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Original Article

Outcomes and prognostic factors following surgical treatment of pulmonary large cell neuroendocrine carcinoma

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ABSTRACT

Background: Pulmonary large cell neuroendocrine carcinoma (LCNEC) is a rare subtype of lung cancer with a poor prognosis, making its management challenging. This study aimed to evaluate the surgical outcomes of patients who underwent resection for LCNEC at our clinic during the past 10 years and to identify prognostic factors.

Materials and Methods: Patients who underwent surgery for lung cancer were retrospectively reviewed. Those with a postoperative histopathological diagnosis of LCNEC were included. Demographic and clinicopathological characteristics were analyzed, and factors affecting survival were investigated.

Results: Between January 2016 and December 2025, pulmonary resection was performed in 1066 patients with primary lung cancer, of whom 36 (3.4%) had LCNEC. The mean overall survival (OS) was 56.4 ± 8.0 months, with a 5-year OS rate of 42.8%. The mean disease-free survival (DFS) was 37.7 ± 7.4 months, with a 5-year DFS rate of 26.1%. Patients who received adjuvant therapy had significantly better OS ($p < 0.001$) and a trend toward improved DFS ($p = 0.215$) compared to those who did not, particularly in stage II and higher disease ($p < 0.001$ and $p = 0.177$, respectively). The presence of spread through air spaces (STAS) and higher N stage were associated with worse survival outcomes, although these differences did not reach statistical significance.

Conclusions: Adjuvant therapy is associated with improved survival in patients undergoing surgery for LCNEC.

Keywords: pulmonary large cell neuroendocrine carcinoma, surgical resection, prognosis

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Introduction

Large-cell neuroendocrine carcinoma (LCNEC) of the lung is a rare and aggressive malignancy. Histopathologically, it exhibits features that overlap with both small-cell lung cancer (SCLC) and non-small cell lung carcinoma (NSCLC). LCNEC accounts for approximately 3% of all lung cancer cases [1]. Due to its low incidence, heterogeneous histopathological structure, and aggressive clinical course, LCNEC presents a significant diagnostic and therapeutic challenge.

Under the World Health Organization (WHO) classification of lung tumors, LCNEC is categorized within the neuroendocrine neoplasms group, alongside typical carcinoid, atypical carcinoid, and SCLC. Compared to carcinoid tumors, LCNEC exhibits a higher Ki-67 proliferation index and increased mitotic counts. This profile is directly associated with tumor aggressiveness and a poor prognosis [2]. The Ki-67 index, even when obtained from small biopsies, serves as a crucial diagnostic aid for neuroendocrine tumors. Due to its aggressive nature and high propensity for early metastasis, LCNEC is classified as a high-grade neuroendocrine tumor, similar to SCLC [3]. In light of these characteristics, adjuvant therapy is recommended to prevent recurrence and improve overall survival [4].

Due to the rarity of pulmonary large cell neuroendocrine carcinoma (LCNEC), the number of studies focusing on this tumor is limited. In this study, we aimed to analyze the 10-year surgical outcomes of patients who underwent surgery for LCNEC, and to evaluate their demographic characteristics as well as tumor-related clinicopathological factors.

Materials and Methods

Patients

Patients who underwent surgery for lung cancer at our clinic were retrospectively reviewed. Among these cases, those whose postoperative pathology reports identified LCNEC or an LCNEC component were included in the study. Patients who did not undergo therapeutic surgery or those with incomplete medical records were excluded. This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Approval No: 2026/010.99/26/1, date: 01.04.2026) and was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from each participant.

Data collection

The demographic characteristics of the included patients, the type of surgical treatment performed, tumor invasion parameters, PET/CT findings, the administration of adjuvant therapy, staging according to the 9th edition of the TNM system [5], overall survival, and disease-free survival were evaluated. Overall survival (OS) and disease-free survival (DFS) were defined as the time from the date of surgery to the date of death or recurrence, respectively.

Preoperative period

All patients who underwent surgical treatment for lung cancer at our institution were preoperatively evaluated using computed tomography (CT) and positron emission tomography (PET/CT). Patients presenting with lesions suggestive of primary lung malignancy on PET/CT without evidence of mediastinal lymph node involvement or distant metastasis underwent direct surgical intervention. In these cases, wedge resection followed by intraoperative frozen section examination was performed and upon confirmation of malignancy, subsequent anatomical resection was carried out. For central lesions and tumors larger than 3 cm, transthoracic needle aspiration biopsy (TTNA) was utilized as the initial diagnostic modality. Invasive mediastinal staging, via endobronchial ultrasonography (EBUS) or mediastinoscopy, was indicated for tumors exceeding 3 cm in diameter. Patients with confirmed single-station N2 disease on preoperative invasive staging proceeded to surgery following neoadjuvant therapy, whereas those with multi-station N2 involvement were excluded from surgical resection [6]. Patients who received neoadjuvant therapy due to pN2 disease and were downstaged to cN0 in the preoperative period were included in the study. Functional status was evaluated through pulmonary function tests and echocardiography, while preoperative risk stratification was documented using the Charlson Comorbidity Index.

Surgical approach

The extent of anatomical resection comprising lobectomy, bilobectomy, sleeve lobectomy, or pneumonectomy was determined based on tumor size and localization. Complete macroscopic tumor clearance was achieved in all patients. In cases with chest wall involvement, additional en bloc chest wall resection was performed. Furthermore, systematic mediastinal lymph node dissection was carried out in every patient to ensure accurate pathological staging.

Postoperative follow-up

Patients who underwent surgical resection for LCNEC were monitored with thoracic CT scans every 3 months for

the first 2 years and subsequently every 6 months for up to 5 years. While adjuvant therapy is conventionally recommended in routine NSCLC practice for patients with tumors larger than 4 cm or those with N1/N2 disease, in our study cohort, adjuvant treatment was recommended for LCNEC patients starting from Stage I. Adjuvant therapy was not administered in cases of patient refusal or due to an inability to tolerate chemotherapy-related toxicities. If follow-up assessments suggested recurrence, further evaluation via PET/CT was conducted and biopsy procedures were performed when clinically indicated.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were expressed as mean ± standard deviation and compared using the Student's t-test. Overall survival (OS) and disease-free survival (DFS) were estimated using the Kaplan–Meier method, with statistical differences assessed by the log-rank test. Survival analyses are carried out after excluding operative mortality. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS version 26.0 (IBM Corporation, Armonk, NY, USA).

Results

Between January 2016 and December 2025, a total of 1,066 patients underwent anatomical resection for lung cancer at the Thoracic Surgery Clinic of Kartal Dr. Lütfi Kırdar City Hospital. Among these patients, 36 patients (3.4%) were diagnosed with LCNEC.

Demographic characteristics, surgical approaches, invasion parameters, and TNM stages of the patients are presented in Table 1.

The mean age of the patients included in the study was 62.8 ± 8.7 years and the average tumor size was 4.56 ± 2.33 cm. On PET/CT examination, the mean maximum standardized uptake (SUVmax) value was calculated as 11.9 ± 7.3. In the resected tumors, the mean Ki-67 proliferation index was found to be 72.6 ± 14.7.

During the follow-up period, 19 patients (52.8%) remained alive, while 17 patients (47.2%) died; of these, 3 patients (8.3%) passed away within the first three postoperative months. The mean overall survival (OS) of the study cohort was 56.4 ± 8.0 months, with a 5-year OS rate of 42.8%. During the follow-up process, recurrence or metastasis was observed in 17 patients (47.2%). The mean disease-free survival (DFS) was 37.7 ± 7.4 months, and the 5-year DFS rate was found to be 26.1% (Figure 1). The sites of recurrence are presented in Table 2.

Analysis on spread through air spaces (STAS) reveals mean overall survival was 52.7 ± 9.6 months for STAS-positive patients, with a 5-year OS rate of 51.1%. For STAS-negative patients, mean OS was 61.5 ± 11.8 months, with a 5-year OS rate of 52.5% (p = 0.517). STAS-positive patients had a mean DFS of 40.4 ± 8.4 months and a 5-year DFS rate of 47.3%, whereas STAS-negative patients exhibited a mean DFS of 39.0 ± 12.0 months, with a 5-year DFS rate of 22.2% (p = 0.910).

All patients included in the study were preoperatively staged as cN0. Occult hilar/mediastinal lymph node metastasis was observed in 11 patients (30.5%). In patients with mediastinal lymph node positivity, the mean overall survival was 36.4 ± 7.7 months, with a 5-year survival rate of 44.2%. For patients without mediastinal lymph node involvement, the mean overall survival was 56.7 ± 9.3 months, with a 5-year OS rate of 42.1% (p = 0.906). Regarding disease-free survival, the mean DFS for patients with mediastinal lymph node metastasis was 17.7 ± 2.8 months, with a 5-year DFS rate of 26.5%. In the group without mediastinal lymph node metastasis, these values were calculated as 40.2 ± 8.5 months and 29.5%, respectively (p = 0.769).

The impact of adjuvant therapy on mean survival values is detailed in Table 3 and illustrated in Figure 2.

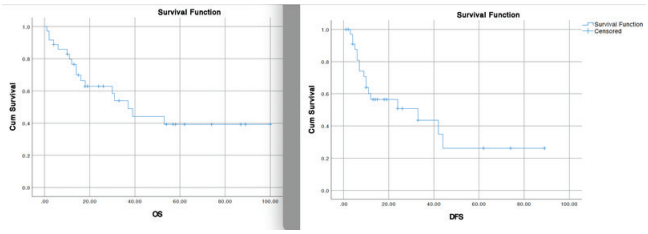

Figure 1. Overall survival and disease-free survival of patients included in the study.

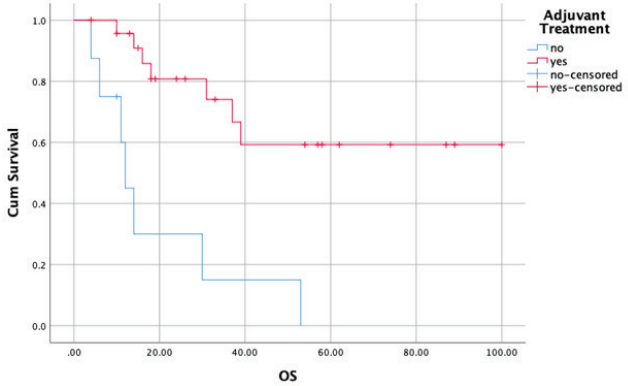

Figure 2. Overall survival depending on adjuvant treatment.

Table 1. Demographics of the patients, surgical approach, invasion parameters and staging.			
Gender		STAS	
Male	33 (91.66%)	Negative	10 (27.77%)
Female	3 (8.33%)	Positive	20 (55.55%)
Preoperative Biopsy		Not investigated	6 (16.66%)
Malignant	24 (66.66%)	Pleural invasion	
LCNEC/NE	5 (13.88%)	PL0	26 (72.22%)
AdC	1 (2.77%)	PL1	5 (13.88%)
SqCC	2 (5.55%)	PL 2	0 (0.00%)
Non-diagnostic	1 (2.77%)	PL 3	1(2.77%)
Not performed	3 (8.33%)	Vascular invasion	
Definitive diagnosis		No	21 (58.33%)
Pure LCNEC	22 (61.11%)	Yes	15 (41.66%)
AdC component	8 (22.22%)	Perineural invasion	
SqCC component	4(11.11%)	No	32 (88.88%)
Pleomorphic C component	1 (2.77%)	Yes	4 (11.11%)
SCLC component	1 (2.77%)	T Status	
Symptoms		T1b	5 (13.88%)
Incidental	9 (25.00%)	T1c	7 (19.44%)
Chronic cough	13 (36.11%)	T2a	8 (22.22%)
Fatigue	6 (16.66%)	T2b	4 (11.11%)
Hemoptisis	1 (2.77%)	T3	6 (16.66%)
Dizziness	1 (2.77%)	T4	6 (16.66%)
Surgery		N Status	
RUL	11 (30.55%)	N0	25 (69.44%)
RML	1 (2.77%)	N1	7 (19.44%)
RLL	4 (11.11%)	N2a	3 (8.33%)
LUL	7 (19.44%)	N2b	1 (2.77%)
LLL	9 (25.00%)	M Status	
Lower bilobectomy	1 (2.77%)	M0	33 (91.66%)
Right Pneumonectomy	1 (2.77%)	M1b	3 (8.33%)
Left Pneumonectomy	2 (5.55%)	Stage	
Incision		IA2	3 (8.33%)
VATS	11 (30.55%)	IA3	5 (13.88%)
Thoracotomy	18 (50.00%)	IB	5 (13.88%)
Conversion	7 (19.44%)	2A	3 (8.33%)
Neoadjuvant Treatment		2B	9 (25.00%)
No	33 (91.66%)	3A	5 (13.88%)
Yes	3 (8.33%)	3B	3 (8.33%)
Mediastinal Staging		IVA	3 (8.33%)
Not performed	13 (36.11%)		
EBUS	18(50.00%)		
Mediastinoscopy	5 (13.88%)		

Abbrev.: AdC: Adenocarcinoma, EBUS: Endobronchial ultrasound, LCNEC/NE: Large cell neuroendocrine carcinoma/neuroendocrine carcinoma, LLL: Left lower lobectomy, LUL: Left upper lobectomy, RLL: Right lower lobectomy, RML: Right middle lobectomy, RUL: Right upper lobectomy, SCLC: Small Cell carcinoma, SqCC: Squamous cell carcinoma, STAS: Spread through air spaces, VATS: Video-assisted thoracoscopic surgery

Table 2. Recurrence sites of patients included in the study.	
Recurrence Site	
Lung	2 (5.55%)
Mediastinum	7 (19.44%)
Brain	3 (8.33%)
Bone	4 (11.11%)
Liver	1 (2.77%)
Total	17 (47.22%)

Table 3. Survival based on adjuvant treatment. DFS: Disease-free survival, OS: Overall survival.

	Mean OS (months) based on presence of adjuvant treatment			Mean DFS (months) based on presence of adjuvant treatment		
	Adjuvant (-)	Adjuvant (+)	p value	Adjuvant (-)	Adjuvant (+)	p value
All stages	19.25±6.61	69.76±9.05	<0.0001	23.05±8.01	42.35±8.75	0.215
Stage 1	41.50±11.50	73.64±15.26	0.248	27.00±17.00	35.85±11.63	0.925
Stage 2-3-4	9.88±1.68	62.17±9.41	<0.0001	8.67±2.12	45.09±10.56	0.177

Discussion

Pulmonary LCNEC was previously classified as a subtype of large-cell lung cancer in the 2004 World Health Organization (WHO) classification [7]. With subsequent updates to immunohistochemical criteria, it was recategorized in 2015 within the neuroendocrine tumor group of the lung, along with typical carcinoid, atypical carcinoid, and small-cell lung cancer [8]. In the 2021 WHO classification, neuroendocrine neoplasms were categorized as low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), and high-grade neuroendocrine carcinomas, the latter consisting of LCNEC and SCLC [9].

Despite improvements in the diagnostic yield of small-needle biopsies in recent years, establishing a preoperative diagnosis of LCNEC remains challenging using limited biopsy specimens. Due to the presence of excessive necrosis typically associated with these tumors, larger tissue samples are required to identify neuroendocrine morphology and perform specific immunohistochemical staining for neuroendocrine markers [10]. Consequently, patients with a final pathology of LCNEC are frequently preoperatively misdiagnosed as having other types of NSCLC or SCLC [11,12]. In a study by Chen et al., it was reported that a diagnosis of LCNEC was achieved in only 6 out of 20 patients who underwent preoperative bronchoscopic or transthoracic biopsy [13]. Consistent with these findings, the majority of patients in our study could not be diagnosed with LCNEC preoperatively through small biopsies obtained via TTNA or transbronchial biopsy.

In patients with good performance status and adequate cardiopulmonary function, surgical intervention remains the primary therapeutic approach for early-stage LCNEC [14]. Previous studies have demonstrated that sublobar resections, such as segmentectomy and wedge resection, do not provide survival benefits comparable to those of lobar resections [15-18]. Due to the high growth potential of these tumors, extensive tumor necrosis and hemorrhage may be encountered intraoperatively [19], necessitating heightened caution, particularly when managing large masses. It has also been documented that spontaneous tumor rupture can lead to hemorrhagic shock [20]. At our clinic, the minimum extent of resection performed for all LCNEC patients

was lobectomy. Our surgical experience indicates that these tumors contain significant necrosis and are prone to persistent, oozing-type bleeding due to excessive angiogenesis—though not necessarily massive hemorrhage. Consequently, this characteristic may contribute to an increased rate of conversion from video-assisted thoracoscopic surgery (VATS) to thoracotomy in this specific tumor type.

The optimal stage at which adjuvant therapy should be recommended for resectable LCNEC remains a subject of ongoing debate. Existing studies have reported benefits of postoperative adjuvant treatment in Stage I disease [21], Stage IB or higher disease, and Stage IIB or higher disease [15]. Although the number of studies on this topic is limited, the standard approach for early-stage LCNEC similar to that for SCLC is platinum-etoposide or irinotecan combinations. When all stages included in our study were analyzed, adjuvant therapy was found to provide a statistically significant benefit in OS. While a survival benefit was also observed in Stage I disease, it did not reach statistical significance. In contrast, for Stage II and higher disease, a statistically significant improvement in OS was observed. These findings suggest that while adjuvant therapy benefits the entire cohort, its efficacy is more pronounced in Stage II and higher disease. In DFS analyses, although adjuvant therapy appeared more beneficial, this advantage did not achieve statistical significance.

First described by Kadota et al. in 2015 [22], spread through air spaces (STAS) refers to clusters of tumor cells or single tumor cells within the air spaces beyond the edge of the main tumor. Although STAS was formally recognized as a prognostic feature only for non-mucinous adenocarcinoma in the 2021 WHO classification of lung tumors [23], it has been shown to adversely affect prognosis in other histopathological subtypes as well, despite its prevalence and prognostic significance being more extensively documented in adenocarcinomas [24-26]. In a study by Aly et al. focusing on STAS in neuroendocrine lung cancers, the prevalence of STAS in LCNEC was reported as 43%, and its presence was identified as a poor prognostic factor for both disease-free survival and overall survival [27]. Consistently, our study suggested that STAS is a poor prognostic factor for LCNEC, although this association did not reach statistical significance.

Preoperative PET/CT is mandatory for patients with confirmed or suspected lung cancer. Invasive mediastinal staging is indicated when the tumor size exceeds 3 cm or if PET/CT reveals suspicious uptake in mediastinal or hilar lymph nodes [28]. Nodal upstaging is recognized as a poor prognostic factor in lung cancer. Previous studies have demonstrated nodal upstaging rates of 10% in clinical Stage I LCNEC and 8% in clinical Stage II LCNEC [15]. In our study, the rates of occult pN1 and pN2 disease were consistent with the literature. Furthermore, although the association did not reach statistical significance, nodal upstaging was found to be associated with a worse prognosis.

Ki-67 is an antigen expressed by the MKI67 gene and has been identified as a parameter associated with a poor prognosis [29]. In neuroendocrine lung tumors, the Ki-67 proliferation index is typically below 20% to 30% in typical and atypical carcinoids, whereas it often exceeds 50% and frequently surpasses 70% to 80% in LCNEC and SCLC [30]. Consequently, the Ki-67 index plays a pivotal role in refining the differential diagnosis of neuroendocrine neoplasms, particularly in small-needle biopsy specimens where tissue samples are limited.

Due to the rarity of LCNEC and the limited number of publications in the literature, reported survival rates vary within a wide range, despite the well-established aggressive nature and poor prognosis of this tumor. Studies have demonstrated that 5-year OS rates for all stages of LCNEC range from 18% [31] to 53.8% [32], and even in Stage I disease alone, these values fluctuate between 18% and 88%. These studies indicate that adjuvant therapy following surgery in resectable patients is associated with improved OS, with N and M stages being the most prominent factors influencing OS [13]. The number of publications reporting DFS rates for this tumor is considerably lower. One study reported a 5-year DFS of 32.2% and identified adjuvant chemotherapy and TNM stage as the primary factors affecting DFS [33].

In conclusion, our study reveals the administration of adjuvant therapy provides a statistically significant benefit in overall survival, it was also observed that STAS status and N status influence survival outcomes. These parameters were further found to be associated with disease-free survival.

Limitations of the study

Our study has several limitations. First is its retrospective design; however, clinical records at our institution were meticulously maintained and documented. The second limitation is the relatively small number of the sample size. This constraint is commonly encountered in the majority of existing literature on this specific subject. The primary reason why parameters such as STAS presence and N status did not reach statistical significance in their impact on overall and disease-free survival is likely the limited sample size. Nevertheless, this limitation is inherent to most studies focusing on this exceptionally rare tumor type.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Ethics approval

This study was approved by the Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Approval No: 2026/010.99/26/1, date: 01.04.2026).

Use of Generative AI and AI-assisted technologies in the writing process

Artificial intelligence was utilized solely for writing assistance, grammar correction, and to enhance the clarity and understandability of the manuscript.

Authors' Contribution

BC: Conceptualization, Methodology, Writing - orginal draft, Project administration. MB: Data curation. FTO: Formal analysis, investigation. MTD: Data curation, software. AO: Validation, Supervision. RD: Conceptualization, Supervision

References

1. Fasano M, Della Corte CM, Papaccio F, Ciardiello F, Morgillo F. Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy. J Thorac Oncol 2015; 10: 1133-41.
2. Naheed S, Holden C, Tanno L, Pattini L, Pearce NW, Green, et al. Utility of KI-67 as a prognostic biomarker in pulmonary neuroendocrine neoplasms: a systematic review and meta-analysis BMJ Open 2022; 12: e041961.
3. Iyoda A, Hiroshima K, Nakatani Y, Fujisawa T. Pulmonary large cell neuroendocrine carcinoma: its place in the spectrum of pulmonary carcinoma. Ann Thorac Surg 2007; 84: 702-7.
4. Kim KW, Kim HK, Kim J, Shim YM, Ahn MJ, Choi YL. Outcomes of Curative-Intent Surgery and Adjuvant Treatment for Pulmonary Large Cell Neuroendocrine Carcinoma. World J Surg 2017; 41: 1820-7.
5. Detterbeck FC, Woodard GA, Bader AS, Dacic S, Grant MJ, Park HS et al. The Proposed Ninth Edition TNM Classification of Lung Cancer. Chest 2024; 166: 882-95.
6. Riely GJ, Wood DE, Ettinger DS, Aisner DL, Akerley W, Bauman JR et al. Non-small cell lung cancer, version 4.2024. J. Natl. Compr. Cancer Netw 2024; 22: 249-74.
7. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Geneva: WHO Classification of Tumours; 2004
8. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB et al. The 2015 world health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015; 10: 1243-60.
9. WHO Classification of Tumours Editorial Board. Thoracic Tumours. Lyon: International Agency for Research on Cancer; 2021.
10. Baine MK, Sinard JH, Cai G, Homer RJ. A semiquantitative scoring system may allow biopsy diagnosis of pulmonarylarge cell neuroendocrine carcinoma. Am J Clin Pathol 2020; 153: 165-74.
11. Le Treut J, Sault MC, Lena H, Souquet PJ, Vergnenegre A, Le Caer H, et al. Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: The GFPC 0302 study. Ann Oncol 2013; 24: 1548-52.

12. Zhu S, Wang X, Li H, Zhao P, Liu J, Zhang L et al. Advances in genetic profile and therapeutic strategy of pulmonary large cell neuroendocrine carcinoma. Front Med 2024; 11:1326426.

13. Chen Y, Zhang J, Huang C, Tian Z, Zhou X, Guo C et al. Survival outcomes of surgery in patients with pulmonary large-cell neuroendocrine carcinoma: a retrospective single-institution analysis and literature review. Orphanet J Rare Dis 2021; 16: 82.

14. Yeung AML, Chow JCH. Management of Pulmonary Large-Cell Neuroendocrine Carcinoma (LCNEC): An Updated Review. Clin Lung Cancer 2026; 27: 85-97.

15. Raman V, Jawitz OK, Yang CFJ, Voigt SL, Tong BC, D'Amico T et al. Outcomes for surgery in large cell lung neuroendocrine cancer. J Thorac Oncol 2019; 14: 2143-51.

16. Wakeam E, Adibfar A, Stokes S, Leighl NB, Giuliani ME, Varghese TK, et al. Defining the role of adjuvant therapy for early-stage large cell neuroendocrine carcinoma. J Thorac Cardiovasc Surg 2020; 159: 2043-54.

17. Yu X, Zhang M, Wang F, Guo X, Ma K, Wang L et al. Survival after lobectomy vs. sublobar resection for stage IA large-cell neuroendocrine carcinoma of the lung: a population-based study. Front Surg 2022; 9: 856048.

18. Suzuki Y, Christie IG, Sarkaria IS, Mazur S, Ki S, Levy RM et al. Outcomes with sublobar resection vs lobectomy in patients with cT1N0M0 large-cell neuroendocrine cancer. Ann Thorac Surg Short Rep 2025; 3: 287-92.

19. Yaldız D, Sadık Yaldız M, Tan A. Pulmonary large cell neuroendocrine carcinoma: a diagnostic challenge. Curr Thorac Surg 2021; 6: 078-81.

20. Yoshida K, Takasuna K, Hamanaka K, Saito G, Haniuda M, Amano J. Rupture of a large cell neuroendocrine carcinoma, causing early local recurrence. Ann Thorac Cardiovasc Surg 2006; 12: 56-9.

21. Ogawa H, Tanaka Y, Kitamura Y, Shimizu N, Doi T, Hokka D et al. Efficacy of perioperative chemotherapy for pulmonary high-grade neuroendocrine carcinomas: a propensity score matching analysis. J Thorac Dis 2019; 11: 1145-54.

22. Kadota K, Nitadori J, Sima CS, Ujiie H, Rizk NP, Jones DR et al. Tumour spread through air spaces is an important pattern of invasion and impacts the frequency and location of recurrences after limited resection for small stage I lung adenocarcinomas. J Thorac Oncol 2015; 10: 806-14.

23. Lightner-Ferrer C, Burke L. Pathology of lung tumours: WHO 2021 updates and resection status. Diagn Histopathol 2026; 32: 92-5.

24. Cimenoglu B, Dogruyol T, Buz M, Gecmen G, Kahraman S, Demirhan R. Differential Impact of Spread Through Air Spaces on Subtypes of Early-stage Lung Cancer. J Coll Physicians Surg Pak 2023; 33: 765-9.

25. Han YB., Kim H, Mino-Kenudson M, Cho S, Kwon HJ, Lee KR et al. Tumor spread through air spaces (STAS): prognostic significance of grading in non-small cell lung cancer. Mod Pathol 2021; 34: 549-61.

26. Lu S, Tan KS, Kadota K, Eguchi T, Bains S, Rekhtman N et al. Spread through Air Spaces (STAS) Is an Independent Predictor of Recurrence and Lung Cancer-Specific Death in Squamous Cell Carcinoma. J Thorac Oncol 2017; 12: 223-34.

27. Aly RG, Rekhtman N, Li X, Takahashi Y, Eguchi T, Tan KS et al. Spread Through Air Spaces (STAS) Is Prognostic in Atypical Carcinoid, Large Cell Neuroendocrine Carcinoma, and Small Cell Carcinoma of the Lung. J Thorac Oncol 2019; 14: 1583-93.

28. Dunne EG, Fick CN, Jones DR. Mediastinal Staging in Non-Small-Cell Lung Cancer: Saying Goodbye to Mediastinoscopy. J Clin Oncol 2023; 41: 3785-90.

29. Richards-Taylor S, Ewings SM, Jaynes E, Tilley C, Ellis SG, Armstrong et al. The assessment of Ki-67 as a prognostic marker in neuroendocrine tumours: a systematic review and metaanalysis. J Clin Pathol 2016; 69: 612-8.

30. Pelosi G, Travis WD. The Ki-67 antigen in the new 2021 World Health Organization classification of lung neuroendocrine neoplasms. Pathologica 2021; 113: 377-87.

31. Jiang H, Wu Q, Zhong Y. Survival and prognosis of lung large cell neuroendocrine carcinoma. Bull Cancer 2021; 108: 981-7.

32. Okui M, Yamamichi T, Asakawa A, Harada M, Saito M, Horio H. Prognostic significance of neutrophil-lymphocyte ratios in large cell neuroendocrine carcinoma. Gen Thorac Cardiovasc Surg 2017; 65: 633-9.

33. Han K, Yang H, Fan L, Zhao H. Outcomes of patients with large cell neuroendocrine carcinoma of the lung after complete resection. Transl Cancer Res 2017; 6: 483-92.