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Original article

LUNG NEUROENDOCRINE TUMORS: GRADE AND RECURRENCE RATE AFTER SURGERY

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Abstract

Introduction: Lung neuroendocrine tumors (NETs) are a rare and heterogeneous group of neoplasms. They are classified into low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), and high-grade (large-cell and small-cell neuroendocrine carcinoma) tumors. While surgical resection remains the mainstay treatment for many NETs, recurrence rates differ substantially among subtypes. Our primary outcome is to analyze the association between histologic subtype of lung NETs and tumor recurrence.

Materials and methods: A comparative retrospective study with a prospective case registry was conducted. All adult patients who underwent surgery due to lung NETs from January 2015 to December 2024 in a high-volume center were included. Demographic, perioperative and histopathological variables were analyzed. Tumor recurrence rate was compared between patients who presented with carcinoid tumors and those who presented with large-cell neuroendocrine carcinoma.

Results: A total of 57 patients were included (48 with carcinoid tumors and 9 with large-cell neuroendocrine carcinoma). Recurrence occurred in 33.3% of large-cell neuroendocrine carcinoma cases versus 4.1% in the carcinoid group (p 0.02). Large-cell neuroendocrine tumors also showed significantly larger tumor size (p 0.02), higher Ki-67 index (p 0.001) and more nodal involvement (p 0.04).

Conclusion: Lung NETs exhibit distinct recurrence rates based on histologic grade. High-grade tumors present more aggressive features and a higher risk of recurrence. A multidisciplinary approach and strict long-term follow-up are essential, especially in high-grade lung NETs.

Key words: lung neuroendocrine tumors, recurrence rate, tumor grade, thoracic surgery

Resumen

Tumores neuroendocrinos pulmonares: grado y tasa de recurrencia

Introducción: Los tumores neuroendocrinos pulmonares (TNE) son neoplasias poco frecuentes y heterogéneas, clasificadas en carcinoide típico, carcinoide atípico y carcinoma neuroendocrino de células grandes o pequeñas. Aunque la resección quirúrgica es el tratamiento principal, las tasas de recurrencia varían según el subtipo histológico. El objetivo fue analizar la asociación entre el subtipo histológico de los TNE pulmonares y la recurrencia tumoral.

Materiales y métodos: Se realizó un estudio retrospectivo comparativo basado en un registro prospectivo de pacientes adultos sometidos a resección de TNE pulmonar entre enero de 2015 y diciembre de 2024 en un

centro de alto volumen. Se analizaron variables demográficas, perioperatorias e histopatológicas, y se compararon las tasas de recurrencia entre tumores carcinoides y carcinoma neuroendocrino de células grandes.

Resultados: Se incluyeron 57 pacientes: 48 con tumores carcinoides y 9 con carcinoma neuroendocrino de células grandes. La recurrencia se observó en el 33.3 % de los casos con carcinoma neuroendocrino de células grandes frente al 4.1 % en los tumores carcinoides (p = 0.02). Los tumores de células grandes presentaron mayor tamaño tumoral (p = 0.02), índice Ki-67 más alto (p = 0.001) y mayor afectación ganglionar (p = 0.04).

Conclusión: Los TNE pulmonares muestran un comportamiento distinto según el grado histológico. Los tumores de alto grado exhiben características más agresivas y mayor riesgo de recurrencia. Un enfoque multidisciplinario y un seguimiento prolongado son esenciales, especialmente en los TNE pulmonares de alto grado.

Palabras clave: tumores neuroendocrinos pulmonares, tasa de recurrencia, grado tumoral, cirugía torácica

KEY POINTS
Current knowledge

- Lung NETs exhibit distinct recurrence rates based on histologic grade. High-grade tumors present more aggressive features and a higher risk of recurrence.

Article's contribution to current knowledge

- A multidisciplinary approach and strict long-term follow-up are essential, especially in high-grade lung NETs.

Lung neuroendocrine tumors (NETs) include small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, carcinoid tumors (typical and atypical), tumorlets and neuroendocrine hyperplasia[1]. These tumors are considered together because they share features that reflect their neuroendocrine nature[2-3]. NETs of the lung are extremely rare and account for 1% to 2% of all bronchopulmonary neoplasms. However, carcinoid tumors, both typical and atypical, constitute approximately 25% of well-differentiated neuroendocrine tumors of the lung[4]. Although they share morphologic, ultrastructural, immunologic, and molecular features, their epidemiology, biologic behavior, and evolution are markedly different[5].

Our primary outcome is to analyze the association between histologic subtype of lung NETs and tumor recurrence. Secondly, we aim to describe histopathological differences between tumor types.

Materials and methods

Study design and population

A comparative retrospective study with a prospective case registry was conducted. All patients over 18 years of age who underwent surgery due to lung NETs from January 2015 to December 2024 in a high-volume center were included. Patients whose histopathological results after surgery were other than neuroendocrine tumor of the lung or patients with loss of follow-up were excluded from the study.

Data collection

Demographic and perioperative variables such as age, gender, smoking and the type of surgery performed (lobectomy, pneumonectomy, wedge resection, etc.) were recorded. Postoperative data such as the time of follow-up, histopathological variables and recurrence were registered. Variables were compared between patients who presented with carcinoid tumors and those who presented with large cell neuroendocrine carcinoma.

The institutional review board (IRB) approved this study and the written informed consent was waived by the IRB owing to the study's retrospective nature.

Patient care

All surgeries were performed by the same team of thoracic surgeons with more than 10 years of experience in Thoracic Surgery. The type of surgery performed was decided depending on the anatomical location of the lesion on preoperative CT-scan. Thoracic lymph node sampling was performed in all cases.

All patients were admitted at least for 72 hours of postoperative monitoring. If patients were able to control pain, urinate and restore proper oral intake, they were discharged. Patient´s chest drains placed during surgery, were removed prior to discharge. Patients were examined as outpatients at 7 days, 1, 3 and 6 months of postoperative time. Then they started biannual follow-up. All patients were evaluated multidisciplinary upon confirmation of NET diagnosis. Oncology department took care of adjuvant therapy for those patients with indication upon postoperative staging, following NCCH guidelines, and after multidisciplinary committee discussion[6].

Statistical analysis

Statistical analysis was performed using Jamovi Computer Software (Version 2.4.12.0), Sydney, Australia. Descriptive variables are set as mean and standard deviation (SD) or median and interquartile range (IQR) and the qualitative variables as percentages. Comparison of the groups was performed using the Mann Whitney and Fisher tests, respectively. A p value <0.05 was considered statistically significant.

Results

A total of 57 surgeries due to lung NETs were performed in the studied period, out of which 48 were due to carcinoid tumors and 9 due to large-cell neuroendocrine tumors. Among carcinoid tumors, 2 were tumorlets, 43 were typical and 3 were atypical carcinoid tumors. A 63.1% of patients (36) were female and 36.8% of patients (21) were smokers, with no statistically significant differences between groups. Patients with large-cell neuroendocrine tumors were older than patients with carcinoid tumors (p 0.03). Lobectomies were most frequently performed in both groups, followed by wedge resections and pneumonectomies. The vast majority of procedures consisted of anatomical pulmonary resections, including lobectomies, bilobectomies, sleeve resections and pneumonectomies; non-anatomical resections (wedge resections) accounted for the remaining cases. (Table 1). All patients underwent systematic mediastinal lymph node dissection during surgery.

Of the nine patients diagnosed with large-cell tumors, five received adjuvant therapy. In the remaining four, adjuvant treatment was not indicated following discussion in the institutional oncology board. The decisions were based primarily on individual clinical and pathological

Table 1 | Demographic/perioperative data

	Carcinoid tumors (n = 48)	Large-cell tumors (n = 9)	p
Gender			
Male, n (%)	16 (33.3)	5 (55.5)	0.2
Female, n (%)	32 (66.6)	4 (44.4)	0.2
Mean age, years (± SD)	56.4 (12.6)	65.9 (6.3)	**0.03**
Smoking, n (%)	17 (35.4)	4 (44.4)	0.7
Surgery performed			
Lobectomy			
Superior			
Right, n (%)	12 (25)	5 (55.5)	0.1
Left, n (%)	8 (16.6)	1 (11.1)	1
Middle, n (%)	3 (6.2)	0 (0)	1
Inferior			
Right, n (%)	6 (12.5)	0 (0)	0.5
Left, n (%)	8 (16.6)	1 (11.1)	1
Sleeve			
Right, n (%)	1 (2.1)	0 (0)	1
Left, n (%)	2 (4.1)	1 (11.1)	0.4
Bilobectomy, n (%)	3 (6.2)	0 (0)	1
Pneumonectomy			
Right, n (%)	1 (2.1)	1 (11.1)	0.2
Left, n (%)	1 (2.1)	1 (11.1)	0.2
Wedge Resection			
Right, n (%)	1 (2.1)	0 (0)	1
Left, n (%)	3 (6.2)	0 (0)	1

SD = standard deviation
p < 0.05 are denoted in bold

factors, including small tumor size and absence of lymph node involvement, among other considerations. In the carcinoid group, only the two patients with the atypical subtype and N1 lymph node involvement received adjuvant therapy.

The mean follow-up period was 33.4 (±29.1) months for carcinoid tumors and 32.5 (±33.2) months for large-cell neuroendocrine tumors (p 0.9). All patients had a minimum 6 months' follow-up (Table 2).

Recurrence was a significantly higher in large-cell neuroendocrine tumors, with a recurrence rate of 33.3% (3 patients), compared to carcinoid tumors which had only 4.1% (2 patients) of recurrence (p 0.02) (Table 2). All patients with tumor recurrence in the large-cell neuroendocrine tumor group presented with positive lymph nodes. Both recurrences in the carcinoid group were in patients with diagnosis of atypical carcinoid tumor.

Large-cell neuroendocrine tumors were also found to have a larger tumor size (p 0.02), a higher Ki67 expression (p 0.001) and a higher number of positive lymph nodes after thoracic lymph node sampling (p 0.04) (Table 2). Only 3 patients presented positive lymph nodes in the carcinoid tumor group, two of which were in patients with diagnosis of atypical carcinoid tumor.

Discussion

Lung NETs are classified based on the World Health Organization into low-, intermediate-, and high-grade tumors. Typical carcinoid tumors account for low-grade lung NETs, atypical carcinoid tumors correspond for intermediate-grade NETs and large cell and small cell neuroendocrine carcinomas comprise for high-grade NETs[7]. Within the low-grade category, carcinoid tumorlets are defined as neuroendocrine proliferations measuring less than 0.5 cm. These lesions are benign, usually incidental findings with no clinical relevance[8]. Accurate histologic classification of pulmonary NETs is critical for guiding treatment decisions[9]. Their clinical behavior varies significantly, requiring even distinct therapeutic approaches. The most effective treatment for carcinoid and large cell neuroendocrine carcinoma in an early stage is complete surgical resection with mediastinal node sampling. While adjuvant chemotherapy is widely accepted in the management of high-grade neuroendocrine tumors, its benefit in patients with typical or atypical carcinoid tumors remains less clearly defined[10,11]. Recent reviews have highlighted the lack of prospective evidence supporting the use of adjuvant therapy in carcinoid tumors. While surgical resection remains the gold standard of treatment for early-stage disease, multiple retrospective studies have failed to demonstrate a survival benefit and, in some instances, have suggested potential adverse effects associated with adjuvant treatment in low- and intermediate-grade tumors. Therefore, current guidelines favor postoperative surveillance, reserving adjuvant therapy for selected high-risk cases, such as atypical carcinoid tumors with aggressive features, including local invasion or distant metastasis[11]. In our study, patients with large-cell tumors were more likely to receive adjuvant therapy compared to those

Table 2 | Postoperative/histopathological data

	Carcinoid tumors (n = 48)	Large-cell tumors (n = 9)	p
Mean follow up, months (± SD)	33.4 (29.1)	32.5 (33.2)	0.9
Mean tumor size, cm (± SD)	2.1 (1.1)	3.5 (3.1)	**0.02**
Mean Ki67, % (± SD)	2.6 (2.3)	43.7 (29.8)	**0.001**
Positive Lymph Nodes, n (%)	3 (6.2)	3 (33.3)	**0.04**
Adjuvant Treatment, n (%)	2 (4.1)	5 (55.5)	**0.0006**
Recurrence, n (%)	2 (4.1)	3 (33.3)	**0.02**

SD = standard deviation
p < 0.05 are denoted in bold

with carcinoid tumors, following multidisciplinary committee discussion (p = 0.0006). These findings are detailed in Table 2.

Although surgical outcomes are typically favorable in resected NETs, high-grade tumors continue to exhibit a considerable risk of recurrence following resection[5,12]. Reported recurrence rates are approximately 3–7% for typical carcinoids and 20–30% for atypical carcinoids[11]. Recurrence rates for large-cell neuroendocrine carcinoma are high, typically ranging from 40% to over 60% according to retrospective series[11]. A nonrandomized prospective study reported a significantly lower recurrence rate of 13.3% in patients who received adjuvant platinum-etoposide chemotherapy, compared to 60.9% in historical controls[13]. These findings suggest a potential benefit of adjuvant therapy, although survival outcomes remain variable across studies. In our study, recurrence was significantly more frequent in patients with large-cell neuroendocrine carcinoma, occurring in 33.3% of cases (3 patients), compared to 4.1% (2 patients) in the carcinoid tumor group (p = 0.02) (Table 2). All recurrences in the large-cell neuroendocrine carcinoma group were observed in patients with nodal metastases. In the carcinoid subgroup, both recurrences occurred in patients diagnosed with atypical carcinoid tumors.

In a large retrospective analysis of the National Cancer Database, Kneuertz et al. evaluated 3335 patients with surgically resected pulmonary carcinoid tumors who underwent systematic lymph node dissection. Nodal metastases were identified in 21% of patients overall, with a markedly higher incidence in atypical carcinoids (46%) compared to typical carcinoids (17%). Tumor size and atypical histology were both independent predictors of lymph node involvement. Importantly, the presence of nodal metastases was associated with significantly worse overall survival in patients with atypical carcinoid tumors (5-year OS 58% vs. 87%, p < 0.001), as well as in typical carcinoids larger than 2 cm. However, in typical carcinoids measuring ≤2 cm, lymph node involvement did not impact survival, suggesting a distinct prognostic behavior based on both histologic subtype and tumor size. These findings support the role of thorough nodal assessment, particularly in larger tumors and in those with atypical features[14]. Our findings are consistent with these observations. All patients with tumor recurrence in the large-cell neuroendocrine carcinoma group had nodal involvement, supporting its role as a key prognostic factor in high-grade tumors. In the carcinoid group, both recurrences occurred in patients with atypical histology, further emphasizing the more aggressive behavior of atypical carcinoids and the need for vigilant follow-up in this subgroup.

Our study's strength lies on the fact of it being a high-volume single-center study with a multidisciplinary approach for management of patients. However, follow-up was limited. Consequently, a longer follow-up will make the outcome analysis more interesting.

Lung neuroendocrine tumors share a neuroendocrine origin but differ greatly in clinical behavior depending on tumor grade. We believe a multidisciplinary approach is mandatory in lung neuroendocrine tumors along with a strict follow-up, especially in high-grade tumors, since they are more prone to recur.

Conflict of interest: None to declare

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