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Prognostic model of survival for typical bronchial carcinoid tumours: analysis of 1109 patients on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours Working Group[†]

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Abstract

OBJECTIVES: Typical carcinoids (TCs) are uncommon, slow-growing neoplasms, usually with high 5-year survival rates. As these are rare tumours, their management is still based on small clinical observations and no international guidelines exist. Based on the European Society of Thoracic Surgeon Neuroendocrine Tumours Working Group (NET-WG) Database, we evaluated factors that may influence TCs mortality.

METHODS: Using the NET-WG database, an analysis on TC survival was performed. Overall survival (OS) was calculated starting from the date of intervention. Predictors of OS were investigated using the Cox model with shared frailty (accounting for the within-centre correlation). Candidate predictors were: gender, age, smoking habit, tumour location, previous malignancy, Eastern Cooperative Oncology Group (ECOG) performance status (PS), pT, pN, TNM stage and tumour vascular invasion. The final model included predictors with $P \leq 0.15$ after a backward selection. Missing data in the evaluated predictors were multiple-imputed and combined estimates were obtained from five imputed data sets.

RESULTS: For 58 of 1167 TC patients vital status was unavailable and analyses were therefore performed on 1109 patients from 17 institutions worldwide. During a median follow-up of 50 months, 87 patients died, with a 5-year OS rate of 93.7% (95% confidence interval: 91.7–95.3). Backward selection resulted in a prediction model for mortality containing age, gender, previous malignancies, peripheral tumour, TNM stage and ECOG PS. The final model showed a good discrimination ability with a *C*-statistic equal to 0.836 (bootstrap optimism-corrected 0.806).

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CONCLUSIONS: We presented and validated a promising prognostic model for TC survival, showing good calibration and discrimination ability. Further analyses are needed and could be focused on an external validation of this model.

Keywords: Lung • Neuroendocrine tumours • Typical carcinoid • Surgery • Survival • Recurrence • Metastases • Prognostic score

INTRODUCTION

Neuroendocrine tumours (NETs) of the lung are a separate clinical subgroup of primary lung tumours, which share particular morphological, ultrastructural, immunohistochemical and molecular characteristics. According to the 2004 World Health Organization (WHO) tumours classification [1] they are categorized into four major groups, ranging from the low-grade typical carcinoids (TCs), to highly aggressive, poorly differentiated tumours [large-cell neuroendocrine carcinoma (LCNC) and small-cell lung cancer (SCLC)]. Amid them, an intermediate-grade neoplasm [atypical carcinoid (AC)] is characterized by a greater aggressive biological behaviour compared with TC, a poorer 5-year survival and a higher tendency to lymph-nodal involvement at presentation. A recent study [2], according to the surveillance, epidemiology and end results (SEER) data, demonstrated a significant increase in the reported overall NET incidence in the last decades. Actually, the estimated NET incidence is 5.25 cases/100 000 persons and their predictable prevalence in the USA is 35 cases/100 000 [2], making these neoplasms significantly more common than oesophageal, gastric, pancreatic and hepatobiliary cancers in the USA [3].

Bronchial carcinoids (BCs) actually represent 1.2% of all primary lung tumours [3] and can be histologically divided into: TCs, with highly organized carcinoid architecture and less than two mitoses/10 high-power fields (HPFs), and ACs, with greater mitotic activity (2–10/10 HPF) and focal or discrete necrosis [1]. Their incidence has also rapidly increased in the last three decades [4], partly explained with the improvement of diagnostic procedures, and with the lung cancer screening programme development and diffusion. Although BCs generally have a better prognosis than adenocarcinomas, they become incurable once they advance to an unresectable metastatic disease. New therapeutic approaches (systemic chemotherapy, biological agent, targeted therapy or peptide receptor radiotherapy) have been proposed, with conflicting results, and the lack of randomized clinical studies is mainly due to the rarity of the disease.

In 2012, the European Society of Thoracic Surgeons (ESTSs) launched a new scientific project, the NETs of the Lung Working Group (WG), with the aim of gathering a group of experts worldwide, developing knowledge on such rare neoplasms and disseminating it within the scientific community. A dedicated database was designed, approved by the ESTS NETs-WG Steering Committee and used to start a retrospective patient database.

Up to 31 January 2014, a series of 2059 NETs patients have been collected among 17 Thoracic Surgery Institutions worldwide (see Supplementary material, Table S1). Using this retrospective database, we intentionally focused on the outcome of TCs. The aim of this study was to develop an additive scoring system and to assess its association with survival in patients who underwent curative resection for TC.

PATIENTS AND METHODS

This is a retrospective, multicentre cohort study of patients operated for TCs between 1994 and 2012 at 17 high-volume European Thoracic Surgery Institutions. Data were obtained from the ESTS NETs-WG retrospective database.

Demographic and clinico-pathological characteristics were collected: age, gender, smoking habit, previous malignancies, tumour location, Eastern Cooperative Oncology Group (ECOG) performance status (PS), type of intervention, TNM stage, tumour vascular invasion, induction/adjuvant therapy.

We adopted the 'tumour location' definition previously reported by Detterbeck [5]: all those tumours directly visualized at bronchoscopy or in association with lung atelectasis and/or obstructive pneumonia were classified as 'central', whereas 'peripheral' lesions where those not observed at bronchoscopy.

The type of surgical resection was recorded and classified as 'anatomical' (segmentectomy, lobectomy, bilobectomy or pneumonectomy) and 'non-anatomical' (wedge resection). Bronchoplastic procedures (i.e. sleeve lobectomy) were included within the lobectomy group. Lymph-nodal dissection data were also collected.

All the histological samples were reviewed by local pathologists and the definitive TC histological diagnosis was done according to the 2004 WHO lung tumours classification [6] and to the Travis' histological guidelines for lung NETs diagnosis [7]. Tumours staging was classified according to the seventh edition of the TNM staging system for malignant lung tumours [8].

Statistical analysis

For patient characteristics, continuous data are presented as median (interquartile (IQR)] and categorical data as frequency with percentage.

Overall survival (OS) was the primary outcome. OS was calculated from the date of surgery to the date of death from any cause or the date of the last follow-up. OS curves were computed using the Kaplan–Meier method. Predictors of OS were investigated using the Cox model with shared frailty (accounting for the within-centre correlation). Candidate predictors were: age (as continuous), gender, smoking habit (never or former/current smoking), previous malignancy, tumour location (central or peripheral), ECOG PS (0, 1-2, ≥3), pT, pN, TNM stage and tumour vascular invasion. Missing data in the evaluated baseline predictors were multiple-imputed and combined estimates were obtained from five imputed data sets. The imputation of missing data was not performed for the outcome variables. A sensitivity analysis based on complete data patients was also performed.

To prevent overfitting, the final model included predictors with $P \leq 0.15$ after a backward selection. *C*-statistic was used to determine the discrimination ability of the proposed model. The predicted 5-year survival probabilities were compared with the observed frequencies using a calibration plot to assess the calibration of the model. It was internally validated in order to evaluate the optimism of the model. Two hundred bootstrap samples were drawn from the original data set with replacement and within each bootstrap sample the entire modelling process described above, including the backward stepwise selection of predictors, was repeated. The optimism-corrected *C*-statistic was estimated according to bootstrap process results. To simplify the calculation

of the survival probabilities for single patients, the Cox model has been displayed through an easy-to-use nomogram.

For the purpose of designing an additive score, numerical variables were computed according to the proportion between each predictor's coefficient and the lowest one. To simplify the score calculation, the selected final model was re-estimated including age as categorical (<55, 55–64, 65–74, ≥75 years). Patients were then grouped in classes of risk according to their total score.

Statistical analyses were performed with Stata (version 12.1) and R (version 3.0.2).

RESULTS

Figure 1 shows the study flow of the patient population.

Between 1994 and 2012, a series of 2059 patients operated for NETs were evaluated; of these, 1167 (57%) cases were identified as TC. Analyses were performed on data of 1109 patients with complete information for OS analysis. Clinical and demographic characteristics of analysed population are summarized in Table 1.

Patients affected by TC were more frequently females (712, 64%) and never-smokers (601, 54%). One-hundred and ninety-one (17%) experienced a previous malignancy. Median age at intervention was 59 years (IQR: 46–68); centrally located neoplasms were 457 (61%) on the 754 with available information. Surgical procedures are summarized in Table 2.

During a median follow-up of 50 months, 87 patients died; the 5-year OS was 93.7% [95% confidence interval (CI): 91.7–95.3] (Fig. 2).

The final Cox model (Table 3), deriving from the backward selection, showed that mortality was associated with: increased age [*per* 1 year increase, hazard ratio (HR): 1.07; 95% CI: 1.05–1.09, $P < 0.001$], male gender (HR: 2.18; 95% CI: 1.39–3.43, $P = 0.001$), the presence of previous malignancies (HR: 1.88; 95% CI: 1.16–3.05, $P = 0.010$), pTNM stage (II vs I: HR: 2.19; 95% CI: 1.13–4.21, $P = 0.019$; III vs I: HR: 3.77; 95% CI: 1.56–9.13, $P = 0.003$) and ECOG PS (1-2 vs 0: HR: 2.04; 95% CI: 1.1–3.76, $P = 0.023$; ≥3 vs 0: HR: 3.49; 95% CI: 0.32–38.7, $P = 0.300$). The final model showed a good discrimination ability with a *C*-statistic equal to 0.836 (optimism-corrected 0.806). Using an approach based on a standard Cox model without taking into account the shared frailty, the same predictors were selected by obtaining very similar effect estimates.

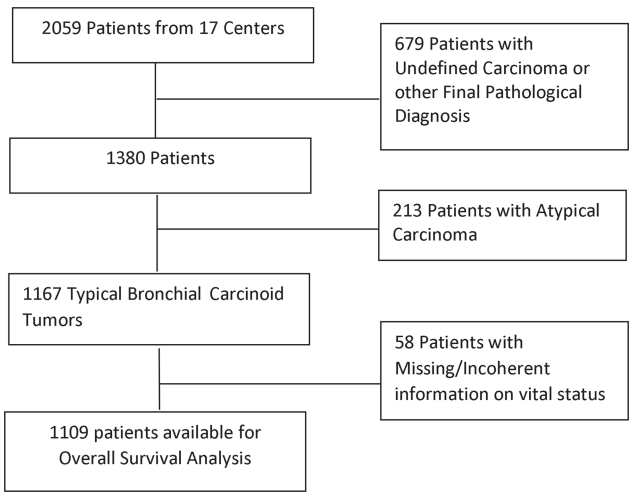

Figure 1: Study flow chart.

The sensitivity analysis based on patients with complete data showed a reduction of the effect on risk of death for previous malignancy (HR: 1.41 vs 1.88) and intermediate pTNM (HR: 1.17 vs 2.19), whereas we observed an increase of effect on risk of death for male gender (5.01 vs 2.18) and high ECOG PS (8.60 vs 3.49). However, the subgroup of patients with incomplete data on all

Table 1: Patient characteristics ($n = 1109$)

	n		Missing (%)
Age	1109		0
Median (IQR)		59 (46;68)	
Mean (range)		56.7 (11–90)	
Males	1109	397 (36%)	0
Smokers (current/former)	1109	508 (46%)	0
Previous malignancy	1109	191 (17%)	0
Central tumour	754	457 (61%)	355 (32%)
ECOG PS	902		207 (19%)
0		785 (87%)	
1-2		113 (13%)	
≥3		4 (0%)	
pTNM	1109		0
I		955 (86%)	
II		109 (10%)	
III		45 (4%)	
Pt	1078		31 (3%)
t1		828 (77%)	
t2		214 (20%)	
t3		30 (3%)	
t4		6 (1%)	
pN	1109		0
N0		975 (88%)	
N1		65 (6%)	
N2		29 (3%)	
Nx		40 (4%)	
cN	869		240 (22%)
n0		806 (93%)	
n1		40 (5%)	
n2		23 (3%)	
Adjuvant therapy	908	17 (25)	201 (18%)
Induction therapy	908	6 (<1%)	201 (18%)
Vascular invasion	880	79 (9%)	229 (21%)
Missing variables[a]	1109		
None		380 (34%)	
Only 1		435 (39%)	
Only 2		257 (23%)	
3 or more		37 (3%)	

[a]Considering all the variables mentioned in the table.

Table 2: Surgical interventions ($n = 1109$)

Type of intervention	*n*	%
Wedge resection	130	11.8
Segmentectomy	81	7.3
Lobectomy	706	63.7
Sleeve resection	77	6.9
Bilobectomy	82	7.4
Pneumonectomy	29	2.6
Extended resection	1	0.1
Missing data	3	0.2

the above selected covariates showed a significantly lower probability of survival compared with patients with complete data (HR: 1.74, 95% CI: 1.11–2.71, $P = 0.015$). Figure 3 shows the calibration of the model, with a good agreement between observed and predicted 5-year survival, over the whole range of probabilities. Finally, Fig. 4 shows the designed Nomogram, which is able to predict 5-year survival of TCs.

Table 3 also summarizes results of Cox model according to age as categorical variable (<55 years; 55–64 years; 65–74 years and >75 years), in order to simplify the calculation of additive score. This simplification results in a little reduction of discrimination ability of the model with a *C*-statistic equal to 0.822 (optimism-corrected 0.795).

Based on their regression coefficients of similar magnitude, a weighted score was created, assigning points according to the rounded to integer proportion with the lower one (peripherally located tumour equal to 1 point).

Based on the additive score results, patients were grouped into four risk classes: A (≤1 point, 378 patients), B (2–3 points, 459 patients), C (4–5 points, 234 patients) and D (≥6 points, 38 patients). Figure 5 shows the overall survival (OS) Kaplan–Meier estimates by additive risk score classes ($P < 0.001$). The 5-year survival rates for the four classes were: A: 99.7%, B: 96.3%, C: 84.2% and D: 53.9%.

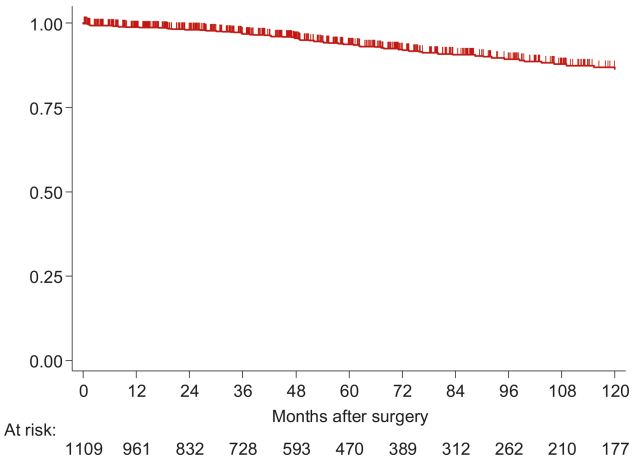

Figure 2: Overall survival (OS) Kaplan–Meier estimates. Marks represent censoring times.

DISCUSSION

The incidence of BCs has rapidly increased in the last three decades, partly due to the improvement in diagnostic procedures as well as in their recognition through simplified histopathological procedures [4]. A key role has also been played by the dramatic development and diffusion of lung cancer screening programmes which increased the likelihood of detecting small peripheral lung nodules in high-risk subjects.

On the other hand, lung NETs clinical management has recently become more multidisciplinary, involving not only surgeons, but also medical and radiation oncologists, pathologists, interventional pulmonologists. The recent development of new, effective chemotherapeutic molecules, along with biological agents, has resulted in a more effective treatment of advanced tumours, which were previously regarded as untreatable.

The interest in lung NETs and the recognition that a global effort is needed in their management has led to the development of multicentre experiences [9], retrospectively collecting a cohort of patients as large as possible, to establish outcome and potential prognostic factors for such rare neoplasms. ESTS has taken steps in this direction, creating an international working group of experienced physicians in lung NETs; within the first 2 years

Table 3: Predictors of overall survival using Cox proportional hazard models ($n = 1109$)

	Age as continuous		Age as categorical			
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	Coefficient	Score
Age as continuous, (per 1 year increase)	1.07 (1.05–1.09)	<0.001	–	–	–	–
Age as categorical						
<55 (Ref.)	–	–	1	–	–	0
55–64	–	–	2.54 (1.15–5.59)	0.021	0.931	1
65–74	–	–	4.18 (1.99–8.79)	<0.001	1.431	2
≥75	–	–	10.36 (4.66–23.03)	<0.001	2.338	3
Male	2.18 (1.39–3.43)	0.001	2.2 (1.4–3.47)	0.001	0.790	1
Previous malignancy	1.88 (1.16–3.05)	0.010	1.95 (1.2–3.16)	0.007	0.669	1
Peripheral tumour	1.89 (0.78–4.59)	0.142	2.05 (0.88–4.81)	0.091	0.719	1
pTNM						
I (Ref.)	1	–	1	–	–	0
II	2.19 (1.13–4.21)	0.019	2.1 (1.09–4.04)	0.026	0.743	1
III	3.77 (1.56–9.13)	0.003	3.74 (1.55–9.02)	0.003	1.320	2
ECOG PS						
0	1	–	1	–	–	0
1–2	2.04 (1.1–3.76)	0.023	2.05 (1.11–3.8)	0.023	0.718	1
≥3	3.49 (0.32–38.7)	0.300	4.16 (0.34–50.87)	0.255	1.425	2
C-statistics						
Original sample	0.836		0.822			
Optimism-corrected	0.806		0.795			

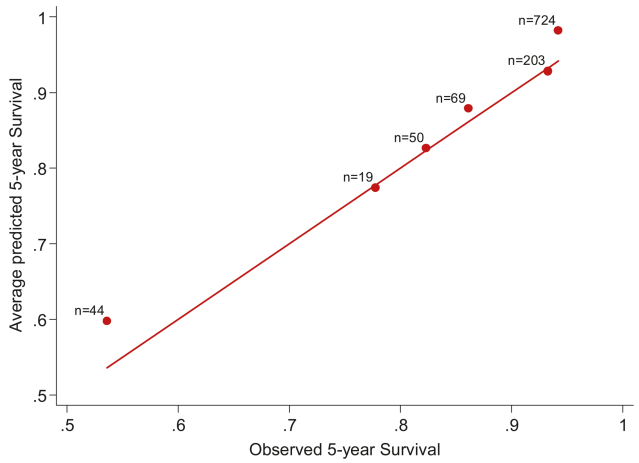

Figure 3: Calibration plot describing the relationship between the predicted versus observed 5-year survival. Predictions were based on the model including age as a continuous variable).

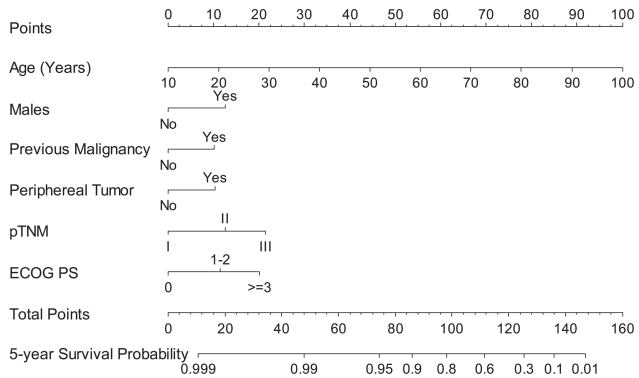

Figure 4: Nomogram derived from the Cox model.

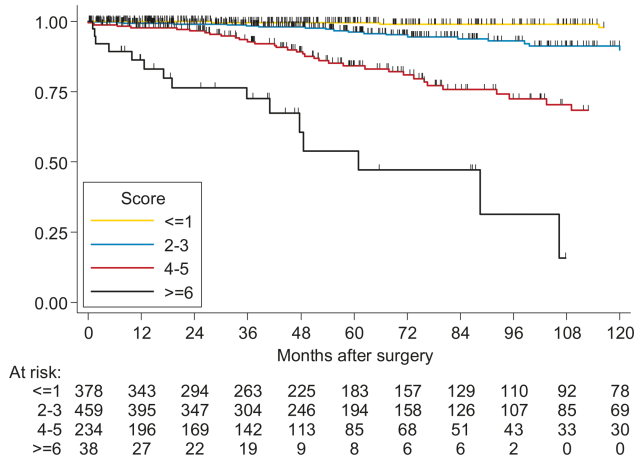

Figure 5: Overall survival Kaplan–Meier estimates by additive risk score. Data points represent censoring times.

activity, more than 2000 patients have been retrospectively collected from 17 high-volume international Thoracic Surgery Centres through an ad hoc designed database. This database has been use for the purposes of this study.

Main findings

Several papers have been recently published on single-centre experiences on lung NETs [10–13], but to the best of our knowledge, this is the first report focussing on identifying factors associated with survival and incorporating them into a single additive score.

We found that mortality was associated with increased age, male gender, the presence of previous malignancies, peripheral tumours, TNM stage and ECOG PS. These variables were used to construct an additive score, enabling one to identify four risk classes, according to the specific weight of each independent predictor. In this way, Class A patients experienced a 5-year survival of 99.7%, Class B, 96.3%, Class C, 84.2% and Class D, 53.9%.

Evidence

There are several reports on the association of age and prognosis in patients affected by non-small-cell lung cancers (NSCLCs): in general, most of them indicate that surgery in early-stage NSCLC is effective in elderly patients, and produces similar survival results than in younger ones [14]. On the contrary, a recent SEER analysis found that elderly patients presented with a worse survival, which was independent of sex, stage or histology [15].

Our results confirm that age (both as continuous and as categorical covariates) as well as male gender have a negative impact on patients' survival, as recently reported [16, 18]. The correlation between lung neoplasm and male gender may be partly explained by the smoking habits of the patients.

This is the first time in which a previous malignancy is reported to be a negative predictive variable in BCs. A recent SEER analysis [19] described 329 (13.9%) out of 2374 carcinoid patients who had a primary cancer diagnosed prior to the lung neoplasm, and 163 (7.4%) who presented with another cancer at the same time of the carcinoid diagnosis; however, no data are reported about both outcome of these patients and the possble prognostic role of second cancers. In particular, an increased risk to develop prostate and breast cancer was observed. The authors postulated that the growth of BCs may be partly the result of a genetic predisposition or environmental factors, particularly with regard to hormonally-related neoplasms. The role of genetics and sex hormones in lung carcinoid development, as well as the identification of other risk factors, should be further explored.

A possible explanation for the negative prognostic value of a peripheral tumour location may be the absence of symptoms compared with the central site. When the carcinoid grows in a main bronchus, in fact, cough, dyspnoea, recurrent pneumonia and haemoptysis usually occur, and an earlier tumour diagnosis is often possible [5, 20]. A prolonged treatment for an infection or asthma is sometimes possible, and this may predate tumour diagnosis, especially in young patients. In the absence of clinical symptoms, peripheral lesions remain undetected for a long time, or are occasionally discovered on chest X-rays performed for other reasons.

In 2008, the International Association for the Study of Lung Cancer (IASLC), joining SEER and IASLC databases, proposed to extend the seventh TNM classification to also include bronchopulmonary carcinoids [21]. Since then other publications have followed this suggestion [13, 17]; our data strongly confirm that the new TNM stage classification is effective in predicting prognosis in BCs.

There is a large body of evidence concerning the prognostic role of the patient's PS in primary lung cancers. PS can be assessed using several tools: we adopted the ECOG scale [22], which demonstrated to be an independent variable influencing survival.

Study limitations

Possible study limitations are as follows:

(i) A potential intrinsic limitation is its retrospective and multicentric nature. Nevertheless, the use of the ESTS NETs lung database allowed us to collect a large cohort of patients from high-volume International Thoracic Surgery Institutions. Their well-known clinical expertise in the field of NETs as well as the use of shared frailty survival models add a statistical robustness to our results.

(ii) A centralized histological review process was not available; however, all the histological specimens were reviewed by local pathologists and the definitive TC diagnosis was done according to uniform histological guidelines (the 2004 WHO Lung Tumors Classification and Travis' histological advice for NETs diagnosis).

(iii) The lack of a 'really' independent data set for model validation represents a weakness of this work; despite the model being internally validated using bootstrapping techniques, an external validation will be needed to evaluate the performance in other populations before implementing the prediction model in clinical practice.

Clinical inferences and conclusions

We presented a promising prognostic model for TC survival, showing a good calibration and discrimination ability. Its discriminative ability can be used to refine prognostic stratification in patients with TC who have undergone lung resection. Patients with a high score can be easily identified and counselled for a stricter follow-up. Future clinical investigations can be proposed to explore the feasibility of adjuvant treatments in patients with a high score, as well as their possible enrolment in prospective clinical trials to test the efficacy of new chemotherapeutic molecules in treating such rare neoplasms.

Further analyses could also focused on an external validation of this model, to facilitate its possible clinical application.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

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APPENDIX. CONFERENCE DISCUSSION

Dr P.-E. Falcoz *(Strasbourg, France)*: You clearly show in your work the interest of the thoracic surgical community in lung neuroendocrine tumours, which recognizes that a global effort is needed in their management. In fact, ESTS has taken steps in this direction, creating a worldwide Working Group of experienced physicians in lung neuroendocrine tumours. In the first two years of activity of this Working Group, through an *ad hoc* designed database, more than 2,000 patients have been retrospectively collected in 17 high volume international centres. This database has been used for the purpose of your study.

Dr Filosso, your study is the first report focused on identifying factors associated with survival and incorporating them into a single additive score. You found that mortality was associated with increased age, male gender, the presence of previous malignancy, peripheral tumours, TNM stages, and ECOG PS. You used these variables to construct your additive score, making it possible to identify four risk classes. Few studies in the past 10 years have sought to address this very interesting but seldom debated question of the prognosis of typical bronchial carcinoid tumours, and, for the most part, as you acknowledge, have been single institutions and retrospective cohorts. I am sure that your article will help to clarify some of these controversies, and its main findings may well have a relevant impact on the follow-up of these patients. I have three questions for you.

First, you postulate in your discussion that bronchial carcinoid growth may be partially the result of a genetic predisposition. Exploring the role of genetics and sex hormones in lung carcinoid could be very innovative indeed. Do you have any key data and clues to go one step further in this discussion?

Dr Filosso: Looking at your first question, very few data are available in the literature concerning the role of both sex hormones and genetic abnormalities in tumour growth and outcome of these rare tumours. If you consider the Lung Cancer Genomic Program, a loss of heterozygosity has been observed, especially in high grade tumours (large cell neuroendocrine carcinoma as well as small cell lung cancer), but it was not observed in the bronchial carcinoid. This means that even if they belong to the same biological family, those two types of tumours are different in terms of genetics. Loss of heterozygosity was detected especially in RP locus, in 3P and in p53; p53 was observed in high grade tumours, but was absent in typical carcinoids, and present in 23% of atypical carcinoids, showing the genetic differences between typical and atypical carcinoids. Currently we have no data concerning the genetic abnormalities in our patients.

During the business meeting of the ESTS Neuroendocrine Tumours Working Group yesterday we discussed the implementation of data and probably genetics will be included in the future.

Dr Falcoz: Second question. As you acknowledge in your manuscript, an external validation of your prognostic model is in fact mandatory. How do you plan to perform this external validation? By means of a pure bootstrap artificial statistical technique or by link with an historical cohort? Could you please give us more information and your point of view on this particular point?

Dr Filosso: I think that there are two possibilities to answer your question. First, keeping in mind that this is probably the largest series ever collected, we could improve the numbers of our patients and we could perform further bootstrapping and statistical analysis to validate the model. But we also have another possibility. We could propose this model to other institutions which have not yet uploaded their data to our database, and if it fits, we could achieve an external validation of the model.

Dr Falcoz: I think that is a nice idea. Finally, what will your next step be in your research work? Will you consider refining your score when more patients are included prospectively?

Dr Filosso: Thank you very much for this question because it allows me to remind everybody that there is a next step with this database: a prospective database has recently been elaborated. We used the retrospective one and we merged it with the ESTS-endorsed database, making possible a sort of new NETs registry, which is actually available for a demo at the Dendrite booth during the Congress. Finally, as soon as the definitive version is elaborated, each of you could include your patients in this database. I hope that in two or three years we will dramatically improve the numbers of neuroendocrine tumours in the database and we will be able to assess new prognostic factors, especially for the so-called grey zone (atypical carcinoid), which was the object of another paper from this group at the Birmingham meeting last year.

Dr Falcoz: You are to be congratulated for your in-depth work, and from the point of medical care, your results will certainly prove to be very beneficial to the thoracic surgical community.

Mr P. Goldstraw *(London, UK)*: Carcinoid tumours, and in particular typical carcinoid tumours, are indolent and even relapsed patients can live for many, many years with recurrent disease. If we are to understand how to use your nomogram, then we need disease-specific survival. Have you got any data on this? Are you collecting the causes of death and disease-specific survival?

Dr Filosso: We had 87 patients who died in the period of the study, and the majority of them died from tumour-related causes. Currently we have no data concerning disease-specific survival, but I am confident we will be able to improve our data regarding this issue in the future.

Mr D. Waller *(Leicester, UK)*: I have two young female, non-smoking, good performance patients in whom I have diagnosed typical carcinoid tumours by endobronchial laser ablation. In view of your knowledge of the subject and your prognostic indicators, do I now need to perform any further surgery on these good prognosis patients?

Dr Filosso: I think that you have to operate.

Mr Waller: Will I get any data to support that decision in the future based on your 1,000-patient database?

Dr Filosso: I don't have the exact number of bronchial resected tumours (probably 25-–28 cases), but all the patients went to surgery after the bronchoscopic resection.

Dr J. Schirren *(Wiesbaden, Germany)*: I think it is a good idea to find scores. It is interesting that in your series you have only 6% N1 disease and 3% N2 disease. This is very low if you compare this with the literature. Now, the question is, you have 17 centres: how extensive was lymph node dissection?

Dr Filosso: The majority performed lymph node dissection, not lymph node sampling. Therefore data concerning N1 and N2 are real in terms of removal of all lymph nodes, even if this is a retrospective database. We now know that we are moving to systematic lymph node resection, and I can assure you that the majority of centres did perform this procedure.

Dr Schirren: How many nodes did you resect?

Dr Filosso: I am not able to answer your question at this time, but will include it in the paper.

Dr E. Lim *(London, UK)*: I have one comment and one question. My comment is that bootstrap analysis is a different way of getting a confidence interval. It won't help you revalidate or redesign your model. So that is not the appropriate use of bootstrapping. Looking at the overall predictors, I noticed that TNM is probably the strongest influencing predictor, with T4 and stage 4 status having odds ratios of 51 and 24 respectively. So my question is, how much better is this prognostic model compared to the use of TNM alone?

Dr Filosso: This is a very good question. I think that only by improving the number of the patients included in this model could we have an answer to your question. I think that TNM should be the best variable in the model.