNC.

Paraneoplastic syndromes were registered in 9 cases (5 of them among ACs). Interestingly, 1 case of carcinoid syndrome and 1 case of acromegaly were observed in LCNCs and, to our knowledge, this has never been observed before. Furthermore, no AC had a clinical history of multiple neuroendocrine neoplasia 1 (MEN1). Both cases of LCNC associated with paraneoplastic syndromes were submitted to histological revision and were confirmed to be LCNC according to the WHO classification parameters. This could suggest that the use of the histological parameters to differentiate subtypes of NETs may not have a complete correspondence in the biological behaviour; in other terms, the manifestation of paraneoplastic syndromes is not an absolute characteristic of TC or AC, but may be associated with neuroendocrine tumours that have the biological behaviour of an AC but the histological aspect of an LCNC.

Treatment, survival and prognosis

Although adjuvant chemo- and/or radiotherapy show some potential benefit, surgery remains the gold standard for the treatment of bronchial carcinoid, based on the general principle of complete resection and preservation of as much normal lung tissue as possible [2, 6, 8, 11, 12, 17]. Surgery attains 5- and 10-year survival rates of more than 90% for TC and 70% and 50% for AC, respectively.

The optimal treatment for LCNC is not known. Because of its rarity, prospective randomized trials have never been performed. Retrospective case series [9, 11, 13–15, 18], however, have provided some interesting insights, the most important being that surgery alone is not sufficient to treat even early stage LCNCs [14, 18, 19].

In the present series, 'open' surgery—in particular thoracotomy—was the surgical approach of choice, with VATS being used only in 3 cases. The data reflect the relatively infrequent use of VATS surgery during the period among the participating institutions; another explanation might be the central location of half of the tumours. One might think that with the increasing use of thoracoscopic lobectomy, peripheral neuroendocrine tumours will always be more frequently treated by such a minimally invasive approach in the future.

The most frequently performed resections were anatomical ones for both ACs and LCNCs even if in some cases wedge resections have also been carried out and this was justified by the need to resect a peripherally located tumour in patients with poor preoperative functional status. Sleeve lobectomies and other bronchoplastic procedures, although highly advocated in centrally located tumours, were rarely carried out. This might be explained by the skills required and fear of complications associated with these procedures.

Table 2: Variables influencing AC/LCNC overall survival

	AC								LCNC							
	Univariate models				Multivariate model				Univariate models							
	HR	*P*-value	95% Confidence interval		HR	*P*-value	95% Confidence interval		HR	*P*-value	95% Confidence interval		HR	*P*-value	95% Confidence interval	
			Lower	Upper			Lower	Upper			Lower	Lower			Lower	Upper
Gender (male)	1.27	0.470	0.66	2.44	2.40	0.098	0.85	6.78	0.97	0.916	0.50	1.86	0.74	0.498	0.30	1.80
Age (years continuous)	1.08	<0.001	1.04	1.12	1.08	<0.001	1.04	1.12	0.99	0.478	0.95	1.02	0.98	0.484	0.94	1.03
Smoking history (yes)	1.51	0.256	0.74	3.05	1.14	0.808	0.39	3.31	0.59	0.140	0.29	1.19	0.69	0.502	0.23	2.07
Paraneoplastic syndromes (yes)	2.05	0.253	0.60	7.00	2.68	0.282	0.44	16.30	0.75	0.710	0.16	3.58	0.64	0.676	0.07	5.63
Symptoms (yes)	0.85	0.618	0.44	1.63	1.33	0.564	0.50	3.49	1.10	0.794	0.52	2.36	0.71	0.571	0.20	2.49
Previous malignancies (yes)	0.63	0.439	0.19	2.04	0.31	0.148	0.06	1.51	1.08	0.872	0.40	2.93	1.67	0.418	0.48	5.81
Tumour location (peripheral)	1.37	0.346	0.71	2.66	0.99	0.987	0.34	2.87	0.85	0.573	0.48	1.49	1.02	0.970	0.43	2.38
Size (cm continuous)	1.15	0.073	0.99	1.33	1.56	0.015	1.09	2.22	1.16	0.010	1.04	1.30	1.07	0.435	0.90	1.28
pT (pT1 as reference)																
pT2	1.09	0.819	0.51	2.36					0.97	0.943	0.47	2.02				
pT3	1.03	0.964	0.24	4.46					2.03	0.076	0.93	4.43				
pT4	3.87	0.032	1.13	13.29					3.89	0.085	0.83	18.24				
Lymph-nodal involvement (yes)	1.49	0.271	0.73	3.05	4.94	0.349	0.15	163.40	0.76	0.361	0.42	1.37	0.26	0.049	0.07	0.99
TNM stage (Stage I as reference)																
Stage II	1.17	0.714	0.50	2.74	0.16	0.261	0.01	4.24	0.93	0.830	0.47	1.83	1.57	0.374	0.58	4.29
Stage III	2.63	0.021	1.16	5.97	0.33	0.557	0.01	15.94	2.06	0.057	0.98	4.32	7.24	0.016	1.44	36.39
Stage IV	1.30	0.797	0.17	9.86	0.07	0.170	0.00	3.26	1.29	0.655	0.43	3.87	2.13	0.374	0.40	11.36
Surgery (lobectomy as references)																
Wedge resection or segmentectomy	2.25	0.078	0.91	5.54	8.42	0.005	1.89	37.57	1.36	0.572	0.72	0.47	2.25	0.189	0.67	7.52
Pneumonectomy or bilobectomy	0.98	0.970	0.40	2.41	0.72	0.631	0.19	2.76	1.36	0.465	0.91	0.37	1.55	0.369	0.59	4.07
Radicality (no)	7.89	0.052	0.98	63.44					4.28	0.024	1.21	15.07				
Adjuvant chemotherapy (yes)	1.12	0.794	0.47	2.66	1.45	0.568	0.40	5.24	1.11	0.725	0.62	1.99	1.01	0.983	0.36	2.84
Local recurrence (yes)	1.01	0.993	0.30	3.40					1.30	0.449	0.66	2.53				
Distant metastasis (yes)	4.28	0.002	1.75	10.46					3.05	0.001	1.55	5.98				

AC: atypical carcinoid; HR: hazard ratio; LCNC: large-cell neuroendocrine carcinoma.

Table 3: Variables influencing AC/LCNC DFS[a]

	AC				LCNC			
	Univariate models				Univariate models			
	HR	*P*-value	95% Confidence interval		HR	*P*-value	95% Confidence interval	
			Lower	Upper			Lower	Upper
Gender (male)	3.03	0.036	1.08	8.54	0.76	0.51	0.33	1.73
Age (years continuous)	1.04	0.048	1.00	1.09	0.96	0.12	0.91	1.01
Smoking history (yes)	1.98	0.24	0.63	6.19	0.39	0.068	0.14	1.07
Paraneoplastic syndromes (yes)	0.00	1.00	0.00		0.73	0.76	0.10	5.37
Symptoms (yes)	0.78	0.62	0.29	2.09	0.91	0.82	0.40	2.06
Previous malignancies (yes)	1.05	0.94	0.30	3.64	2.10	0.18	0.71	6.16
Tumour location (peripheral)	1.27	0.66	0.44	3.63	1.19	0.67	0.54	2.62
Size (cm continuous)	0.99	0.96	0.68	1.45	1.15	0.06	1.00	1.34
pT (pT1 as reference)								
pT2	0.84	0.76	0.26	2.67	0.86	0.75	0.33	2.20
pT3	1.72	0.61	0.22	13.71	1.49	0.42	0.57	3.94
pT4	5.21	0.037	1.11	24.48	0.00	1.00	0.00	
Lymph-nodal involvement (yes)	2.29	0.079	0.91	5.77	0.58	0.17	0.26	1.27
TNM stage (Stage I as reference)								
Stage II	1.96	0.19	0.71	5.42	0.88	0.76	0.39	1.98
Stage III	2.42	0.20	0.63	9.28	1.03	0.96	0.36	2.97
Surgery (lobectomy as references)								
Wedge resection or segmentectomy	1.86	0.33	0.53	6.49	1.95	0.38	0.44	8.60
Pneumonectomy or bilobectomy	0.25	0.18	0.03	1.90	1.33	0.48	0.61	2.92
Adjuvant chemotherapy (yes)	1.06	0.94	0.24	4.60	0.77	0.52	0.35	1.71

[a]Disease-free survival.
AC: atypical carcinoid; HR: hazard ratio; LCNC: large-cell neuroendocrine carcinoma.

Table 4: AC/LCNC 5-year survival rates in the most recent series reported in the literature

Author [Reference]	AC (*n*)	AC 5-year survival	LCNC (*n*)	LCNC 5-year survival	Year
Garcia-Yuste *et al.* [9]	43	72% (all stages)	22	21% (all stages)	2000
Iyoda *et al.* [13]	–	–	50	35.3% (Stage I)	2001
Filosso *et al.* [17]	44	77% (all stages)	–	–	2002
Battafarano *et al.* [15]	–	–	82	30.3% (all stages)	2005
Rossi *et al.* [18]	–	–	83	27.6% (all stages)	2005
Asamura *et al.* [11]	9	77.8% (all stages)	141	40.3% (all stages)	2006
Veronesi *et al.* [14]	–	–	144	52% (Stage I)	2006
Present series	126	82% (Stage I)	135	48% (Stage I)	2013

AC: atypical carcinoid; LCNC: large-cell neuroendocrine carcinoma.

Radical resections have been reported in about 98% of cases; this suggests that the surgical indication was always correct and the surgical skill of the members of the participating institutions was of a high level. Data about the execution of a staging lymph-nodal sampling/dissection also underline that the intention to stage was correct in about 98% of patients.

According to the different biological behaviour of the two histological subtypes, N-positive tumours were more frequently observed among LCNC patients. This influences the disease staging distribution and ACs were found more frequently at pathological stage I at the time of resection.

Although data about preoperative clinical staging are not readily available, the low utilization of induction treatment among both ACs and LCNCs could be explained by the lack faith in preoperative treatments during the investigated period.

Survival analysis was partially consistent with the conclusions drawn from the previous literature; Table 4 reports the 5-year survival rates of the most recent series for both AC and LCNC. In particular, LCNC showed a poor survival when compared with AC and this significant difference was still registered when only Stage I was considered, emphasizing the different biological behaviour of the two subtypes. LCNCs are confirmed as very aggressive and highly lethal tumours even at an early stage (28% 5-year OS in all stages and 42% 5-year OS in Stage I disease).

The two histotypes also varied when the survival analysis was carried out to identify factors influencing prognosis. The prognosis for ACs was influenced by age, tumour dimension and advanced stage at diagnosis (T4 and/or pathological stage III), with primary tumour dimension and anatomical resection being independent prognostic factors.

In contrast, the prognosis for LCNCs was influenced by tumour dimension, incomplete resection and advanced pathological stage, with advanced stage being the only independent prognostic factor. Thus, primary tumour dimension and the completeness of local control by an anatomical resection have a more important effect on the prognosis for ACs (i.e. probably related to the less aggressive behaviour of this histological subtype when compared with LCNCs), whereas only advanced pathological stage (directly influenced by the biologically aggressive behaviour of the disease) is an indicator of a poor prognosis for LCNCs.

While LCNCs have been identified as highly aggressive tumours and the recent literature recommends aggressive multimodal treatment even at early stages, the main dispute today concerns the consensus on ACs [20]. In fact, this subtype has been sometimes erroneously characterized by an intermediate prognosis. In the present series, surgery for pathological stage I ACs presented a 5-year life expectancy of ∼80%, which is similar to that recently reported for some subtypes of lung adenocarcinoma (i.e. acinar or papillary) [21].

This study presents some possible limitations such as the retrospective and multicentre design and the long recruitment period (over 17 years). Nevertheless, the use of the ESTS NETs lung database allowed us to collect a large cohort of patients from high-volume European Thoracic Surgery Institutions.

In conclusion, AC and LCNC have been confirmed as clearly separate histological subtypes with regard to presentation, biological behaviour and response to treatments. Whereas LCNC is confirmed to be a highly lethal disease and surgery alone is unsuccessful even at early stages, AC is still not completely understood. The biological behaviour of the tumour indirectly measured by the patients' life expectancy is similar to that of other more frequent subtypes of NSCLC like acinar or papillary adenocarcinoma. Future efforts should concentrate on translating genetically the biology of this tumour in order to develop best treatment protocols.

Conflict of interest: none declared.

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APPENDIX A. CONFERENCE DISCUSSION

Dr P. Ferolla *(Perugia, Italy)*: One of the most interesting and intriguing issues is, as you mentioned, the grey zone. We know that the subdivision between atypical carcinoid and the poorly differentiated is based only on the mitotic count. Don't you think that we have to work with this group of patients, in a further subdivision probably, because we have large cells that grow slowly and atypical carcinoid that seems more aggressive than others, so to work on a new group that is an intermediate form may be necessary. In the gastro-enteropancreatic NETs we are now also working on the subdivision of the group of the so-called G3 tumours, and probably subdividing this subgroup may be crucial. What do you think?

Dr Filosso: It is a very interesting question. I completely agree with you. In particular, this subclassification was done according to the Travis' neuroendocrine tumours histological classification (number of mitoses, presence of necrosis, and not, for example, the Ki76 percentage, which is, from a biological point of view, a very important cell proliferation marker). I believe that the biological tumour characteristics should be taken into account for the new NETs pathological classification.

Furthermore, this study has some intrinsic biases, since it is retrospective and multicentric, with data coming from several institutions around Europe, and sometimes we had difficulties in updating them (i.e. the Ki67 percentage or number of mitoses or other biological indicators). One of the future goals of this database is the opportunity to collect as much biological data as possible, allowing us to show differences in outcome between patient subgroups.

Dr Ferolla: My proposal is to design a prospective study in a joint venture within the ESTS, ENETS, and maybe the International Lung Cancer Society.

Dr Filosso: Of course.

Dr J. Schirren *(Wiesbaden, Germany)*: Nice study, but my question is as the speaker before asked. You have high volume centres. I am sure that they have done good surgery. But how did they do lymph node dissection in the beginning of the '90s and, very important I think for this study, how did you control the pathologists over eight centres? And you also said that you find necrosis, you find more activated tumour cells less than grade 1, 2, and 3, and we know the pathologists have to speak only one language, not eight languages.

Dr Filosso: During the Business Meeting of the ESTS Neuroendocrine Tumours of the Lung Working Group, the issue of a central pathologic review emerged, and we are going to decide to do this for the future. Concerning the role and the type of lymphadenectomy, I agree with you, this is another very important problem. Anyway, we wanted to start with our project using this "ad hoc" design of database. It is the type of thing that has happened with other ESTS projects, working groups and databases. Today we present the results of our first year's scientific activity – this is our starting point. Now we want to move forward with a prospective planned database.

Dr H. Date *(Kyoto, Japan)*: Regarding the preoperative pathologic diagnosis, sometimes it is very difficult in this population. How often did you see that the final pathologic result was different from the preoperative pathologic diagnosis?

Dr Filosso: This is a very interesting issue. We frequently observed a strong disagreement between the preoperative and the postoperative diagnosis, especially in the group of large cell neuroendocrine tumours, since a high number of patients presented with a preoperative cyto-histological diagnosis of non-small cell lung cancer, or cancer, whilst after operation a definitive histological diagnosis of large cell neuroendocrine tumour was achieved. One should argue that in this case with a correct preop finding, induction chemotherapy should be proposed, taking into account the poor outcome of these patients, even in case of early cancer and radical resection.