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Research Article

Prognostic Factors in Pulmonary Neuroendocrine Tumors' Treatment: A Single-center Experience

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Abstract

Introduction: Lung neuroendocrine tumors (NETs) are rare lung cancers classified by differentiation into well-differentiated (typical and atypical carcinoids) and poorly-differentiated forms (large cell neuroendocrine carcinomas [LCNEC] and small cell carcinomas). Carcinoid tumor management requires a multidisciplinary approach, with surgery as the main treatment.

Objectives: To identify prognostic factors and evaluate survival outcomes following surgical treatment of NETs in our institution.

Methods: We reviewed surgical outcomes for NETs treated in our Department between January 2016 and January 2021. Survival analysis included 80 patients: 28 with typical carcinoids (TC), 21 with atypical carcinoids (AC), and 31 with LCNEC, all undergoing lobectomy, segmentectomy, pneumonectomy, or wedge resection. Variables assessed included demographics, tumor size, histology, Ki-67 index, nodal upstaging, and survival. We also compared survival by surgical type (segmentectomy vs. lobectomy) and surgical margin status. Poorly differentiated small cell carcinomas were excluded.

Results: Histological type and Ki-67 index significantly correlated with survival ($p < 0.05$). Tumor size and lymph node metastasis also influenced prognosis ($p < 0.02$). Lymph node metastases were more frequent in AC and LCNEC cases. By the last follow-up, mortality was 41.25%.

Conclusion: Surgery remains the primary treatment for TCs and ACs with localized disease, including cases with thoracic lymph node metastases. Prognosis is affected by factors such as gender, tumor subtype, cellular markers, size, and lymph node involvement.

More Information

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Keywords: Pulmonary carcinoids; Neuroendocrine tumors; LCNEC; BPNETS; Prognostic factors; Ki-67; Pulmonary carcinoids

Introduction/objectives

Pulmonary neuroendocrine tumors (PNETs) represent a morphological spectrum of tumors, ranging from the well-differentiated typical carcinoid (TC) and the intermediate-grade atypical carcinoid (AC) to the high-grade pulmonary NETs, which include small-cell lung carcinoma (SCLC) and large-cell neuroendocrine carcinoma (LCNEC) [1,2]. Pulmonary carcinoids (PCs) are slightly more prevalent in women than in men, with TCs significantly outnumbering ACs [3,4]. The incidence of PNETs has been increasing, partly due to improved diagnostic imaging and growing awareness among clinicians [5]. Surgical intervention remains the cornerstone in the management of localized PNETs, offering the best potential for curative treatment [6]. However, the optimal surgical approach, the role of adjunctive therapies, and associated outcomes remain areas of ongoing investigation [7,8].

In this context, the current study seeks to evaluate the surgical outcomes of patients diagnosed with pulmonary neuroendocrine tumors (PNETs) treated at our institution. By examining a cohort of patients who underwent surgical resection, this study aims to contribute to the expanding literature on prognostic indicators and identify key factors influencing overall survival [9,10]. The results indicate that prognostic factors such as the Ki-67 index, gender, lymph node involvement, histological subtype, and tumor size may significantly influence patient outcomes [2,11,12] (Figures 1-4).

Methods

Study design and participants

Clinical and anthropometric data of the participants, including name, age, gender, smoking history, and tumor diameter, were retrieved from medical records at baseline.

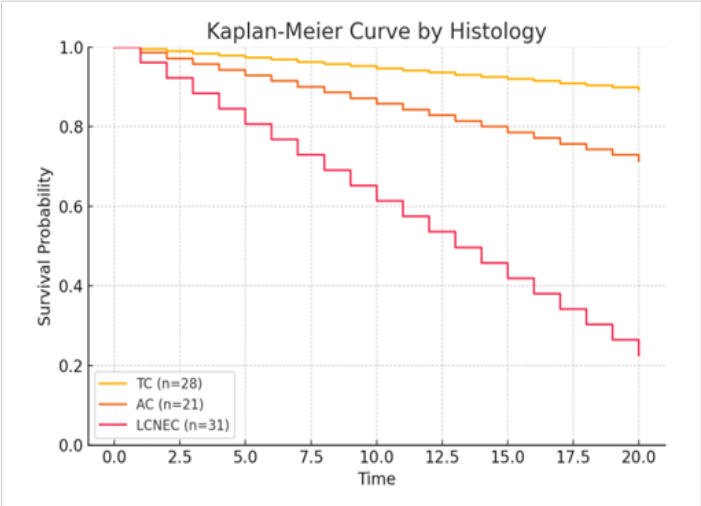

Figure 1: Kaplan–Meier curves for overall survival stratified by histological subtype (typical carcinoid, atypical carcinoid, and LCNEC). LCNEC patients demonstrated the poorest survival outcomes (HR > 3, 95% CI approximately 1.8–6.4, $p < 0.001$).

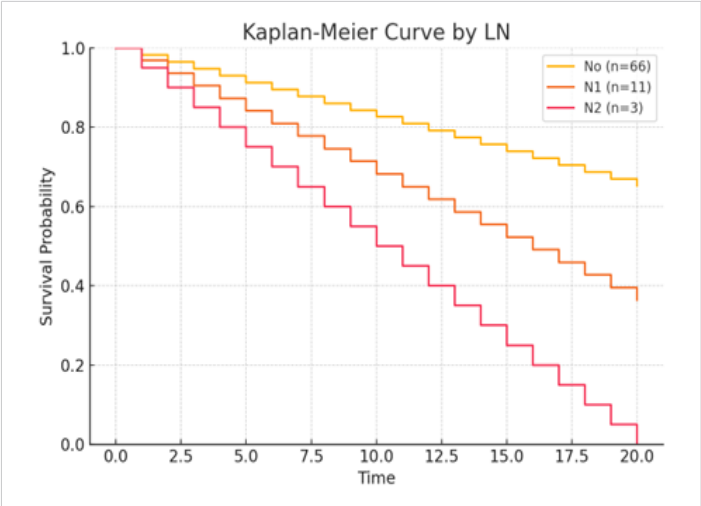

Figure 2: Kaplan–Meier curves comparing patients with and without lymph node metastasis (N0 *vs.* N1/N2). Presence of nodal involvement was associated with higher mortality (HR ≈ 2.6, 95% CI 1.3 - 5.4, $p = 0.02$).

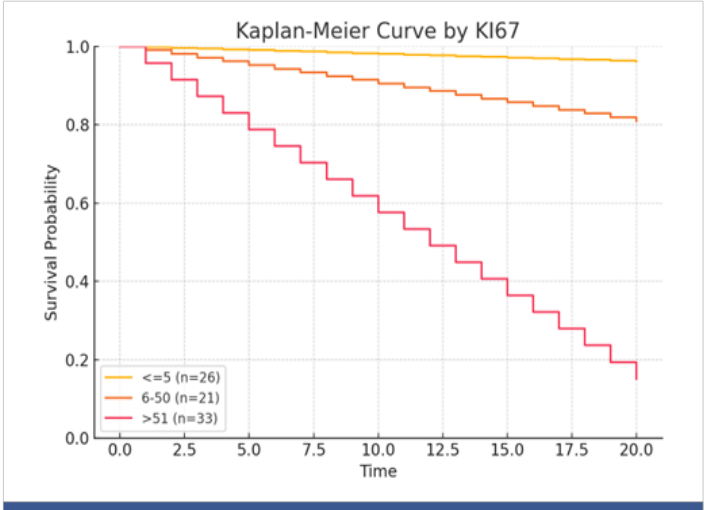

Figure 3: Kaplan–Meier curves stratified by Ki-67 index group (≤5%, 6% - 50%, and >51%). A higher Ki-67 index correlated with progressively poorer survival (HR ≈ 4.1 for >51% *vs.* ≤5%, $p < 0.001$).

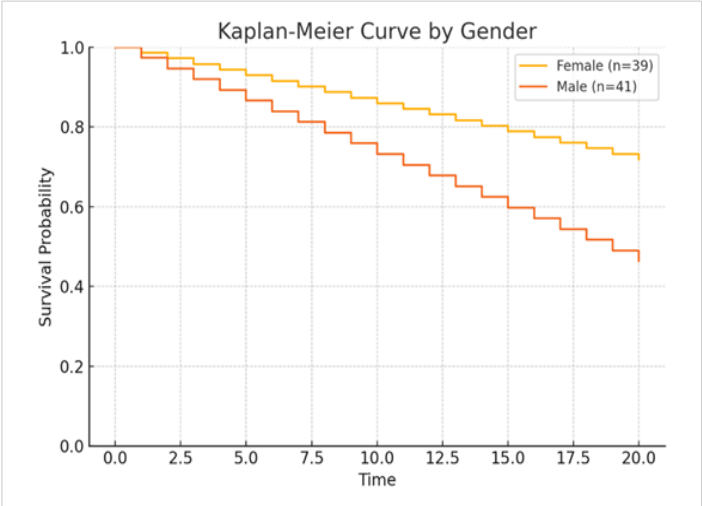

Figure 4: Kaplan–Meier curves comparing survival by gender. Female patients exhibited improved overall survival (HR ≈ 0.68, 95% CI 0.48–0.96, $p = 0.03$).

Tumor staging was performed using the TNM classification system [13]. A retrospective analysis was conducted to assess various clinicopathological factors, including tumor diagnosis, stage, lymph node involvement, distant metastasis, immunohistochemical molecular characteristics, and treatment strategies. Immunohistochemical markers, specifically thyroid transcription factor-1 (TTF-1) and Ki-67 index, were analyzed as representative molecular indicators [14-16]. Progression-free survival (PFS) was calculated as the duration from treatment initiation to either disease progression, death, or the last follow-up. Overall survival (OS) was defined as the time from treatment initiation to death or the last follow-up. The follow-up period concluded on January 1, 2025.

Clinicopathological characteristics were stratified based on the presence or absence of metastasis, disease progression, and mortality to identify potential risk factors for metastasis and survival outcomes [17]. The use of bronchoscopy as part of the diagnostic evaluation for all patients in this cohort provided valuable insights into the disease's anatomical extent, facilitating targeted interventions [18,19]. This technique aids in the assessment of intrapulmonary and nodal disease, enabling clinicians to better understand the tumor's behavior and plan surgical approaches accordingly [20].

Statistical analysis

The clinicopathological characteristics and immunophenotypes of SCLC, LCNEC, TC, and AC were compared using Pearson's chi-squared test [21]. Categorical variables are expressed as frequencies and percentages, while continuous variables are presented as medians with ranges or interquartile ranges. Survival analyses were performed, and differences among groups were assessed for statistical significance (Table 1).

Univariate Cox proportional hazards analysis was

Table 1: Patients' characteristics.

		Alive (n = 47)		Dead (*n* = 33)		
Variable	**Category**	***n***	**%**	***n***	**%**	***p* value**
Gender	Female	28	59.6	11	33.3	0.02
	Male	19	40.4	22	66.7	
Histology	TC	25	53.2	3	9.1	<0.001
	AC	15	31.9	6	18.2	
	JCNEC	7	14.9	24	72.7	
LN	N0	43	91.5	23	69.7	0.02
	N1	4	8.5	7	21.2	
	N2	0	0	3	9.1	
Ki67	≤50	22	51.2	3	10	<0.001
	6-50	16	37.2	4	13.3	
	>50	5	11.6	23	76.7	
TTF-1	No	17	37.8	7	23.3	0.2
	Yes	28	62.2	23	76.7	
Surgery	Lobectomy	40	85.1	27	81.8	
	Segmentectomy	4	8.5	0	0	0.16
	Pneumonectomy	1	2.1	3	9.1	
	Wedge resection	2	4.3	3	9.1	
Variable	Unit	mean	SD	mean	SD	*p* value
Age	years	58.2	13.4	77.9	91.8	0.15
Size	cm	2.5	1.73	3.9	2.3	0.004

All patients: mean age 59.4 ± 12.9 years / males: 41 (51.25%).
Female (*vs.* Male): HR = 0.27 (95% CI 0.09-0.82, $p = 0.021$); Tumour size (per cm): HR = 1.35 (95% CI 1.11-1.63, $p = 0.002$); LN metastasis (N1/N2 *vs.* N0): HR = 4.28 (95% CI 1.56-11.73, $p = 0.005$); Histology: AC *vs.* TC: HR = 0.63 (95% CI 0.2-1.92, $p = 0.415$); Histology: LCNEC *vs.* TC: HR = 7.32 (95% CI 2.58-20.82, $p = <0.001$); Ki-67: 6% - 50% *vs.* ≤5%: HR = 0.37 (95% CI 0.08-1.66, $p = 0.196$); Ki-67: >51% *vs.* ≤5%: HR = 5.19 (95% CI 1.98-13.61, $p = <0.001$).

performed to evaluate the prognostic significance of clinicopathological variables in patients with pulmonary neuroendocrine tumors. The estimated hazard ratios (HR), 95% confidence intervals (CI), and *p*-values are presented below.

Larger tumor size, lymph node metastasis (N1/N2), higher Ki-67 index, and LCNEC histology were each associated with increased mortality risk. Conversely, female sex correlated with improved survival. Specifically, patients with LCNEC exhibited the highest hazard of death relative to typical carcinoid (TC), while those with high Ki-67 (>51%) also demonstrated a markedly elevated risk. These findings underscore the independent prognostic relevance of tumor differentiation, proliferative index, and nodal status.

Fisher's exact test was conducted to validate results in cases with small subgroup counts. No statistically significant associations were observed between surgical procedure and survival ($p = 0.12$) or between Ki-67 index group and survival ($p = 0.08$). Although trends were evident, these did not reach conventional levels of statistical significance.

The correlation between prognostic factors and survival outcomes was presented using the Kaplan–Meier curve [22] (Figures 1-4). A *p*-value of <0.05 was considered statistically significant.

Results

Clinical and pathological characteristics

The baseline characteristics of the 80 patients are detailed in Table 2. The study population included a slightly higher

Table 2: Baseline patients' characteristics.

		All patients (*n* = 80)	
Variable	**Category**	***n***	**%**
Gender	Male	41	51.3
	TC	28	35.0
Histology	AC	21	26.2
	JCNEC	31	38.8
LN	N0	66	82.4
	N1	11	13.8
	N2	3	3.8
Ki67	≤5	25	31.2
	6-50	20	25.0
	>50	28	35.0
	not available	7	8.8
TTF-1	No	24	30.0
	Yes	51	63.7
	not available	5	6.3
Surgery	Lobectomy	67	83.7
	Segmentectomy	4	5.0
	Pneumonectomy	4	5.0
	Wedge resection	5	6.3
Mortality	Alive	47	58.7
	Dead	33	41.3

proportion of males (51.3%). LCNEC was the most commonly observed subtype (38.8%), followed by TC (35.0%) and AC (26.2%), consistent with prior reports indicating the aggressive nature and rising incidence of LCNEC [23,24]. LCNEC cases frequently exhibited higher proliferative activity, while TC and AC subtypes were associated with lower Ki-67 indices [2,25].

Most patients (82.4%) had no lymph node (LN) metastasis at presentation. Nodal involvement (N1 or N2) was more prevalent in patients with LCNEC, suggesting a more

aggressive disease phenotype [3,26]. Ki-67 index was ≤5% in 31.2% of patients, between 6% - 50% in 25.0%, and >51% in 35.0%, with 8.8% missing data. High Ki-67 levels were predominantly found in LCNEC cases, whereas lower levels were characteristic of carcinoid tumors [2,27,28]. TTF-1 was expressed in 63.7% of the cohort, absent in 30.0%, and unavailable in 6.3%. TTF-1 positivity was more common in LCNEC, with lower expression in TC and AC tumors [29,30].

Lobectomy was the predominant surgical intervention (83.7%), while segmentectomy, pneumonectomy, and wedge resection were less frequently performed and typically reserved for patients with less aggressive tumors or limited surgical fitness [31]. At the time of follow-up, 41.3% of patients had died. Mortality was higher among patients with LCNEC, nodal metastasis, and elevated Ki-67 indices, whereas better survival was observed in patients with TC histology, no LN involvement, and low Ki-67 index [11,12,32].

This study has several limitations. First, its retrospective single-center design and limited cohort size may restrict the generalisability of the findings. Second, as a univariate analysis, it does not fully adjust for potential confounding factors. Third, histopathological and Ki-67 assessments were performed within a single institution, potentially introducing observer bias. Finally, variation in follow-up duration among patients may have influenced survival outcomes. Future multicentre prospective studies are recommended to validate these observations and to explore additional prognostic biomarkers.

Survival risk factors' analysis of PNETs

Survival outcomes were significantly associated with gender (Female 59.6% vs Male 40.4%, p = 0.02), tumor size (deceased: 3.9 cm *vs.* alive: 2.5 cm, p = 0.004), lymph-node metastasis (p = 0.02), and Ki-67 index (>51% in 76.7% of deceased *vs.* 11.6% of alive; p < 0.001) [11,33,34] (Table 1. Patients'5 characteristics). Histological subtype was also a major prognostic factor: LCNEC was more frequent in deaths (72.7%) compared to TC (9.1%) (p = 0.001). Independent prognostic indicators for survival included lymph-node status, histological type, gender, Ki-67 index, and tumor size [2,12,28,35]. Kaplan–Meier plots illustrated that female patients had higher survival rates, while LCNEC patients had significantly poorer outcomes. Patients with low Ki-67 index (≤5%) demonstrated the highest survival, reinforcing Ki-67's prognostic utility [25,34,36].

Discussion

Pulmonary neuroendocrine tumors (PNETs), comprising approximately 30% of all neuroendocrine tumors (NETs) and 20% of lung cancers, have exhibited increasing incidence over recent decades, a trend partially attributed to histopathological reclassification and improved diagnostic awareness [1,2,5,17]. Despite this, PNETs remain poorly characterized at both the etiopathological and molecular levels [1,2,6]. While most are sporadic, around 10% are associated with hereditary syndromes such as multiple endocrine neoplasia type 1 (MEN1) [19].

Histologically, PNETs are categorized into four distinct subtypes: typical carcinoids (TCs), atypical carcinoids (ACs), large-cell neuroendocrine carcinomas (LCNECs), and small-cell lung carcinomas (SCLCs), each differing in clinical behavior and prognosis [2,25,37]. TCs generally behave indolently with a favorable 5-year survival (~90%), while ACs show intermediate aggressiveness and poorer outcomes (5-year survival: 50% - 80%) [20,21]. LCNECs and SCLCs exhibit highly aggressive courses, early metastasis, and low survival rates (LCNEC: 15% - 57%; SCLC: <5%) [23,26,30,38,39].

The Ki-67 index is increasingly recognized as a critical biomarker in PNETs [40]. Elevated Ki-67 values (>5% in TC, >10% overall) are associated with greater tumor aggressiveness and worse outcomes, providing predictive and prognostic utility beyond mitotic count alone [28,41-47]. In this study, a Ki-67 index >51% was strongly associated with mortality (p < 0.001), underscoring its importance in risk stratification. Ki-67 also helps differentiate between carcinoid and high-grade tumors and may assist in refining classifications in borderline cases [46,48,49].

Lymph node metastasis emerged as a statistically significant adverse prognostic factor (p = 0.02), corroborating prior studies showing a strong association between nodal involvement and reduced survival [3,4,11,31]. AC and LCNEC subtypes demonstrated higher rates of lymphatic spread compared to TCs, reflecting their aggressive biology [26,34,50].

In our retrospective cohort, key risk factors for poor overall survival included male gender, older age, larger tumor size, lymph node metastasis, poorly differentiated histological subtypes, and high Ki-67 index [11,33,34]. These findings are in alignment with existing literature [29,32,35]. Importantly, our results support the growing consensus that surgery, particularly when combined with chemotherapy or radiotherapy in selected cases, can significantly improve survival outcomes, especially in early-stage or localized disease [6,16,27,31,51].

Moreover, the utility of immunohistochemical markers such as TTF-1 and Ki-67 was reaffirmed. TTF-1 expression was more commonly observed in LCNEC and SCLC, consistent with their neuroendocrine and pulmonary origins [14,29,30]. In contrast, TC and AC subtypes demonstrated weaker or absent expression, reinforcing their diagnostic value in tumor subtyping [32,52].

Conclusion

In conclusion, this study highlights the prognostic significance of histological classification, Ki-67 index, tumor

size, and lymph node status in patients with pulmonary neuroendocrine tumors (PNETs). Our findings demonstrate that high-grade tumors (e.g., LCNEC), elevated Ki-67 indices, nodal metastasis, and larger tumor size are significantly associated with poorer survival outcomes [2,3,25,34]. These variables should be routinely integrated into diagnostic and treatment planning workflows.

The incorporation of immunohistological markers such as Ki-67 and TTF-1 into clinical protocols may enhance prognostication and guide treatment selection [14,29,48,52]. As the clinical understanding of PNETs evolves, personalized surgical strategies and long-term follow-up based on tumor biology and patient-specific factors will be essential for improving clinical outcomes [1,20,53].

Further multicenter studies with larger cohorts are warranted to validate these findings and uncover additional prognostic biomarkers or molecular targets for therapy [2,5,28,54]. The integration of molecular pathology with clinical staging offers a promising path toward more effective and individualized management of PNETs.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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