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Introduction

Pulmonary neuroendocrine tumors (NETs) are rare neoplasms, accounting for 1-2% of all lung cancers, and include typical carcinoid (TC) and atypical carcinoid (AC). TC is usually indolent, while AC is more aggressive. Surgery is the primary treatment, but recurrence remains a concern, particularly in AC or locally advanced-stage disease. We sought to identify factors associated with recurrence after radical surgery in patients with pulmonary carcinoid.

Patients and Methods

This retrospective study analyzed data from patients who underwent surgery for a TC or AC between January 2005 and April 2024. Primary endpoint was disease-free survival (DFS), defined as the time from surgery to relapse or death from any cause, whichever occurred first. Patients with diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) were excluded from DFS analysis. Clinical and pathological factors, including tumor size, Ki-67 index, mitotic count, necrosis, and TNM stage, were collected. Kaplan-Meier survival curves and Cox regression were used to estimate DFS and identify recurrence risk predictors. Multivariate analysis adjusted for confounding variables.

Results

Among the 125 patients, radical surgery was performed in 107 patients (85.6%). The primary endpoint analysis included 91 patients (85.0%) after excluding 16 cases with DIPNECH (Table 1): 67.0% were female, median age was 58 (range 14-76). Smoking data were available for 49 patients, 53.1% of whom were smokers. Of this cohort, 51.7% had typical carcinoids, and 48.3% had atypical carcinoids. Tumor necrosis was present in 21.6%, with a median tumor size of 20 mm. The median Ki-67 index was 5%, and the mitotic count ranged from 0 to 10 (median 1.9). The most common type of surgery was lobectomy (75.6%), 32 (29.9%) patients experienced recurrence. Overall, the median DFS was 281 months (95%CI: 38.4-523.6). Patients with TC had a significantly longer DFS compared to those with AC (median 401 vs 59 months, $p < 0.001$). Patients with T1/2 tumors had longer DFS compared to T3/4 ones (median not reached vs 11 months, respectively; $p < 0.001$). Similarly, patients without tumoral lymph node involvement had longer DFS than those with node metastases (not reached vs 31 months, respectively; $p < 0.001$). Univariate analysis identified several predictors of recurrence (Table 2), including AC (HR: 17.08, $p < 0.001$), necrosis (HR: 7.64, $p < 0.001$), Ki-67 as a continuous variable (HR: 1.20, $p < 0.001$), mitotic count as a continuous variable (HR: 1.34; $p < 0.001$), and tumor size as a continuous variable (HR: 1.04, $p = 0.011$). After adjusting for confounding factors in multivariate analysis, Ki-67 (HR: 1.22, 95%CI: 1.11-1.35; $p = 0.017$) and tumor size (HR: 1.05, 95%CI: 1.01-1.09; $p = 0.023$) retained their independent association with DFS.

Figure 1. Kaplan-Meier survival estimates of disease-free survival (A) of the primary endpoint analysis, (B) by histology, (C) by T status, and (D) by N status.

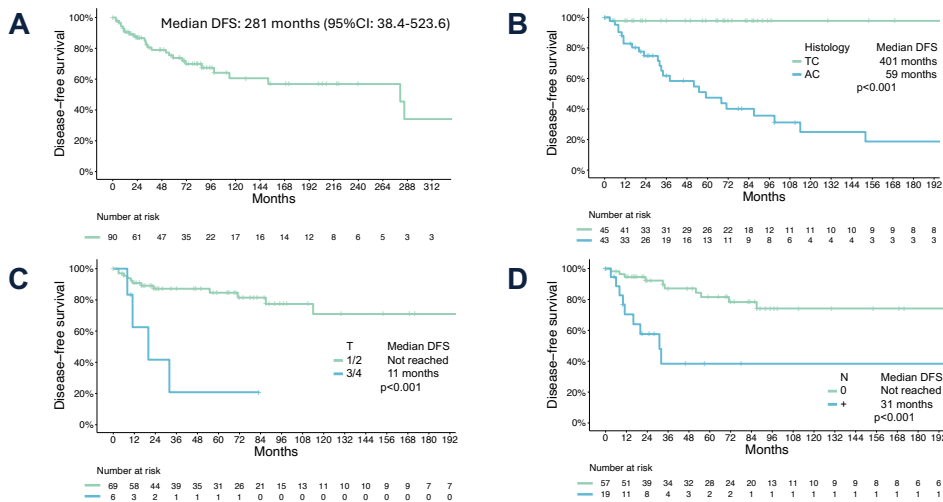


Table 1. Primary endpoint analysis population.

Patient characteristics	Patients n. (%)
Demographic	
Sex (Female), n. (%)	91 (100)
Smoker, n. (%)	61 (67.0)
Yes	26 (53.1)
No	23 (46.9)
Missing	42
Median age (range) at diagnosis, years	58 (14-76)
Histopathological findings	
WHO Classification	
Typical Carcinoid	46 (51.7)
Atypical Carcinoid	43 (48.3)
Missing	2
Necrosis	
Yes	16 (21.6)
No	58 (78.4)
Missing	17
Ki67 (%) - Median (range)	5 (1-35)
Mitoses - Median (range)	1.9 (0-10)
Lesion Size (mm) - Median (range)	20 (7-75)
Tumour staging	
Tumor Stage	
T1	50 (68.5)
T2	17 (23.3)
T3	3 (4.1)
T4	3 (4.1)
Missing	18
Lymph Node Status	
N0	58 (75.3)
N1	10 (13.0)
N2	9 (11.7)
N3	0 (0)
Missing	14
Lesion	
Central	46 (79.3)
Peripheal	12 (20.7)
Missing	33
Side	
Right	57 (63.3)
Left	33 (36.7)
Missing	1
Surgery Details	
Type of Surgery	
Pneumectomy	4 (4.4)
Bilobectomy	7 (7.8)
Lobectomy	68 (75.6)
Segmental resection	2 (2.2)
Sleeve resection	7 (7.8)
Wedge	2 (2.2)
Missing	1
Recurrence	29 (31.9)

Table 2. Cox proportional hazard models for the risk of recurrence.

Characteristic	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Sex (male)	1.62	0.69 - 3.78	0.264			
WHO (CA)	17.08	4.02 - 72.57	<0.001			ns
Necrosis (present)	7.64	2.91 - 20.05	<0.001			ns
Mitotic Count	1.34	1.16 - 1.56	<0.001			ns
Ki67	1.20	1.13 - 1.27	<0.001	1.22	1.11 - 1.35	<0.001
Central Lesion	30.43	0.15 - 6156.41	0.207			
Lesion Side (right)	0.6	0.28 - 1.30	0.197			
N1	5.17	2.04 - 13.09	0.001	4.05	0.86-19.11	0.077
T3/T4	7.05	2.14 - 23.15	0.001			ns
Tumor Size	1.04	1.01 - 1.07	0.011	1.05	1.01-1.09	0.023

Conclusion

Ki-67 index and tumor size are independent predictors of DFS in patients with TC/AC. These findings have crucial implications for post-surgical surveillance and design of clinical trials investigating adjuvant treatment strategies.

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