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Prognostic factors in neuroendocrine tumours of the lung: a single-centre experience†

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Abstract

OBJECTIVES To assess the independent prognostic role of histological subtypes, tumour size and lymph nodal involvement upon survival in lung neuroendocrine tumours (NETs).
METHODS A retrospective search of the database of the Department of Thoracic Surgery (Turin, Italy) identified 157 patients operated on for a newly diagnosed NET between January 1995 and December 2011. Multivariable Cox models were used to analyse predictors of overall survival and progression-free survival.
RESULTS According to histology, 71 (45.2%) were typical carcinoids (TCs), 35 (22.3%) atypical carcinoids (ACs), 37 (23.6%) large-cell neuroendocrine carcinomas (LCNCs) and 14 (8.9%) small-cell lung carcinomas (SCLCs). After a median follow-up time of 6.5 years, 60 patients died and 73 had a recurrence or died. The overall 5-, 10- and 15-year survival rates were 64%, 53% and 46%, respectively. Older age, histology (ACs, LCNCs and SCLCs vs TCs) and lymph nodal involvement were confirmed to be independent negative prognostic factors in the multivariable models for overall survival and progression-free survival.
CONCLUSIONS Tumour histology and lymph nodal involvement are definitively the predominant and relevant factors influencing survival. ACs showed an intermediate prognosis between TCs and poorly differentiated NETs.

Key words: Neuroendocrine tumours, Lung cancer, Carcinoid, Small-cell lung cancer, Large-cell neuroendocrine carcinoma, Metastases, Surgery

## INTRODUCTION

Neuroendocrine tumours (NETs) of the lung are considered a distinct subset of lung cancers, which share morphological, ultrastructural, immunohistochemical and molecular characteristics as suggested by the most recent Neuroendocrine Lung Tumours classification by Travis et al.[1]. There are four major categories of morphologically recognizable NETs, ranging from ‘similar to benign forms’ (typical carcinoids—TCs) to highly aggressive, poorly differentiated tumours (small-cell lung cancers—SCLCs and large-cell neuroendocrine carcinomas—LCNCs). Among them, the intermediate-grade atypical carcinoids (ACs), if compared with TCs, are characterized by a higher biological aggressiveness, with a significant reduced 5-year survival and a higher tendency to lymph nodal spread at presentation.
Several authors [2–5] pointed out that the spectrum of biological tumour behaviour should be considered a primary prognostic factor and should guide possible surgical and/or induction/adjuvant treatment.
Numerous papers have recently been published regarding TC and AC surgical treatment; however, very few articles compare the outcomes of different NET subtypes and the most relevant prognostic factors [6, 7].
The aim of this study is to describe the overall behaviour of all surgically treated NETs in our institution during the past 15 years, and to assess whether, in addition to the cell type, tumour size and nodal involvement are still important and independent factors influencing prognosis.

## PATIENTS AND METHODS

This is a single-centre (Department of Thoracic Surgery, University of Torino, Italy) retrospective study of all patients operated on for a NET of the lung. Ours is a high-volume referral surgical and oncological institution involved in the multimodal management of primary lung cancers.

We retrospectively selected all patients submitted to surgery with a radical intention and a final histological diagnosis of TC, AC, LCNC or SCLC in the period between January 1995 and December 2011.

The main endpoints of this study are overall survival (OS) and progression-free survival (PFS).

Information collected at the time of diagnosis included electrocardiogram, lung functional test, bronchoscopy and a complete radiological work-up with total body computed tomography (CT). If clinically required, magnetic resonance was performed. In case of a peripherally located nodule, transthoracic fine-needle aspiration biopsy was often performed. Perfusion lung scanning and echocardiography were requested when a major surgical procedure was planned. Outcome data were obtained from hospital records, ambulatory controls or telephone interviews. The survival follow-up was updated for all patients in April 2013 through contacts with the municipalities of residence (only 1 patient, a LCNC case, could not be found).

Posterolateral or anterolateral thoracotomies were the standard surgical approaches, and the extent of the surgical resection was planned on the basis of the tumour's local growth and lung parenchyma condition. Bronchial sleeve resections were performed whenever feasible, and frozen sections of bronchial margins were executed in all bronchoplastic procedures. Sublobar resections (especially segmental ones) were performed when patients were functionally at high risk of lobectomy.

Systematic lymphadenectomy was performed in the majority of patients. Surgery was considered radical if a complete tumour resection (R0) was achieved and incomplete in case of micro/macroscopic residuals (R1–R2).

For the present study, two expert pathologists reviewed all histological sections and achieved a definitive diagnosis of ‘neuroendocrine tumour’ and its differentiation in TC, AC, LCNC and SCLC according to the Travis histological guidelines for NET diagnosis [2]. Patients with a mixed (neuroendocrine and non-neuroendocrine) histology were excluded from the study. Tumour staging was reviewed according to the 2009 IASLC/UICC Staging System (7th Edition) [8].

### Statistical analysis

Continuous data are presented as median (interquartile range (IQR)) and categorical data as frequency (%). Probabilities of time-to-event endpoints were estimated by the Kaplan–Meier method. OS was calculated from the date of intervention to the date of death from any cause, or to the last available follow-up; PFS was calculated from the date of intervention to the date of local recurrence, or distant metastases, or death from any cause, or to the last available follow-up. We performed both univariable and multivariable analyses using the Cox proportional hazard regression model to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for histological subtypes and for a list of other predefined factors (age, sex and stage; Model I). Stage was also analysed in separate models of the T and N components of TNM classification (Model II) or using tumour size (in cm) and lymph nodal involvement (Model III).

To prevent biased results due to the exclusion of a few patients with some missing variables, we did an imputation of missing values using the hotdeck procedure, where missing values were replaced by random values from the same variable, using the Schonlau implementation for the Stata software [9]. Hotdeck imputation has the advantage of being simple to use, it preserves the distributional characteristics of the variable and performs nearly as well as the more sophisticated imputation approaches [10]. STATA SE version 11.0 (StataCorp LP, TX, USA) was used for all analyses.

## RESULTS

Clinical presentation and histological classification

One hundred and fifty-seven patients (82 males, 52.2%, median age 65 years) were included in this study. The characteristics of this group of patients are reported in Table 1.

Table 1:
Patient baseline characteristics

Histologically, 71 TCs (45.2%), 35 ACs (22.3%), 37 LCNCs (23.6%) and 14 SCLCs (8.9%) were observed. In 101 cases (64.3%), the tumour was a peripheral nodule.

Nine paraneoplastic syndromes were observed (3 acromegaly, 2 encephalitis, 1 Cushing syndrome, 2 flushing syndromes and 1 myasthenia gravis) in TCs and ACs. No paraneoplastic syndromes were observed in patients with LCNC or SCLC.

Surgical and adjuvant treatment

An anatomical resection was performed in all but 15 cases (atypical resections). Lobectomy was the most frequent intervention (126 cases, 80.3%; 5 sleeves). Ten patients were submitted to a bilobectomy and 6 to a pneumonectomy.

Hilar and mediastinal systemic lymphadenectomy was the standard of care; only in 9 cases (5.7%), it could not be accomplished.

Postoperative complications included atrial fibrillation in 2 cases (2 pneumonectomies), pneumonia in 2, severe respiratory insufficiency in 4 (1 patient required prolonged intensive care unit recovery), stroke in 1, prolonged pleural effusion in 3 and prolonged air leaks in 5.

No postoperative mortality was registered. Thirty-seven patients (24.0%, 5 TCs, 8 ACs, 14 LCNCs and 10 SCLCs) underwent adjuvant therapy (chemo/radio/biological therapy).

Chemotherapy was managed by our Medical Oncologist team. Generally, cisplatin/etoposide-based regimens were reserved to intermediate-/high-grade tumours, while a biological treatment with Somatostatin analogues was proposed in some TCs/ACs.

Overall and progression-free survival

The median follow-up was 6.5 years (8.0 IQR). At the end of the follow-up, 60 patients died (9 TCs, 18 ACs, 23 LCNCs and 10 SCLCs) and 73 either experienced a local/distant relapse or died.

Table 2 summarizes patient outcomes according to the histological tumour subtypes. Overall, the 5- and 10-year survival rates were 64% and 53%, respectively. The corresponding rates by histology were: TCs: 89% and 83%; ACs: 58% and 38%; LCNCs: 27% and 20%; SCLCs: 20% and 0% (Table 2 and Fig. 1). According to histology, similar differences were observed for PFS rates (Table 2 and Fig. 2).

Table 2:
Patient outcomesa

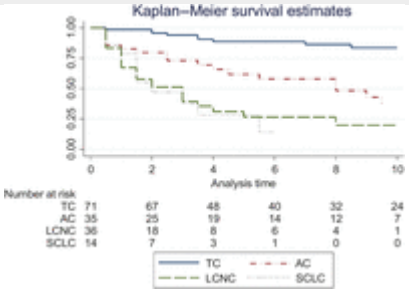

Figure 1:
Survival curves by histology (n = 156, 60 failures).

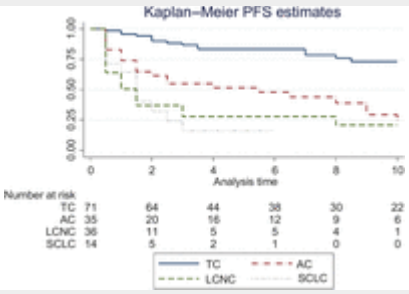


Figure 2:
Progression-free survival curves: metastasis (MTS)/local recurrence or death (n = 156, 73 failures: 31 deaths, 35 MTS and 7 relapses)

To estimate possible risk factors for death, we performed both the univariable and the multivariable analyses with the following variables: age, gender, tumour histology and stage, size (cm), T, N and stage. Results are presented in Table 3.

Table 3:
Risk factors for death

The univariable analysis highlights that increasing age ($P < 0.001$), male gender ($P = 0.008$), intermediate-/high-grade tumours (LCNCs and SCLCs vs TCs) ($P < 0.001$), greater tumour size ($P = 0.001$) and presence of lymph nodal metastases (N+) ($P < 0.001$) are strong negative prognostic factors.
At the multivariable analysis, age (HR 1.06; 95% CI 1.03–1.09, $P < 0.001$), histology different from TC (AC: HR 3.77; 95% CI: 1.59–8.91, $P = 0.003$; LCNC: HR 7.48; 95% CI: 3.15–17.78, $P < 0.001$; SCLC: HR 7.72; 95% CI: 2.90–20.56, $P < 0.001$) and N+ disease (N2; HR 2.28; 95% CI: 1.16–4.48, $P= 0.017$) were the only variables confirmed to be predictors of a worse survival (Model I). Neither the T category (Model II), nor the size of tumour (Model III), showed an independent prognostic role on survival when adjusted for age, histology and N category.
Forty-four patients (28%; 8 TCs, 17 ACs, 12 LCNCs and 7 SCLCs) developed distant metastasis during the follow-up time. Median time to metastasis was 1.5 years (2.5 IQR) and was longer for the TC group.

Nine patients (5.7%; 2 TCs, 3 ACs, 4 LCNCs and 0 SCLCs) developed local tumour relapse and the median time to relapse was 2.5 years (5.5 IQR): again, in the TC group, it proved to be longer.

Table 4 summarizes the results of the PFS analyses. At the univariable analysis, all the considered variables showed a statistically significant association with PFS. Increasing age, histology different from TC and advanced stage (III or IV) were confirmed to be negative prognostic factors at the multivariable analysis (Model I). The N2 category was confirmed to be a strong negative predictor of PFS, while T category and tumour size did not confirm an independent role (Models II and III).

Table 4:
Risk factors for metastasis/local recurrence or death

## DISCUSSION

This study puts into evidence that there is a large heterogeneity in NET behaviour. In fact, TCs show a very favourable clinical behaviour and survival; ACs are intermediate-grade tumours, characterized by a more aggressive biological behaviour compared with TCs, but with a better survival if compared with high-grade tumours. In contrast, LCNCs and SCLCs are poorly differentiated and highly aggressive neoplasms.

To our knowledge, only a couple of articles present in the literature [6, 7] discuss treatment of NET clinical outcomes. Several papers focus on the biological and molecular differences between them [11–13], and many concern TC clinical outcomes alone [14–17]. Compared with the two above cited studies [6, 7], our dataset is more recent and concerns a single institution. The limitations of our study may be attributed to the heterogeneity of treatment in a wide span of time and the small numbers for each histological subtype, indeed effecting the statistical power of the study. On the other hand, the accurate revision of all histological

sections and the systematic update of the follow-up, managed through municipalities of residence, should be considered as points of strength.

Tumour histology and lymph nodal involvement were the two important variables that showed a negative impact on prognosis. As expected, LCNC and SCLC survival analyses showed an overlapping trend already described in the literature [18, 19]. On the contrary, ACs presented a halfway behaviour between TCs and poorly differentiated NETs, a described a grey zone [11]. This means a high percentage of metastasis/local recurrences and almost a halved survival at 10 years compared with TCs. ACs have been considered relatively benign forms of NETs, but they may reach the aggressiveness of the poorly differentiated and highly aggressive ones. Erroneously, TCs have been considered 'benign' tumours for several decades [20], but actually they may present with lymph nodal metastasis or spread, even if rarely. For these tumours, our data suggest that only nodal involvement plays an independent prognostic role, while tumour size seems to be less important, unless its prevalent hilar location is considered.

An adjuvant platin/etoposide regimen of chemotherapy [21, 22], eventually supported by mediastinal radiotherapy, is the actual standard of care for resected poorly differentiated NETs.

So far, there is a lack of information about to the rarity of these tumours and publications are based on single-centred experiences. Focusing on this particular category, joining forces between international scientific oncological and thoracic surgical societies are mandatory to achieve sufficient knowledge and increase the feasibility of promoting new therapeutic randomized trials and more evidence-based guidelines for the treatment of advanced ACs.

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Conflict of interest: none declared.

## APPENDIX. CONFERENCE DISCUSSION

Dr P. Licht (Odense, Denmark): You have presented a straightforward, single-centre, retrospective follow-up series of 178 patients operated on for neuroendocrine tumours of the lung, which are relatively rare tumours, as you say. Your results confirm other similar follow-up studies and confirm previous investigations from your group and, as such, it is not surprising that older age, spread of cancer to the mediastinal or the hilar lymph nodes, and histologic subtypes separating the carcinoids from the small-cell carcinomas are all poor prognostic predictors of survival. As such, there is not a lot of new information for the thoracic surgeons present, yet you are to be congratulated for collecting such a large series. Of particular note to those present, I think it is an interesting observation that eight patients out of 83 with typical carcinoids developed metastases within a median follow-up of two years and, conversely, 40% of small-cell lung cancer and 60% of large-cell neuroendocrine carcinomas did not develop any local recurrence or any distant metastases during your long follow-up, yet not one single patient survived more than five years. It would be interesting to hear how you explain that.

Also, I would like your comments on how you stage the mediastinum before surgery. From your figures and from your tables, it appears that you have patients with small-cell lung cancer that are stage T3 and also N2-positive. How do you stage your mediastinum? That is one question.

I would like to have your expert opinion also if it is justified in 2012, after 10 years of molecular genetic studies showing that there is no relationship between the typical carcinoids, the atypical carcinoids, the small-cell lung cancers, and the large cell neuroendocrine carcinomas, there is no evidence to support that it is actually the same disease, although they have neuroendocrine granules. Is it still justified to consider this a continuum of the same disease?

Dr Sandri: We do believe that there is a continuum and that there is a common background. All of them may have different expressions, as an example, even if rarely, typical carcinoids sometimes have a very aggressive behaviour. The continuum of the neuroendocrine tumours is something which can be related to the

neuroendocrine cells, as the background, but there is a difference in their behaviour. It is not what to do concerning the treatment of the typical carcinoids, since it is something which we all know. I think we should focus upon the atypical carcinoids which express a different behaviour: most of them have an indolent behaviour while some have a very aggressive one. Also, there is not much of an option in the treatment of large cell and small cell tumours. In fact, in that case we do not know exactly what to do, whether to submit the patient to surgery or not, in order to define which is the best treatment for them.
Dr Licht: So are you saying that it is not certain if we should operate on atypical carcinoids now?
Dr Sandri: No, I am not saying that. Atypical carcinoids have an intermediate grade of aggressiveness and therefore some of them should be treated surgically. Others, especially N1 and N2, which have a higher metastasis and relapse rate, do not respond to chemotherapy or radiotherapy: the question is how to treat them. Probably after submitting them to surgery, they may relapse, and just one line of chemotherapy is presently available which is platinum/etoposide. It is the same chemotherapy regimen used for large cells and small cells. Therefore there is something which we should ponder upon regarding the treatment of atypical carcinoids, since after the first chemotherapy line there is no good strategy in case of relapse or metastasis.
Dr Licht: Could you just clarify for us how you stage the mediastinum before operating on small-cell lung cancer?
Dr Sandri: All patients are submitted to CT scan and bronchoscopy.
Dr Licht: Any invasive procedures, like EBUS or mediastinoscopy?
Dr Sandri: Mediastinoscopy is performed when we have a clinical doubt, but it is not scheduled for each patient.
Dr L. Spaggiari (Milan, Italy): I have one question. Do you have any experience today in the adjuvant setting of atypical carcinoid tumours with the use of new drugs, such as everolimus/sorafenib, that have a great place today in the less aggressive tumour?
Dr Sandri: Usually the aggressive atypical carcinoids which are already submitted to surgery get an adjuvant treatment, and the first line is the platinum/etoposide line. At times our oncologists do use the everolimus/temozolomide, in case of aggressive tumours with a high chance of relapse or metastasis.

Footnotes

- ↲† Presented at the 26th Annual Meeting of the European Association for Cardio-Thoracic Surgery, Barcelona, Spain, 27–31 October 2012.

REFERENCES


1. ↲

1. Travis WD,
2. Brambilla E,
3. Mueller-Hermelink HK,
4. Harris CC
   . Pathology and Genetics of Tumors of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press;2004.

5. Travis WD
   . Advances in neuroendocrine lung tumors. Ann Oncol2010;21:s65-71.
2.

1. Righi L,
2. Volante M,
3. Rapa I,
4. Scagliotti G,
5. Papotti M

. Neuro-endocrine tumours of the lung. A review of relevant pathological and molecular data. Virchows Arch2007;451:s51-9.
Lim E,
Goldstraw P,
Nicholson AG,
Travis WD,
Jett J,
Ferolla P,
6. et al
. Proceedings of the IASLC international workshop on advances in pulmonary neuroendocrine tumors 2007. J Thorac Oncol 2008;3:1194-201.
3.

1. Vorlotto JM,
2. Medford-Davis LN,
3. Recht A,
4. Flickinger JC,
5. Schafer E,
6. Zander DS,
7. et al
. Should large cell neuroendocrine lung carcinoma be classified and treated as a small cell lung cancer or with other large cell carcinomas? J Thorac Oncol2011;6:1050-8.
8. Lim E,
9. Yap YK,
10. De Stavola BL,
11. Nicholson AG,
12. Goldstraw P
. The impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors. J Thorac Cardiovasc Surg 2005;130:969-72.
13. Asamura H,
14. Kameya T,
15. Matsuno Y,
16. Masayuki N,
17. Tada H,
18. Ishikawa Y,
19. et al
.Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol2006;24:70-6.
20. Goldstraw P
. International Association for the Study of Lung Cancer (IASLC) Staging Manual in Thoracic Oncology. Orange Park, FL, USA: Editorial Rx Press;2009.
21. Roth P
. Missing data: a conceptual review for applied psychologists.Personnel Psychol 1994;47:537-60.
22. Schnonlau M
. Stata Software Package, Hotdeckvar.pkg, for Hotdeck Imputation, 2006 http://www.schonlau.net/stata.
23. Volante M,
24. Rindi G,
25. Papotti M
. The grey zone between pure (neuro)endocrine and non-(neuro)endocrine tumors: a comment on concepts and classification of mixed exocrine-endocrine neoplasms. Virchows Arch 2006;449:499-506.
4.

1. Lantuejoul S,
2. Soria JC,
3. Moro-Sibilot D,
4. Morat L,
5. Veyrenc S,
6. Lorimier P,
7. et al
.Differential expression of telomerase reverse transcriptase (hTERT) in lung tumors. Br J Cancer 2004;90:1222-9.

8. Lantuejoul S,
9. Moro D,
10. Michalides RJ,
11. Brambilla C,
12. Brambilla E
. Neural cell adhesion molecules (NCAM) and NCAM-PSA expression in neuroendocrine lung tumors. Am J Surg Pathol 1998;22:1267-76.

13. Filosso PL,
14. Rena O,
15. Donati G,
16. Casadio C,
17. Ruffini E,
18. Papalia E,
19. et al
. Bronchial carcinoid tumors: surgical management and long-term outcome. J Thorac Cardiovasc Surg 2002;123:303-9.
5.

1. Cardillo G,
2. Sera F,
3. Di Martino M,
4. Graziano P,
5. Giunti R,
6. Carbone L,
7. et al
. Bronchial carcinoid tumors: nodal status and long-term survival after resection. Ann Thorac Surg 2004;77:1781-5.
8. Ferolla P,
9. Daddi N,
10. Urbani M,
11. Semeraro A,
12. Ribacchi R,
13. Giovenali P
. Tumorlets, multicentric carcinoids, lymph-nodal metastases, and long-term behavior in bronchial carcinoids. J Thorac Oncol 2009;4:383-7.
6. ↵

1. Naalsund A,
2. Rostad H,
3. Strom EH,
4. Lund MB,
5. Strand TE

. Carcinoid lung tumors—incidence, treatment and outcomes: a population-based study. Eur J Cardiothorac Surg 2011;39:565-9.

6. Fernandez FG,
7. Battafarano RJ
. Large-cell neuroendocrine carcinoma of the lung. Cancer Control 2006;13:270-5.
7.

1. Veronesi G,
2. Morandi U,
3. Alloisio M,
4. Terzi A,
5. Cardillo G,
6. Filosso P,
7. et al
. Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. Lung Cancer 2006;53:111-5.

8. Detterbeck FC
. Management of carcinoid tumors. Ann Thorac Surg2010;89:998-1005.
9. Rossi G,
10. Cavazza A,
11. Marchioni A,
12. Longo L,
13. Migaldi M,
14. Sartori G,
15. et al
. Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRalpha, PDGFRbeta, and Met in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol2005;23:8774-85.
16. Rossi G,
17. Mengoli MC,
18. Cavazza A
. Pulmonary large cell neuroendocrine carcinoma: a true high-grade neuroendocrine tumor needing prospective therapeutic data. J Thorac Oncol 2011;6:1775.