RESEARCH ARTICLE / *Araştırma Makalesi*

Clinical Features and Survival Outcomes of Unclassified High-Grade Neuroendocrine Carcinoma of the Lung

Akciğerin Sınıflandırılamayan Yüksek Dereceli Nöroendokrin Karsinomaların Klinik Özellikleri ve Sağ Kalım Sonuçları

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Abstract

Introduction	Differentiating high-grade neuroendocrine carcinomas (HGNEC) is difficult. We aimed to assess the clinical features and survival outcomes of unclassified HGNEC (uHGNEC) and to compare it with small-cell lung cancer (SCLC).
Materials and Methods	This was a retrospective and observational study of HGNEC patients. Kaplan-Meier method was used to estimate progression-free survival (PFS) and overall survival (OS). Cox-regression analyses were used to determine the risk factors independently associated with PFS and OS.
Results	One hundred twenty-one patients [uHGNEC (n = 35), SCLC (n = 86)] were analysed. The primary tumour was mostly right-sided, located in the centre of the lungs. The IASLC stage at diagnosis was locally advanced in 43 (35.5%) patients and advanced in 78 (64.5%) patients. uHGNEC and SCLC groups shared similar clinical features. The study population's median PFS and OS were 8.8 (95%CI 7.29 – 10.30) and 10.9 (95%CI 9.9 – 11.8) months, respectively. uHGNEC- and SCLC groups had a similar PFS (9.4 vs 8.6 months, p = 0.99) and OS (12 vs 10.7 months, p = 0.51). The six-month, one- and two-year PFS and OS of the two groups were also similar. Among all patients, a right-sided tumour (HR: 1.558, 95%CI 1.044 – 2.325, p = 0.03) and advanced-stage disease (HR: 1.928, 95%CI 1.292 – 2.877, p = 0.001) were prognostic factors for poor OS. Cox-regression analysis indicated that histopathology did not have an impact on PFS and OS.
Conclusion	HGNEC patients who cannot be classified pathologically behave like SCLC.
Keywords	high-grade neuroendocrine carcinoma, pulmonary neuroendocrine carcinomas, small-cell lung cancer

Öz

Amaç	*Bu çalışmanın amacı patolojik olarak tiplendirilemeyen yüksek dereceli nöroendokrin karsinomların (uYDNEK) klinik özelliklerini ve sağ kalım sonuçlarını değerlendirmek ve küçük hücreli akciğer kanseri (KHAK) ile karşılaştırmaktır.*
Yöntem ve Gereçler	*Bu retrospektif ve gözlemsel çalışmada YDNEK hastalarının klinik özellikleri değerlendirildi. Progresyonsuz sağkalım (PFS) ve genel sağkalım (OS) Kaplan-Meier yöntemi kullanılarak hesaplandı. PFS ve OS ile ilişkili bağımsız risk faktörlerini belirlemek için Cox-regresyon analizleri yapıldı.*
Bulgular	*Çalışmaya 121 hasta [uYDNEK (n=35), KHAK (n=86)] dahil edildi. Primer tümör çoğunlukla sağ tarafta ve santral yerleşimliydi. Tanı anındaki evre 43 (%35,5) hastada lokal ileri, 78 (%64,5) hastada ileri idi. uYDNEK ve KHAK grupların klinik özellikleri benzerdi. Çalışma popülasyonunun medyan PFS ve OS'si sırasıyla 8,8 (%95 Cl 7,29 – 10,30) ve 10,9 (%95 Cl 9,9 – 11,8) ay olarak hesaplandı. uYDNEK ve KHAK grupları arasında PFS (9.4 ve 8.6 ay, p = 0.99) ve OS (12 ve 10.7 ay, p = 0.51) istatistiksel olarak benzer bulundu. 6-aylık, 1-yıllık, 2-yıllık PFS ve OS hesaplandı, iki grup arasında istatistiksel fark bulunmadı. Cox regresyon analizinde primer tümörün sağ tarafta yerleşimi (HR: 1.558, 95%Cl 1.044 – 2.325, p = 0.03) ve ileri evre hastalık (HR: 1.928, 95%Cl 1.292 – 2.877, p = 0.001) OS için kötü prognostik faktör olarak bulundu. Cox regresyon analizinin sonuçları, histopatolojik alt tiplerin PFS ve OS üzerinde bir etkisinin olmadığını gösterdi.*
Sonuç	*Patolojik olarak sınıflandırılamayan YDNEK hastaları KHAK hastaları ile benzer klinik ve sağ kalım özellikleri göstermektedir.*
Anahtar Kelimeler	*yüksek dereceli nöroendokrin karsinoma, küçük hücreli akciğer kanseri, nöroendokrin tümörler*

INTRODUCTION

Pulmonary neuroendocrine carcinoma (pNEC) is a special subtype of lung cancer with an incidence of approximately 15-20%.[1] The diagnostic criteria are clearly defined based on morphology, occurrence and extent of necrosis, and mitotic count. With the growing advances in immunochemistry, its use in the diagnosis of pNEC is recommended according to the 2015 WHO Classification. pNEC was grouped into one category including four major types in this edition.[2] Subsequently, the recent edition of the WHO Classification of lung tumours was released in 2021. The principles, which emphasise using morphology, immunohistochemistry, and molecular techniques, seem similar.[3] Accordingly, pNEC has a wide spectrum of tumours from low-grade typical carcinoid tumours and intermediate-grade atypical carcinoid tumours, to high-grade neuroendocrine carcinomas (HGNEC), including small-cell carcinoma (SCLC) and large-cell neuroendocrine carcinoma (LCNEC).[4] SCLC and LCNEC are present in 13–15% and 3% of lung cancers, respectively.[5] The subtypes of HGNEC have strong similarities with each other in terms of poor histologic differentiation, aggressive behavior, and poor prognosis.[6–8] Furthermore, differentiating HGNEC from its subgroups as SCLC and LCNEC is complex in numerous cases and may not always be achievable due to several pitfalls including sampling issues, fixation artefacts, and the morphologic variability of tumour cells.[4,9] Patients diagnosed with HGNEC but cannot be classified (unclassified HGNEC-uHGNEC) are followed up and treated with the recommendations for SCLC in line with the guidelines. However, it is still controversial to use the same strategy of management since there have been few studies about the disease course, treatment response or survival status of patients with uHGNEC. Therefore, we aimed to assess the clinical characteristics and survival outcomes of patients with uHGNEC and compared them to those of patients with SCLC in the current study.

MATERIAL and METHODS

Study population and design

Three hundred forty-four patients whose pathological specimens were evaluated by a professional pulmonary pathologist (F.D.) in our centre between 2009 and 2021 were analysed in this retrospective and observational study. All pathologic specimens were evaluated for a series of immunohistochemically staining, including CD56, thyroid transcription factor 1 (TTF-1), epithelial membrane antigen (EMA), pankeratin, synaptophysin and Ki-67. Patients with a Ki-67 proliferation index of >70% and immunohistochemistry positive results for neuroendocrine markers were enrolled in the analysis. All patients were restaged according to the 8th edition TNM staging system proposed by the International Association for the Study of Lung Cancer (IASLC).[10] Tumours involving the main carina or a main segmental bronchus were evaluated as central, while the other locations were evaluated as peripheral.[11]

As shown in the study flow chart (Figure 1), patients were excluded if they were under the age of 18, underwent an operation for tumour resection, had another known cancer apart from HGNEC / SCLC (before, at the same time or after diagnosis of HGNEC / SCLC), did not complete their first-line anti-cancer treatment due to medical reasons, self-refusal or death, received all or part of their treatment at an outside centre, and loss of medical record/ follow-up data. Of note, patients who had an early-stage disease were excluded from this study because of the small number. Finally, 121 patients were included in the study and grouped as patients with uHGNEC (uHGNEC group) and patients with SCLC (SCLC group).

Data for each patient extracted from patients' files and the hospital's medical record system included demographic and clinical characteristics (age, gender, comorbidity, smoking habit), tumour data (histopathology, clinical TNM stage, tumour size, lymph node involvement, metastasis area), and primary tumour's laterality (right / left), location (central/peripheral). The primary survival

outcomes were determined as median progression-free survival (PFS) and median overall survival (OS). PFS was calculated as time (months) from the first treatment to disease progression or death. OS was calculated as time (months) from the date of diagnosis of SCLC / uHGNEC until the date of death from any cause or analysis time. The cut-off date for follow-up was September 1, 2022.

Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Number: 2012-KAEK-15/2559 Date: 23.08.2022) was approved this study. Good Clinical Practice guidelines and assent specific to our country were performed and the Declaration of Helsinki and its subsequent revisions were followed. An informed consent form was waived because this was a retrospective study.

Statistical analysis

Categorical data were expressed as number of cases (%) and compared using the chi-square test or Fisher's Exact test. The normality of the distribution of continuous variables was evaluated by the Kolmogorov-Smirnov test. Continuous data were given as mean ± standard deviation (SD) for normal distributions, and median (minimum-maximum value) for skewed distributions. Student's t-test or Mann-Whitney U test was used to compare groups depending on normality. The reverse Kaplan–Meier method was used to calculate the median follow-up duration. The Kaplan–Meier method was used to estimate PFS and OS, and the log-rank test was used to compare groups. Cox regression analysis was performed to identify risk factors independently associated with OS and PFS, and presented with the hazard ratios (HRs) and 95% confidence interval (95% CI). Variables associated with OS and PFS which had a P- value lower than 0.1 in univariate analysis were included in multivariate analysis. Statistical analyses were carried out with IBM Corp. Released in 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. A p-value of < 0.05 was considered statistically significant.

RESULTS

The demographic and clinical features of uHGNEC and SCLC groups

A total of 121 patients (106 males and 15 females, with a mean age of 61.07 ± 10.65) were enrolled in the study. The primary tumour was mostly right-sided and located in the central of the lungs. The most common tumour size was > 7 cm (n = 63, 52.1%) and almost all of the patients were N (+) (n = 116, 95.8%). The IASLC stage at diagnosis was locally advanced in 43 (35.5%) patients and advanced in 78 (64.5%) patients. There were 35 (28.9%) patients in the uHGNEC group and 86 (71.1%) patients in SCLC (SCLC group). uHGNEC- and SCLC groups shared almost similar demographic and clinical features, and the covariates related to tumour data showed no significant difference between the two groups (Table 1).

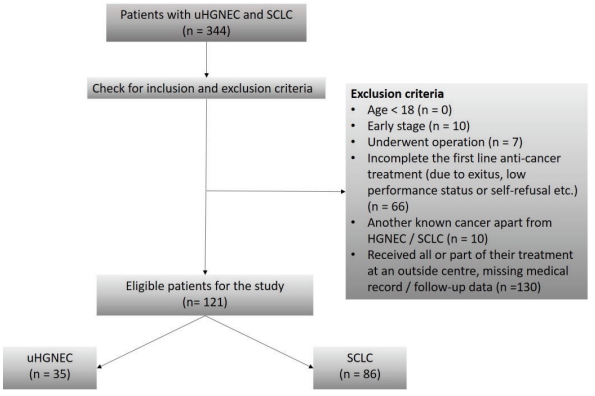


Figure 1. The flowchart of the study population
Abbreviations: SCLC, Small cell lung cancer; uHGNEC, Unclassified high-grade neuroendocrine carcinoma

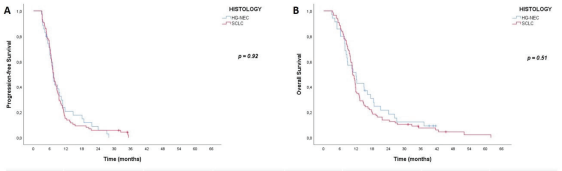
Table 1. The clinical features of the entire study population and comparison of uHGNEC- and SCLC groups

	ALL POPULATION (N = 121)	**UHGNEC (N = 35, 28.9%)**	**SCLC (N = 86, 71.1%)**	**P VALUE**
AGE (YEAR ± SD)	61.07 ± 10.65	63.49 ± 9.4	60.09 ± 11.02	0.11
AGE, N (%)				
<65	76 (62.8)	19 (54.3)	57 (66.3)	0.21
≥65	45 (37.2)	16 (45.7)	29 (33.7)	
SEX, N (%)				
FEMALE	15 (12.4)	3 (8.6)	12 (14)	0.55
MALE	106 (87.6)	32 (91.4)	74 (86)	
SMOKING HISTORY † (+)	94 (77.6)	27 (77.1)	68 (79)	0.24
COMORBIDITY (+), N (%)	66 (54.5)	22 (62.8)	46 (53.4)	0.14
LATERALITY ‡, N (%)				
LEFT	56 (46.3)	19 (54.3)	37 (43)	0.26
RIGHT	65 (53.7)	16 (45.7)	49 (57)	
LOCATION ‡, N (%)				
PERIPHERAL	28 (23.1)	8 (22.9)	20 (23.3)	0.96
CENTRAL	93 (76.9)	27 (77.1)	66 (76.7)	
TUMOUR SIZE, N (%)				
≤ 3 CM	7 (5.8)	4 (11.4)	3 (3.5)	
3 CM - ≤ 5 CM	13 (10.7)	3 (8.6)	10 (11.6)	0.14
5 CM - ≤ 7 CM	38 (31.4)	14 (40)	24 (27.9)	
> 7 CM	63 (52.1)	14 (40)	49 (57)	
NODAL STATUS, N (%)				
N0	5 (4.1)	3 (8.6)	2 (2.3)	
N1	14 (11.6)	5 (14.3)	9 (10.5)	0.94
N2	68 (56.2)	14 (40)	54 (62.8)	
N3	34 (28.1)	13 (37.1)	21 (24.4)	
M STATUS, N (%)				
M0	43 (35.5)	14 (40)	29 (33.7)	
M1A	7 (5.8)	1 (2.9)	6 (7)	0.58
M1B	12 (9.9)	2 (5.7)	10 (11.6)	
M1C	59 (48.8)	18 (51.4)	41 (47.7)	
IASLC STAGE, N (%)				
LOCALLY-ADVANCED	43 (35.5)	14 (40)	29 (33.7)	0.51
ADVANCED	78 (64.5)	21 (60)	57 (66.3)	

† current or former smokers, ‡ Primary tumour, Abbreviations: uHGNEC, unclassified high-grade neuroendocrine carcinoma; SCLC, small cell lung carcinoma; SD, Standard deviation; T, tumour size; N, lymph node; M, metastasis; IASLC, 8th edition TNM staging system proposed by the International Association for the Study of Lung Cancer

The comparison of OS and PFS between two groups

During a median follow-up of 41.6 (95% Cl: 36.41 – 46.79) months, 97.5% of the entire study population (n = 118) progressed and 94.2% of them (n = 114) died. The median PFS was 7.40 (95% Cl 6.82 – 7.97) months. uHGNEC- and SCLC groups had a similar PFS (7.30 vs 7.50 months, p = 0.94). The six-month, one-and two-year PFS for the two groups were also similar (Figure 2A). The median OS was 10.90 (95% Cl 9.97 – 11.82) months. uHGNEC- and SCLC groups had a similar median OS (12 vs 10.7 months, p = 0.51). The estimated OS rates for the uHGNEC group were 85.7% at 6 months, 45.7% at 12 months, and 20% at 24 months, while the estimated OS rates for the SCLC group were 88.4%, 36% and 14 %, respectively. The six-month, one- and two-year OS for the two groups were also similar (Figure 2B).



PFS	6-MONTHS	1-YEAR	2-YEAR	OS	6-MONTHS	1-YEAR	2-YEAR
uHGNEC	65.7%	20%	8.6%	uHGNEC	85.7%	45.7%	20%
SLCL	70.9%	15.1%	5.8%	SLCL	88.4%	36%	14%
p value	0.57	0.51	0.42	p value	0.44	0.32	0.4

Figure 2: The progression-free survival (A) and overall survival (B) of uHGNEC and SCLC groups

The OS and PFS based on the IASCL stage between the two groups were further evaluated using stratified analysis (Table 2). No significant differences between the two groups in both the locally-advanced (Figure 3A-3B) and advanced subgroups (Figure 3C-3D) were found.

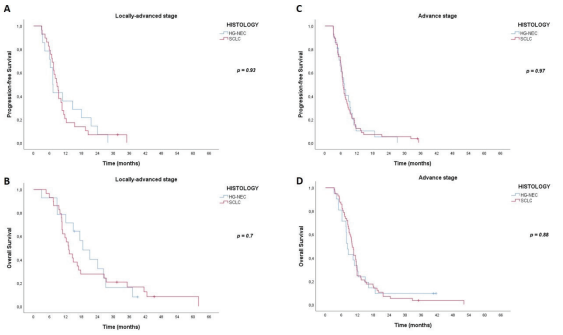


Figure 3: The progression-free survival and overall survival of uHGNEC and SCLC groups according to the IASCL stage subgroups (A-B Locally-advanced stage) (C-D Advanced stage)

Abbreviations: SCLC, Small cell lung cancer; uHGNEC, Unclassified high-grade neuroendocrine carcinoma

The prognostic factors of PFS and OS in the entire study population

Nodal status (N2 and N3 involvement) and stage (advanced) were significantly associated with PFS in the univariate Cox regression analysis (Table 3). However, no covariates reached statistical significance in the multivariate analysis. Laterality, nodal status and stage were significantly associated with OS in the univariate analysis (Table 3). These covariates in the univariate analysis were further evaluated in the multivariate analysis. A right-sided tumour (HR: 1.558, 95%Cl 1.044 – 2.325, p = 0.03) and an advanced stage disease (HR: 1.928, 95%Cl 1.292 – 2.877, p = 0.001) were poor prognostic factors for OS.

Table 2. The progression-free survival and overall survival of patients

Variables	Estimate survival (95% Cl)		P value
	MEANa	MEDIAN	
Progression-free survival			
All population	9.62 (8.35 – 10.89)	7.40 (6.82 – 7.97)	0.92
All-uHGNEC (n = 35)	9.87 (7.55 – 12.18)	7.30 (6.87 – 7.72)	
All-SCLC (n = 86)	9.52 (8.00 – 11.05)	7.50 (6.68 – 8.31)	
Locally-advanced (n = 43)	11.10 (8.74 – 13.45)	8.60 (6.41 – 10.78)	
LA-uHGNEC (n = 14)	11.55 (7.23 – 15.86)	7.20 (5.97 – 8.42)	0.93
LA-SCLC (n = 29)	10.88 (8.03 – 13.73)	8.80 (6.41 – 10.78)	
Advanced (n = 78)	8.80 (7.33 – 10.27)	6.90 (6.30 – 7.49)	
A-uHGNEC (n = 21)	8.67 (6.18 – 11.16)	7.40 (5.67 – 9.12)	0.97
A-SCLC (n = 57)	8.85 (7.05 – 10.64)	6.80 (6.15 – 7.44)	
Overall survival			
All population (n = 121)	15.41 (13.06 – 17.76)	10.90 (9.97 – 11.82)	
All-uHGNEC (n = 35)	15.57 (11.78 – 19.36)	12 (8.05 – 15.94)	0.51
All-SCLC (n = 86)	14.94 (12.30 – 17.58)	10.70 (9.86 – 11.53)	
Locally-advanced (n = 43)	20.72 (15.98 – 25.46)	14.90 (10.84 – 18.96)	
LA-uHGNEC (n = 14)	20.34 (14.81 – 25.88)	18.50 (12.29 – 24.70)	0.7
LA-SCLC (n = 29)	20.28 (14.25 – 26.31)	13.20 (11.26 – 15.13)	
Advanced (n = 78)	12.62 (10.27 – 14.97)	9.90 (8.49 – 11.30)	
A-uHGNEC (n = 21)	12.21 (7.80 – 16.61)	8.30 (7.40– 9.19)	0.88
A-SCLC (n = 57)	12.41 (9.97 – 14.85)	10.10 (9.26 – 10.93)	

a Estimation is limited to the largest survival time if it is censored.
Abbreviations: uHGNEC, unclassified high-grade neuroendocrine carcinoma; SCLC, small cell lung carcinoma; 8th edition TNM staging system proposed by the International Association for the Study of Lung Cancer

Table 3. The univariate Cox regression analysis of progression-free survival and overall survival

	Progression-free survival			Overall survival		
Variables	**HR**	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age						
< 65 (Ref.)	1	0.568 – 1.207	0.32	1	0.674 – 1.455	0.96
≥ 65	0.828			0.990		
Sex						
Female (Ref.)	1	0.673 – 2.073	0.56	1	0.521 – 1.605	0.75
Male	1.181			0.914		
Comorbidity						
No (Ref.)	1	0.545 – 1.236	0.34	1	0.738 – 1.691	0.6
Yes	0.820			1.117		
Smoking						
No (Ref.)	1	0.577 – 2.285	0.69	1	0.652 – 3.050	0.38
Yes	1.148			1.410		
Histopathology						
SCLC (Ref.)	1	0.679 – 1.518	0.94	1	0.756 – 1.739	0.52
uHGNEC	1.015			1.146		
Laterality						
Left (Ref.)	1	0.839 – 1.751	0.3	1	1.135 – 2.479	**0.009**
Right	1.212			1.677		
Location						
Peripheral (Ref.)	1	0.556 – 1.336	0.5	1	0.610 – 1.494	0.95
Central	0.862			0.955		
Tumour size						
≤ 5 cm (Ref.)	1	0.658 – 1.768	0.76	1	0.490 – 1.301	0.36
> 5 cm	1.078			0.798		
N status						
N 0-1 (Ref.)	1	1.107 – 3.142	**0.01**	1	0.985 – 3.043	**0.05**
N 2-3	1.865			1.731		
Stage						
Locally-advanced (Ref.)	1	0.950 – 2.034	**0.09**	1	1.340 – 2.966	**0.001**
Advanced	1.390			1.994		

DISCUSSION

uHGNEC and SCLC groups have similar clinical features, and apparent differences do not exist between the two groups regarding survival outcomes in this study.

SCLC and LCNEC arise predominantly in older males with a smoking history.[8] The presence of comorbidities is also common in both subtypes of HGNEC, possibly due to a strong association with smoking. However, SCLC is a mostly centrally located tumour whereas LCNEC tends to locate at the periphery lungs.[1] In our study, the SCLC groups' clinical features are consistent with data from the literature, and the uHGNEC group shares similar clinical features with the SCLC group. The majority of SCLC patients with limited-stage cancer and nearly all patients with the metastatic disease eventually develop tumour progression, even if they respond to initial therapy.[12] Median PFS was 6.3 months, with an estimated PFS rate of 53.8% at 6 months, 15.6% at 12 months, and 5.8% at 24 months in a previous study.[13] In our study, the estimated PFS rate for the SCLC group at 6 months was slightly higher than those reported in the previous study, while one- and two-year PFS were similar. The uHGNEC group tended to have longer PFS as compared to the SCLC group, though there was no significant difference. On the other hand, previous studies evaluating metastatic LCNEC treatment have reported that median PFS varies from 4.4 months to 6.2 months. The uHGNEC group had a longer PFS than reported in these studies.[8] Poorer PFS of SCLC is associated with several factors including male sex, increasing age, smoking history and having worse performance status.[13] In our study, these covariates as well as histological subtype were not found to be significantly associated with PFS.

SCLC is a poorly differentiated tumour and has a high mortality rate in comparison to other solid tumours.[14] Since the five-year survival rate was increasing, the OS was only 7 months according to the US SEER registry data analysis for the 1983-2012 period. The prognosis of LCNEC is also poor, with a median OS of 8–12 months.[8] In our study, the OS of the SCLC group was 10.7 months. uHCNEC group had a similar median OS (12 months) than those reported in the SCLC group and patients with LCNEC reported in the literature. Furthermore, the previous study with SCLC patients has reported a median OS of 9.5 months, with an estimated OS rate of 70.3% at 6 months, 38.9% at 12 months, and 14.8% at 24 months after diagnosis. The estimated OS rates the for SCLC- and uHGNEC groups at 6 months were higher than the previous study, while one- and two-year OS were similar.[13] The fact that all patients finished at least the first-line therapy may have allowed for the detection of slightly longer survival rates at 6 months in our study. To date, several negative prognostic factors for SCLC and LCNEC have also been identified.[7,15] Male sex, increasing age, having worse performance status, presence of comorbidities, having extensive stage disease and receipt of no chemotherapy are independently associated with poorer survival in SCLC.[16,17] Older age and mixed histology are significantly associated with prognosis in LCNEC.[7] Right-sided tumour and advanced stage were poor prognostic factors for OS, while histology was not associated with OS in our study.

So far, few studies are comparing the characteristics and prognosis of HGNEC subtypes. Some studies have suggested that genetic, genomic, phenotypic, and survival outcome similarities exist between LCNEC and SCLC, making it reasonable to be categorized them into a single group as HGNEC.[18,19] On the other hand, some studies have found that patients with LCNEC have different characteristics and better prognoses, emphasizing the need for a detailed classification for HGNECs.[1,20] In our study, there were no apparent differences between the uHGNEC and SCLC groups in terms of clinical characteristics and survival outcomes. It may be related to the fact that the majority of them are actually SCLC. Another possible explanation for this is that LCNEC and SCLC are two faces of the same entity, which is HGNEC.

There are several potential limitations. First, our study had a retrospective design from a single hospital with a slightly low number of patients, which may limit an interpretation of the results due to the unrecognized bias. Second, there was no information about the baseline performance status of the patients as the study was retrospective. Third, this study was performed on patients who had locally advanced and advanced due to a small number of patients with early stage.

CONCLUSION

Patients with uHGNEC show similarities regarding clinical features and survival outcomes to SCLC in the current study. Our findings suggest that HGNEC patients who cannot be classified pathologically behave like SCLC. Nonetheless, prospective studies may provide considerable insight to clarify the current topic.

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