The impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors

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Objective: In pulmonary neuroendocrine tumors the realization that the extent of nodal disease is related to cell type has led to a controversy as to which is the dominant prognostic factor, stage or morphology. To clarify this relationship, we studied patients treated at our institution over a 23-year period.

Methods: This is a historical cohort study of patients with confirmed pulmonary neuroendocrine tumors who underwent lung resection from 1980 through 2003. Survivors were contacted by telephone, and recurrences were confirmed by means of histopathology. Cox proportional hazards regression was used to ascertain the joint influence of several risk factors on survival.

Results: The mean age of the cohort was 54 years (standard deviation, 15 years), and 100 (57%) were men. The cell types for the 177 eligible patients were typical carcinoid in 89 (50%), atypical carcinoid in 15 (8%), large cell in 22 (13%), and small cell in 51 (29%). The median time to follow-up was 7 years (first to third quartile, 2-12 years), and overall 5- and 10-year survivals were 86% (79%-90%) and 81% (74%-87%), respectively. The univariable predictors of survival were age ($P = .001$), nodal stage ($P = .01$), and cell type ($P < .001$). In the final multivariable model only age ($P = .04$) and cell type ($P < .001$) remained as independent predictors. The hazard of death among patients with large cell or small cell lung cancer was highest in the first year and a half after diagnosis, reducing drastically thereafter.

Conclusions: In pulmonary neuroendocrine tumors cell type is the predominant determinant of survival. The survival of patients with each cell type is sufficiently diverse to warrant different management strategies. Conservative resection is feasible for typical carcinoids, but the effects of adjuvant chemotherapy need to be evaluated for the other subgroups.

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Received for publication Feb 22, 2005; revisions received April 27, 2005; accepted for publication May 16, 2005.

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J Thorac Cardiovasc Surg 2005;130:969-72
0022-5223/\$30.00

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doi:10.1016/j.jtcvs.2005.05.041

The 2004 World Health Organization/International Association for the Study of Lung Cancer classification for lung tumors recognizes 4 main categories of neuroendocrine tumor, namely typical carcinoid (TC), atypical carcinoid (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC). These categories are based on varying degrees of differentiation toward a neuroendocrine phenotype and differences in clinical behavior that warrant different management strategies.¹ Although this classification is predominantly morphologic,

TABLE 1. Baseline characteristics by cell type

	Typical carcinoid	Atypical carcinoid	LCNEC	SCLC
N	89	15	22	51
Mean age, y (SD)	48 (15)	58 (10)	63 (10)	61 (11)
Men, n (%)	41 (46)	6 (40)	17 (77)	27 (53)
T category				
N/A*	0 (0)	0 (0)	3 (14)	2 (4)
T1	45 (51)	10 (67)	5 (23)	16 (31)
T2	42 (47)	5 (33)	12 (55)	31 (61)
T3	1 (1)	0 (0)	2 (9)	1 (2)
T4	1 (1)	0 (0)	0 (0)	1 (2)
N category				
N/A*	1 (1)	0 (0)	3 (14)	2 (4)
N0	75 (84)	8 (53)	9 (41)	18 (35)
N1	11 (12)	3 (20)	6 (27)	21 (41)
N2	2 (2)	4 (27)	4 (18)	10 (20)
Stage				
N/A*	1 (1)	0 (0)	3 (13)	2 (4)
I	70 (79)	7 (47)	9 (41)	21 (41)
II	15 (17)	3 (20)	5 (23)	17 (33)
III	2 (2)	4 (27)	4 (18)	11 (22)
IV	1 (1)	1 (7)	1 (5)	0 (0)
Operation, n (%)				
Pneumonectomy	4 (4)	3 (20)	1 (5)	26 (51)
Lobectomy	65 (73)	10 (67)	18 (82)	22 (43)
Bilobectomy	6 (7)	1 (7)	1 (5)	2 (4)
Segmentectomy	10 (11)	0 (0)	2 (9)	1 (2)
Nonanatomic	4 (4)	1 (7)	0 (0)	0 (0)
Sleeve resections	30 (34)	3 (20)	0 (0)	0 (0)
No. of deaths (%)	3 (3)	5 (33)	4 (18)	19 (37)

Proportions might not sum to 100% in every category because of rounding. *LCNEC*, Large cell neuroendocrine carcinoma; *SCLC*, small cell lung cancer; *SD*, standard deviation; *N/A*, not available. Numbers in parentheses are percentages. *Unable to extract the exact information from all available data.

these separate categories can be viewed as a spectrum of differentiation within the neuroendocrine phenotype. There are many articles describing prognosis in relation to these tumor types,²⁻⁵ although there are very few studies that cover the entire spectrum of neuroendocrine tumors and look at factors that influence prognosis.⁶ Furthermore, there are few data on the effect of systematic nodal dissection within the 4 subgroups of tumors. The purpose of this study is therefore to retrospectively review resected tumors of neuroendocrine phenotype and assess the influence on survival of disease extent versus both clinical and pathologic parameters.

Methods

A review was undertaken of patients who underwent surgical intervention for TC, AC, LCNEC, and SCLC between 1980 and 2003 at the Brompton Hospital. Cases were identified from the pathology archive up until 1999 and from a prospective lung cancer resection

database thereafter. All slides were reviewed by one pathologist (A.G.N.) and classified according to current histologic criteria for neuroendocrine tumors.¹ We excluded patients if neuroendocrine tumor was not the confirmatory diagnosis, if the neuroendocrine tumor was not of pulmonary origin, and if patients did not undergo anatomic lung resection (bronchoplastic or wedge resection). All included patients undergoing surgical intervention for AC, LCNEC, and SCLC underwent systematic node dissection, whereas those undergoing resection for TC had a more limited nodal dissection. All cases were staged according to the fifth International Union Against Cancer revision.⁷ Some patients with carcinoid tumors have been reported on previously in a series on the feasibility of resection,⁵ and some with LCNEC have been reported on previously in a series on staging and prognosis within this subgroup.⁸

Data Acquisition

Individual patient data were collated from a prospective histopathology database, patients' case notes, and autopsy reports. Mortality was determined by using the National Health Service strategic tracing system, and survivors were contacted by telephone for interview.

Statistical Analysis

Categorical data are presented as frequency (percentage) and continuous data as mean with standard deviation or median with first and third quartiles. Probabilities of survival were estimated by using the Kaplan-Meier method. Cox proportional hazards regression models were used to ascertain the association between individual factors and survival. Their joint effect was assessed in a multivariable Cox model in which the criterion for retention of individual variables was a *P* value of less than .1. The model's assumption of constant hazard ratios over the entire follow-up was assessed by using the Schoenfeld test.⁹ When violated, separate hazard ratios were estimated over different time intervals.

Results

From January 1, 1980, to January 1, 2003, a total of 199 patients underwent surgical intervention with a presumed diagnosis of neuroendocrine tumor. In total, 5 patients were excluded when histologic review excluded a neuroendocrine tumor, 1 patient was excluded because the tumor was metastatic to the lung, 14 patients did not undergo anatomic lung resection, and 2 patients had insufficient data within hospital records. This left 177 patients as a cohort for the study.

The mean age of the cohort was 54 years (standard deviation, 15 years), and 100 (57%) were men. Of 177 patients, histologic review resulted in a diagnosis of TC in 89 (50%), AC in 15 (8%), LCNEC in 22 (13%), and SCLC in 51 (29%).

Baseline characteristics, stage, and operation extent are summarized separately by cell type in Table 1. Overall, patients with LCNEC and SCLC were older, and there was a greater predominance of male subjects among these patients. The incidence of nodal disease and its extent was also greater in these cell types (*P* < .001). Cell type was also

Figure 1. Overall survival by cell type. LCNEC, Large cell neuroendocrine carcinoma; SCLC, small cell lung cancer.

associated with the extent of resection, being progressively less conservative with more aggressive cell type ($P = .01$).

The median time to follow-up was 7 years (first to third quartile, 2-12 years), and overall survivals at 5 and 10 years were 86% (95% confidence interval, 79%-90%) and 81% (95% confidence interval, 74%-87%), respectively. The strong association of both cell type and nodal disease with survival is evident from the Kaplan-Meier plots shown in Figures 1 and 2.

The effects of age, cell type, T category, N category, and overall stage on recurrence-free survival were estimated by using Cox proportional hazards regression (Table 2). For every 10-year increase in age, there is an estimated 67% increase in the hazard of recurrence or death. Sex had no influence on survival. The hazards of death for patients with ACs and LCNECs were approximately 7-fold those of patients with TCs, whereas patients with SCLCs had an ap-

Figure 2. Overall survival by nodal status.

TABLE 2. Univariable risk factors for death

	Hazard ratio	95% confidence interval	P value
Age, per decade	1.67	1.22-2.30	.001
Female sex	0.57	0.27-1.22	.15
Cell type			<.001*
Typical carcinoid	1		
Atypical carcinoid	6.68	1.56-28.61	.01
LCNEC	6.85	1.52-30.73	.01
SCLC	14.70	4.34-49.80	<.001
T category			.23*
T1	1		
T2	1.75	0.79-3.91	.17
T3	2.56	0.32-20.44	.38
T4	8.93	1.11-71.46	.04
N category			.01*
N0	1		
N1	3.29	1.47-7.40	.004
N2	2.18	0.78-6.17	.14
Overall stage†			.07*
I	1		
II	2.59	1.12-6.02	.03
III	2.72	1.01-7.30	.05

LCNEC, Large cell neuroendocrine carcinoma; SCLC, small cell lung cancer. *P value for the overall effect of the category obtained from the likelihood ratio test. †There were no deaths in the 2 patients with stage IV disease.

proximately 15-fold increase in the risk of death compared with patients with TCs. Increased risk was also associated with advancing T and N categories. When jointly modeled, however, only increasing age and cell type were identified as independent predictors of mortality (Table 3).

The risk of death after surgical intervention for the 2 more aggressive cell types (LCNEC and SCLC) were not proportional over time ($P = .03$). Therefore separate hazard ratios were estimated for the first 1.5 years after surgical

TABLE 3. Multivariable risk factors for recurrence or death

	Adjusted hazard ratio	95% confidence interval	P value
Age, per 10-year increase	1.51	1.02-2.20	.04
Cell type			
Typical carcinoid	1		
Atypical carcinoid	3.5	0.99-12.82	.05
LCNEC <1.5 y*	12.51	1.96-79.81	.008
LCNEC >1.5 y†	1.39	0.16-12.45	.76
SCLC <1.5 y*	19.60	4.03-95.32	<.001
SCLC >1.5 y†	4.08	1.16-14.34	.03

LCNEC, Large cell neuroendocrine carcinoma; SCLC, small cell lung cancer. *Adjusted hazard ratio for the time frame immediately after surgical intervention but less than 1.5 years. †Adjusted hazard ratio after 1.5 years since surgical intervention.

intervention and beyond. The 1.5-year cutoff point was chosen because it corresponded to the time when 50% of events had occurred.¹⁰ The results show that the age-adjusted effect of LCNEC and SCLC relative to TC is mainly restricted to the first 1.5 years since surgical intervention, reducing drastically thereafter (Table 3), whereas that of AC was constant over time.

Discussion

The optimum management strategy is not yet defined across the spectrum of neuroendocrine tumors. The good prognosis associated with TC allows lung-conserving operations to be the principle treatment modality in this subgroup,⁵ whereas surgical intervention or combined modality treatment forms the mainstay of therapy for SCLC.¹¹ Less is known about the optimum management of AC and LCNEC because of the comparative rarity of these tumor types and their relatively recent acceptance as specific subgroups of neuroendocrine tumors.

Influence of Stage and Cell Type

The malignant potential of carcinomas is governed by stage (extent of disease) and, to a lesser extent, by grade (reflected by cell type). A knowledge as to which factor predominates could influence decisions on best therapy. If the prognosis of a tumor is governed mainly by the extent of the disease, then complete resection should be the principle aim. However, if prognosis is independent of stage and determined predominantly by cell type, then complete resection alone might be inadequate. The result of our study revealed the close association between progressive stage and more aggressive cell type. We attempted to differentiate between the 2 influences, showing cell type to be the stronger determinant. This is consistent with a previous study from Martini and colleagues.³

Clinical Implications

Because our data suggest that cell type is the stronger determinant of mortality, complete resection alone might be inadequate for any cell type other than TC, and prospective trials evaluating the survival with adjuvant chemotherapy for AC and LCNEC are needed.⁸

Potential Limitations

To ascertain the features associated with death, we have included patients with LCNEC and large cell carcinomas with neuroendocrine morphology in one group in this study. This is necessary because of the small numbers of such cases but justified by the lack of a clear difference in clinical management between the 2 subtypes.

Like most studies on pulmonary neuroendocrine tumors, we have been limited by the relatively small sample size

because of the rarity of these tumors and the small number of deaths. Hence it is difficult to compare our results with those of other studies, especially in the subgroups with small numbers, because discrepancies in survival can arise from statistical variation rather than true differences. The point estimates of our hazard ratios have wide confidence intervals, reflecting the uncertainty posed by the sample size limitations.

Although not specifically designed for this purpose, we applied the International Union Against Cancer/American Joint Committee on Cancer staging system to neuroendocrine tumors, as is widely used in this context, and provided a means for comparing stage-adjusted survival.

Conclusions

In pulmonary neuroendocrine tumors cell type is the predominant determinant of survival. The survival of each cell type is sufficiently diverse to warrant different management strategies. Surgical treatment by means of parenchyma-preserving resection is the optimum treatment for TC, but the effects of adjuvant chemotherapy need to be evaluated in randomized controlled studies for all other subgroups.

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