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Prognostic Factors in Typical and Atypical Pulmonary Carcinoids

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Background: Typical and atypical carcinoids represent approximately 2% of all lung tumors. Survival of patients with typical bronchial carcinoids, unlike the survival of patients with most lung tumors, is generally long but dependent on stage. We report the findings of the Ochsner Medical Center/Louisiana State University (LSU) Health Sciences Center neuroendocrine tumor (NET) program.

Methods: A database with all patients seen at the Ochsner Medical Center/LSU NET program was queried for patients with bronchopulmonary NET. We included patients who had confirmed pathologic bronchopulmonary carcinoid and who had at least 1 clinic visit. Patients with large or small cell NETs or diffuse idiopathic pulmonary neuroendocrine cell hyperplasia were excluded.

Results: A total of 169 patients seen from January 1996 to March 2015 met the inclusion criteria. The mean age at diagnosis was 53 years. Of the tumors, 51% percent (86/169) were well-differentiated, 12% (21/169) were moderately differentiated, and 85% and 53% were positive on positron emission tomography and octreotide scanning, respectively. The 5- and 10-year survival rates were 88% and 81% for well-differentiated tumors and 80% and 42% for moderately differentiated tumors, respectively. The 10-year survival rates stratified by Ki-67 index ranges 0-2%, >2%-10%, and >10% were 90%, 72%, and 44%, respectively ($P<0.05$).

Conclusion: Overall, patients with bronchial carcinoids have long 5- and 10-year survival rates. We found significant survival differences between nodal status, differentiation status, and carcinoid phenotype. Interestingly, the difference in survival stratified by Ki-67 indices was statistically significant despite its absence in the World Health Organization grading system. As with gastroenteropancreatic NETs, Ki-67 index could become a valuable prognostic indicator for bronchial carcinoids.

Keywords: *Carcinoid tumor, Ki-67 antigen, lung cancer*

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INTRODUCTION

Neuroendocrine tumors (NETs) are rare neoplasms that comprise <20% of all lung cancers.[1] Even more infrequent, typical carcinoids (TCs) and atypical carcinoids (ACs) represent approximately 2% of all lung tumors.[1] Queries to the Surveillance, Epidemiology, and End Results (SEER) database show an incidence of lung NETs of 1.35 per 100,000.[2] One report cites an increase in lung carcinoid incidence of approximately 6% per year for 30 years.[1] This increase in incidence most likely stems from an overall increased awareness of neuroendocrine neoplasms or possibly reflects the use of refined histopathologic methodology.

Low-grade lung carcinoids are categorized based on their mitotic rate and the presence of necrosis, according to the 2004 World Health Organization (WHO) criteria for NETs of the lung.[3] TCs are defined as having <2 mitoses per 2 mm^2 and the absence of necrosis, while ACs have 2-10 mitoses per 2 mm^2 and the presence of necrosis. Patients diagnosed with TC generally experience a long survival, with multiple reports citing 5-year survival rates of 88%-92%.[1,4]

Table 1. Patient Demographics and Tumor Characteristics (n=169)

Characteristic	Value, n (%)
Sex	
Male	56 (33%)
Female	113 (67%)
Ethnicity	
White	154 (91%)
Black	10 (6%)
Asian	2 (1%)
Other	3 (2%)
Smoking history	
Yes	56 (33%)
No	81 (48%)
Unknown	32 (19%)
Current smokers	
Yes	13 (8%)
No	153 (90%)
Unknown	3 (2%)
Phenotypic features	
Typical	113 (67%)
Atypical	46 (27%)
Unknown typicality	10 (6%)
Differentiation	
Well	86 (51%)
Moderate	21 (12%)
Poor	0 (0%)
Unknown	62 (37%)
Laterality	
Right	107 (63%)
Left	54 (32%)
Bilateral	8 (5%)
Location	
Right upper lobe	30 (18%)
Right middle lobe	36 (21%)
Right lower lobe	32 (19%)
Left upper lobe	21 (12%)
Left lower lobe	29 (17%)
Multiple in single lobe	18 (11%)
Other	3 (2%)

A limited number of studies evaluate potential prognostic factors among low-grade lung carcinoids. In a retrospective evaluation of 252 patients who underwent surgical resection for low-grade lung carcinoid tumors, Rea et al found that patients with typical phenotype and N0 stage designation experienced a more favorable prognosis than patients with atypical phenotype and N1-2 stage designation.[5] In the majority of primary NET tumor sites, Ki-67 proliferative index has proven to be a reliable prognostic factor and is used to define the histologic grade of these tumors.[6-8] However, its utilization is controversial in defining TC and AC and has only been examined retrospectively.[9,10] Reliable prognostic factors for the management of pulmonary TCs and ACs are necessary.

This retrospective medical record review details the experience of the NET program (a joint Louisiana State University (LSU) Health Sciences Center/Ochsner Medical Center program) with TCs and ACs of the lung. We also attempted to identify any additional factors that would identify patients with a poor prognosis.

METHODS

Data from all patients seen by the New Orleans, LA, Neuroendocrine Tumor Specialists (NOLANETS) were entered into a secure eVelos (Oracle) database for expedient identification and analysis. We performed a retrospective medical record review for patients with a diagnosis of bronchopulmonary primary NET seen at our institution from January 1996 to March 2015 and included patients whose NET was histologically confirmed and who had at least 1 visit to our clinic. Patient demographics, location and size of the primary tumor, metastatic sites, staging, and Ki-67 proliferative index values were collected. Criteria used for staging of lung cancer were also collected from the pathology reports, specifically the American Joint Committee on Cancer (AJCC) 7th edition tumor, node, metastasis (TNM) anatomic stage and AJCC prognostic stage group.[11] Exclusion criteria were a diagnosis of large or small cell NETs, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH), or inaccessible records. This study received institutional review board approval from LSU Health Sciences Center and Ochsner Clinic Foundation in New Orleans, LA.

Median survival in months and 5- and 10-year survival rates were calculated using the Kaplan-Meier method. Survival analysis was sorted by typical or atypical phenotype, AJCC prognostic stage group, tumor differentiation, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) results, somatostatin analog (SSA) usage, and Ki-67 proliferative indices (measured using the MIB-1 antibody as a percentage of cells in the areas of highest nuclear labeling).

In the survival analyses, patients were grouped according to the following Ki-67 ranges: 0-2%, >2%-10%, and >10%. For univariate Kaplan-Meier survival analyses, statistical significance was determined by log-rank test. Multivariate analyses using the Cox proportional hazards model were used to identify individual factors associated with prognosis. All factors proven to be statistically significant in univariate analysis were entered as covariates in this model. We considered P values <0.05 statistically significant. Statistical analyses were performed using MedCalc v.15.6.1 (Medcalc Software).

RESULTS

Patient Demographics

A total of 169 patients seen at the NOLANETS institution who had a histologically confirmed primary bronchopulmonary NET were included for analysis. The mean age at diagnosis was 53 years (range, 12-92 years). Table 1 presents demographics and tumor characteristics.

Table 2. American Joint Committee on Cancer 7th Edition Tumor, Node, Metastasis Staging at Diagnosis (n=169)

Characteristic	Value, n (%)
Tumor stage	
T1a	54 (32%)
T1b	22 (13%)
T2a	34 (20%)
T2b	7 (4%)
T3	20 (12%)
T4	19 (11%)
TX[a]	13 (8%)
Node stage	
N0	92 (54%)
N1	27 (16%)
N2	29 (17%)
N3	1 (1%)
NX[b]	20 (12%)
Metastasis stage	
M0	105 (62%)
M1a	10 (6%)
M1b	31 (18%)
MX[c]	23 (14%)

[a]TX, primary tumor cannot be evaluated; [b]NX, regional lymph nodes cannot be evaluated; [c]MX, distant metastasis cannot be evaluated.

Eighty-six patients (51%) had well-differentiated NETs, 21 patients (12%) had moderately differentiated NETs, no patients had a poorly differentiated NET, and 62 patients (37%) did not have defined differentiation. The Ki-67 value was specified in the pathology report of 88 patients (52%). The majority of patients had NETs with typical phenotypic features (113/169, 67%), 46 patients (27%) had NETs with atypical phenotypic features, and 10 patients (6%) did not have a typical or atypical distinction in their pathology report. The TNM staging distribution for the study cohort is listed in Table 2.

Survival Analysis

Thirty-two patients (19%) died during the course of this study. The median survival for the entire 169-patient cohort was not reached. The 5- and 10-year Kaplan-Meier survival rates for the entire study cohort were 88% and 77%, respectively (Table 3). The difference in survival rates between typical and atypical phenotypes was statistically significant ($P<0.05$; Figure 1). The 5- and 10-year survival rates were 90% vs 84% and 81% vs 59% for TCs and ACs, respectively. Kaplan-Meier 5- and 10-year survival rates were 88% and 81% for well-differentiated tumors, respectively, and 80% and 42% for moderately differentiated tumors, respectively. Differences proved to be statistically significant ($P<0.05$) between groups.

A total of 121 patients (72%) underwent surgical resection for their primary tumor, and 57 patients (34%) had lymph node metastasis at presentation. Patients with N0 staging had an excellent 5-year survival rate (96%), compared to 82% and 64% for N1 and N2, respectively ($P<0.05$). Distant metastases were present in 41 patients (24%) of our cohort.

Table 3. Survival Analysis

Overall Survival for Entire Cohort (n=169)				
	n	Median	5-year	10-year
Overall Survival	169	243 months	88%	77%
Survival by American Joint Committee on Cancer (AJCC) 7th Edition Prognostic Stage (n=159)				
		n	5-year	10-year
I[a]		65	98%	91%
II[a]		25	95%	87%
III[a]		28	84%	66%
IV		41	73%	49%
Survival by Differentiation Status (n=107)				
		Median	5-year	10-year
Well (n=86)		243 months	88%	81%
Moderate (n=21)		119 months	80%	42%
Survival by Typical/Atypical Phenotype (n=159)				
		Median	5-year	10-year
Typical (n=113)		243 months	90%	81%
Atypical (n=46)		126 months	84%	59%
Survival by Ki-67 Range (n=88)				
		Median	5-year	10-year
0-2% (n=40)		Not reached	90%	90%
>2%-10% (n=38)		Not reached	94%	72%
>10% (n=10)		67 months	67%	44%

[a]AJCC 7th edition substages (A and B) were grouped together.

A total of 159 (94%) patients had the AJCC 7th edition prognostic stage of their bronchopulmonary NET available in their pathology reports. Because of the limited numbers of patients with AJCC 7th edition prognostic stage groups reported in their pathology report, A and B substages were grouped for each tumor stage in the survival analysis as shown in Table 3. Kaplan-Meier survival by AJCC 7th edition stage was statistically significant ($P<0.01$). Kaplan-Meier survival rate estimates for groups defined by Ki-67 proliferative index were also significantly different ($P<0.05$). The 5-year survival rates were 90%, 94%, and 67% for Ki-67 ranges of 0-2%, >2%-10%, and >10%, respectively. Patients with Ki-67 values >10% had a significantly worse prognosis than patients with Ki-67 values <10% ($P<0.05$). Figure 2 shows the survival curve sorted by Ki-67 ranges. Multivariate analysis confirmed Ki-67 proliferative index as the only independent prognostic indicator of overall survival for primary lung carcinoids.

FDG-PET/CT imaging was performed in 86 patients, with uptake seen in 73 (85%). Somatostatin receptor scintigraphy (Octreoscan, Mallinckrodt Pharmaceuticals) was also performed in 132 patients, with 70 (53%) showing a degree of uptake. Differences in survival between groups sorted by FDG-PET/CT imaging uptake or octreotide usage were not statistically significant ($P>0.05$).

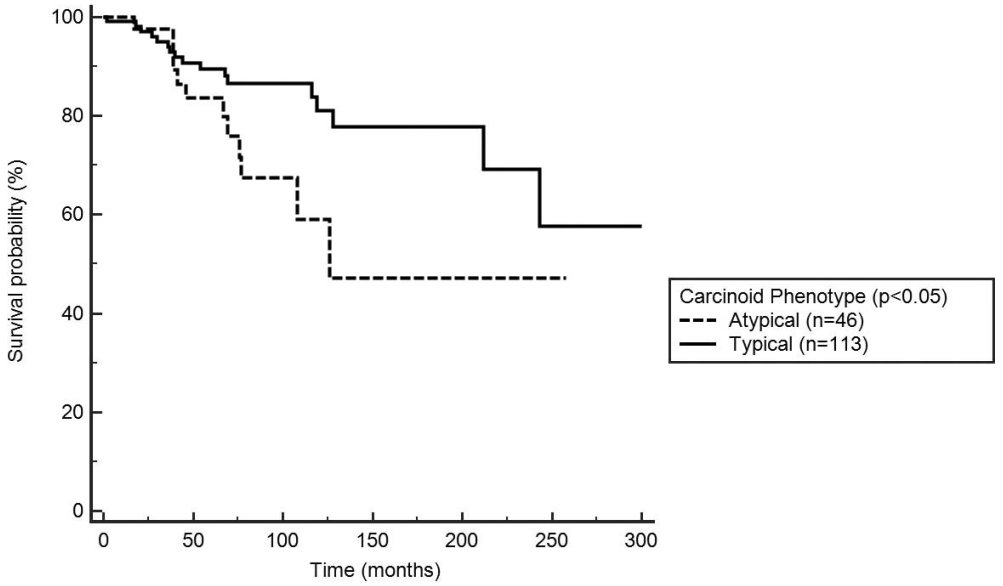

Figure 1. Kaplan-Meier survival curve for lung neuroendocrine tumors stratified by typical vs atypical carcinoid phenotype (n=159). Patients with atypical carcinoids had a poorer prognosis, with 10-year survival rates of 59% compared to 81% for typical carcinoids ($P<0.05$).

DISCUSSION

NETs of the lung represent a minority of lung tumors. TCs and ACs of the lung represent only approximately 2% of all lung tumors.[1] The remainder of NETs of the lung are high-grade large cell or small cell cancers. DIPNECH is thought to represent a premalignant condition. We examined the clinical and pathologic characteristics of 169 pulmonary carcinoids and excluded patients who had DIPNECH or a large or small cell tumor. As reported by Modlin et al, we have found that pulmonary carcinoid tumors are seen more frequently in females and often in patients who do not have a smoking history. While other types of lung carcinoma may arise as a result of smoking, the occurrence of pulmonary carcinoids in nonsmokers suggests that these tumors may result from different etiologic factors than other types of lung carcinomas.[12] The majority of the tumors in our cohort were classified as TCs, while 27% of our cohort had ACs. Our cohort had a lower mean age at diagnosis of 53 years (range, 12-92 years) compared to 70 years in patients with non–small cell lung cancer. Interestingly, non–small cell lung cancer is known to be the most common lung tumor in children.[13,14]

Most patients underwent conventional imaging with CT of the chest; however, 86 patients underwent FDG-PET/CT.

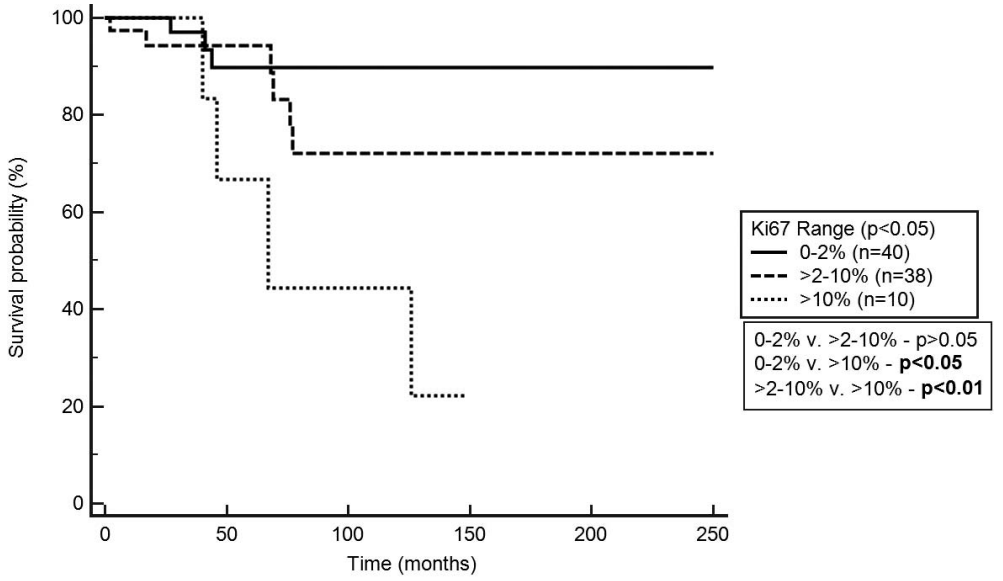

Figure 2. Kaplan-Meier survival curve for lung carcinoids stratified by Ki-67 proliferative index (n=88). Patients with Ki-67 values >10% had a significantly worse prognosis than patients with Ki-67 values <10% ($P<0.05$).

Despite pulmonary carcinoids being considered low-grade tumors, most patients who underwent FDG-PET/CT had some degree of uptake. The standard uptake value maximum for FDG-PET/CT is approximately 3-4 for TC and 7-8 for AC.[14] The majority of patients (78%) underwent somatostatin receptor scintigraphy, and despite this imaging technique being standard for NETs of the gastrointestinal tract, we found that only 53% of patients with bronchial carcinoid tumors had uptake of the radiolabeled somatostatin analog. This percentage of somatostatin-avid receptors is lower than the previously reported 70%-80% in pulmonary carcinoids.[15,16] In general, if patients demonstrate uptake on octreotide scintigraphy, they may benefit from the use of an SSA as in gastroenteropancreatic NETs.[17,18] A trial examining the effect of SSA in lung NETs is currently being conducted (NCT02683941). Additionally, if sufficient uptake is illustrated on octreotide scintigraphy, peptide receptor radionuclide therapy may be useful as shown in a study by van Essen et al.[19] However, their study was performed at a time when the Gallium 68-DOTATATE PET/CT was not yet approved by the US Food and Drug Administration. Because of the greater sensitivity of Gallium 68-DOTATATE PET/CT in detecting uptake in somatostatin receptors, use of this imaging modality in their study may have shown an increase in patients who were eligible for peptide receptor radionuclide therapy.

Interestingly, 34% of our cohort had lymph node metastasis at presentation. Naalsund and colleagues indicated that lymph node metastasis can occur at a 5%-15% rate for TC and up to 50% for AC.[4] The N0 designation has been identified as a predictor of excellent prognosis.[5] In a retrospective review of 126 patients with lung carcinoid, Filosso et al found that lymph node involvement negatively impacted survival in both univariate and multivariate analyses (P=0.0001).[20] Similarly, patients in our cohort with N0 staging have an excellent 5-year survival rate (96%), compared to 82% and 64% for N1 and N2, respectively ($P<0.05$). Distant metastases were present in 24% of our cohort at presentation. Others have suggested this rate to be 3%-20% with TC and AC, respectively.[21]

Ki-67 proliferative index is used in the evaluation of gastroenteropancreatic NETs to identify patients with a poor prognosis.[6-8,22,23] The traditional Ki-67 proliferative index ranges for gastroenteropancreatic NETs, as outlined by WHO 2010, are 0%-2%, 3%-20%, and >20%.[3] Because of the small subset of patients in our cohort with Ki-67 indices >20%, we considered a value >10% to be highly proliferative. We found a statistically significant difference in survival between low (≤2%), intermediate (>2%-10%), and high (>10%) Ki-67 values. Other cohorts have used 5% as a cutoff.[10] In our study, patients with Ki-67 values >10% had a significantly worse prognosis than patients with Ki-67 values <10% ($P<0.05$, Figure 2). Ki-67 has been examined before in NETs of the lung, but unlike its broad acceptance in tumors of gastrointestinal or pancreatic origin, its use has been controversial because it has yet to be prospectively validated.[10,24,25] Several studies indicate the usefulness of the Ki-67 as a prognostic factor, but none of these is prospective, and a degree of variability in the methods used to report Ki-67 indices may exist.[8-10,24] Further prospective studies are warranted to determine the exact role for Ki-67 in evaluating carcinoid tumors of the lung.

Our study is limited by the general nature of its retrospective design. Also, our institution is a referral center, so we frequently see patients present with advanced disease and variable workup data. Therefore, patients may have had their primary treatment elsewhere, and we may not have captured complete details of the demographic or pathologic characteristics. Because of the rarity and heterogeneity of this malignancy, the majority of pathology specimens were reexamined by 1 of 2 pathologists at our institution who frequently examine neuroendocrine cases and are well versed on the diagnosis. Images were reviewed when they were available, but reports alone were used in some instances.

CONCLUSION

Pulmonary carcinoid tumors are uncommon malignancies, and patients with pulmonary carcinoid tumors generally have a long survival time with treatment. Imaging by FDG-PET/CT and somatostatin receptor scintigraphy may be useful in detecting occult disease and making decisions on whether to administer somatostatin analog therapy or peptide receptor radionuclide therapy. Our study shows that the Ki-67 proliferative index may be useful in identifying patients with lung carcinoid who have a poor prognosis. The role of Ki-67 in lung carcinoids is still evolving, and prospective trials are warranted to determine its use.

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