Original Article

Survival comparison of pulmonary neuroendocrine carcinoma, adenocarcinoma with neuroendocrine differentiation, and adenocarcinoma

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Background: Pulmonary adenocarcinoma with neuroendocrine differentiation (ADE_ned) is a relatively uncommon pathological classification, and there exists considerable debate regarding its prognosis and treatment. The purpose of this study was to analyze the survival difference between patients with neuroendocrine carcinoma (NEC), adenocarcinoma (ADE), or ADE_ned and to investigate the prognostic factors influencing the outcomes of individuals diagnosed with pulmonary ADE_ned.

Methods: We retrieved information on 316 cases of ADE_ned, 188,823 cases of ADE, and 71,154 cases of NEC diagnosed between 2004 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database. To account for potential confounding variables, propensity score matching (PSM) was employed. Comparative analyses were conducted to estimate the overall survival (OS) and cancer-specific survival (CSS). Finally, the Cox regression models were used to identify prognostic factors associated with pulmonary ADE_ned.

Results: Prior to PSM, patients with lung ADE_ned had a worse OS rate than did those with lung ADE or NEC (5-year OS rate: 13.3% *vs.* 26.6% *vs.* 15.6%; P<0.001 and P=0.009, respectively). In terms of CSS, the 5-year CSS rate of patients with ADE_ned was superior to that of NEC but inferior to that of ADE (28.7% *vs.* 26.8% *vs.* 43.8%; P=0.006 and P<0.001, respectively). Following PSM, the 5-year survival rate of patients with ADE_ned remained lower than that of individuals with ADE or NEC in terms of OS (13.3% *vs.* 24.4% *vs.* 23.0%; P<0.001 and P<0001, respectively) and CSS (28.8% *vs.* 58.6% *vs.* 43.1%; P<0.001 and P=0.006, respectively). Finally, the results of the competitive risk regression analysis demonstrated that several variables, including sex, T stage, N stage, M stage, and surgery, were found to be independent prognostic factors for patients diagnosed with pulmonary ADE_ned (all P values <0.05).

Conclusions: Patients with lung ADE_ned had a significantly poorer survival outcome compared to those with lung ADE or NEC. Furthermore, sex, tumor-node-metastasis (TNM) stage, and surgery were found to be independent prognostic indicators for cases with lung ADE_ned.

Keywords: Adenocarcinoma with neuroendocrine differentiation (ADE_ned); prognosis; clinical features

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Introduction

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality in the world (1,2). Accurate histological categorization is imperative to proper diagnosis, treatment, and prognosis. In accordance with the World Health Organization (WHO) classification criteria, neuroendocrine carcinoma (NEC) can be identified as tumor tissue exhibiting positive neuroendocrine markers, with a minimum threshold of more than 50% positive cells; otherwise, it is defined as tumor with neuroendocrine differentiation (3-8). Notably, neuroendocrine differentiation is observed in approximately 15% of non-small cell lung cancer (NSCLC) cases, predominantly within the adenocarcinoma (ADE) subtype (9,10). Given the relative rarity of this pathological variant, our current understanding of its clinical characteristics, treatment, and prognosis remains insufficient.

In this study, data of patients with pathologically confirmed ADE with neuroendocrine differentiation (ADE_ned) were extracted from the Surveillance, Epidemiology, and End Results (SEER) database. Subsequently, the survival prognosis of these patients was compared with that of individuals diagnosed with ADE or NEC. Finally, Cox regression analysis was conducted to investigate the clinical features that influenced patient outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1811/rc).

Highlight box

Key findings

- Sex, tumor-node-metastasis (TNM) stage, and surgery are independent prognostic indicators of pulmonary adenocarcinoma with neuroendocrine differentiation (ADE_ned).

What is known and what is new?

- Pulmonary ADE_ned is a relatively uncommon pathological classification.
- Patients with lung ADE_ned exhibited a significantly inferior survival outcome compared to those with adenocarcinoma or neuroendocrine carcinoma. Additionally, variables such as sex, TNM stage, and surgery were identified as independent prognostic indicators for cases involving lung ADE_ned.

What is the implication, and what should change now?

- Greater attention should be paid to patients with ADE_ned.

Methods

Participants

Data were extracted from the SEER database (https://seer.cancer.gov/) using SEER*Stat 8.3.5 software. According to the third edition SEER codes, patients with codes 8140/3, 8230/3, 8250/3, 8251/3, 8252/3, 8253/3, 8254/3, 8255/3, 8260/3, 8310/3, 8480/3, 8481/3, 8490/3, and 8550/3 were defined as ADE. The ADE_ned type was used to restrict the pathology types to 8574/3 and certain NEC (codes 8002/3, 8013/3, 8014/3, 8041–8045/3, 8240/3, 8246/3, 8249/3). All included patients were pathologically confirmed and had complete treatment information. The specific demographic and clinicopathological characteristics were shown in *Table 1*. Cancer-specific survival (CSS), as provided by the SEER database, referred to the time from diagnosis until death specifically attributed to the cancer or until the last follow-up. Furthermore, the SEER database also reported overall survival (OS), defined as the interval from diagnosis to death from any cause or the last follow-up. The date of the last follow-up in the SEER was December 31, 2018. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Statistical analysis

For descriptive statistics, the absolute number with proportions for the categorical variables was employed. Additionally, a chi-squared test was further conducted to compare the categorical variables across various groups. In order to mitigate the influence of confounding variables, we employed propensity score matching (PSM). First, we designated patients with ADE_ned as a common reference and matched them with the other two cohorts, respectively. The PSM model was based upon age, sex, tumor-node-metastasis (TNM) stage, surgery, radiotherapy, and chemotherapy according to a logistic regression model. The matching ratio in PSM was 1:2 among different groups, and the caliper was 0.02. After PSM, the differences in the variables among the groups were rechecked.

The log-rank test was used to compare survival differences based on Kaplan-Meier survival curves. The Cox proportional hazards model was employed to examine the correlation between clinical features and patient survival. Only the variables that exhibited a significant association with outcome in univariate Cox analyses were considered

for inclusion in the multivariate Cox analyses. All statistical analyses were completed with R statistical software (The R Foundation for Statistical Computing, Vienna, Austria). A two-sided P value <0.05 was considered to indicate a statistically meaningful difference.

Results

Patient information and tumor characteristics

As shown in *Table 1*, a total of 316 patients diagnosed with ADE_ned were included from the SEER database between 2004 and 2015. Among the confirmed cases, a relatively high proportion of patients were >65 years old (58.23%) and male (53.80%).

Additionally, the majority of ADE_ned cases were at an advanced stage at the time of initial diagnosis: American Joint Committee on Cancer (AJCC) stage IV in 146 patients (46.20%) and stage III in 79 patients (25.00%). Consequently, the percentage of resectable patients was low (33.86%). Furthermore, 134 patients (42.41%) received radiotherapy and 161 cases (50.95%) underwent chemotherapy.

Compared with ADE, ADE_ned had no significant differences in age (P=0.22), M stage (P=0.70), or surgery (P=0.16). There were notable discrepancies in composition between ADE and ADE_ned in the variables of sex (P=0.03), T stage (P<0.01), N stage (P=0.04), stage (P<0.01), radiotherapy (P=0.01), and chemotherapy (P<0.01). Further comparative analysis between ADE_ned and NEC revealed no meaningful differences in age (P=0.57), T stage (P=0.30), or radiotherapy (P=0.87), but difference were found for the other variables (P<0.05).

After PSM, 632 patients screened from ADE and NEC cohorts were enrolled into new subgroups. Subsequently, we conducted a reevaluation of the variables, revealing no significant differences between the three subgroups for any factor (*Table 2*).

Patient survival

In the survival analysis, we divided all patients into three distinct groups according to disease type (ADE, NEC, or ADE_ned). And excluding patients with unknown survival time, 188,614 ADE and 71,065 NEC were included in the intermediate survival analysis. The findings revealed that the 5-year OS rate was 13.3% in patients with lung ADE_ned, 26.6% in patients with lung ADE, and 15.6% in patients with lung NEC. These results indicated that the survival rate of patients with ADE_ned was inferior to that of those with ADE or NEC (P<0.001 and P=0.009, respectively). Furthermore, the OS of patients with lung ADE was significantly better than that of patients with lung NEC (P<0.001; *Figure 1A*). Meanwhile, the 5-year CSS rate was 28.7% in patients with ADE_ned, 43.8% in patients with lung ADE, and 26.8% in patients with NEC. The CSS rate of patients with ADE_ned was higher than that of patients with NEC and lower than that of patients with ADE (P=0.006 and P<0.001, respectively). Moreover, the CSS rate was also significantly higher in patients with lung ADE compared to those with lung NEC (P<0.001; *Figure 1B*).

Following the implementation of PSM, there was an improvement in the balance of each variable across the three groups, as summarized in *Table 2*. Subsequently, we compared the survival of patients in the three new cohorts. The findings demonstrated that patients with lung ADE_ned exhibited a 5-year OS rate of 13.3%, whereas patients with ADE or NEC had rates of 24.4% and 23.0%, respectively. Notably, patients with pulmonary ADE_ned experienced a significantly lower survival rate compared to those with ADE or NEC (P<0.001 and P<0.001, respectively; *Figure 1C*). Similarly, in terms of the 5-year CSS rates, patients diagnosed with lung ADE_ned had a rate of 28.8%, whereas individuals with ADE or NEC had rates of 58.6% or 43.1%, respectively. It is worth mentioning that the CSS rate was inferior in patients with lung ADE_ned compared to those with lung ADE or NEC (P<0.001 and P=0.006, respectively; *Figure 1D*).

Prognostic factor analysis of lung ADE_ned

Finally, we aimed to identify the possible prognostic factors in patients with lung ADE_ned, with these results being presented in *Table 3*. Kaplan-Meier survival curve analysis revealed a significant correlation between the prognosis of ADE_ned and sex (P=0.014; *Figure 2A*), while age had no statistically significant association with patient outcome (P=0.468; *Figure 2B*). Furthermore, our analysis demonstrated that lesions with higher T stage had a much worse outcome than did those with a relatively lower T stage (P<0.001; *Figure 2C*). Additionally, the prognosis of ADE_ned cases deteriorated significantly with the invasion of lymph nodes (P<0.001; *Figure 2D*). Moreover, the CSS of patients with ADE_ned and distant metastases was significantly shorter than that of individuals without distant metastases (P<0.001; *Figure 2E*). Finally, surgery

Table 1 Baseline characteristics of patients before PSM

Variables	ADE_ned (n=316), n (%)	ADE (n=188,823), n (%)	NEC (n=71,154), n (%)	P value	
				ADE_ned *vs*. ADE	ADE_ned *vs*. NEC
Age (years)				0.22	0.57
≤65	132 (41.77)	72,538 (38.42)	30,863 (43.37)		
>65	184 (58.23)	116,285 (61.58)	40,291 (56.63)		
Sex				0.03	0.04
Female	146 (46.20)	98,882 (52.37)	37,026 (52.04)		
Male	170 (53.80)	89,941 (47.63)	34,128 (47.96)		
T				<0.01	0.30
T1	90 (28.48)	65,548 (34.71)	17,850 (25.09)		
T2	71 (22.47)	51,772 (27.42)	16,125 (22.66)		
T3	59 (18.67)	31,584 (16.73)	12,317 (17.31)		
T4	96 (30.38)	39,919 (21.14)	24,862 (34.94)		
N				0.04	<0.01
N0	135 (42.72)	93,479 (49.51)	19,371 (27.22)		
N1	30 (9.49)	16,541 (8.76)	5,667 (7.96)		
N2	119 (37.66)	58,044 (30.74)	34,533 (48.53)		
N3	32 (10.13)	20,759 (10.99)	11,583 (16.28)		
M				0.70	<0.01
M0	170 (53.80)	103,655 (54.90)	29,445 (41.38)		
M1	146 (46.20)	85,168 (45.10)	41,709 (58.62)		
Stage				<0.01	<0.01
I	61 (19.30)	54,558 (28.89)	9,431 (13.25)		
II	30 (9.49)	16,832 (8.91)	3,874 (5.44)		
III	79 (25.00)	32,265 (17.09)	16,140 (22.68)		
IV	146 (46.20)	85,168 (45.10)	41,709 (58.62)		
Surgery				0.16	<0.01
No	209 (66.14)	117,706 (62.34)	60,358 (84.83)		
Yes	107 (33.86)	71,117 (37.66)	10,796 (15.17)		
Radiotherapy				0.01	0.87
No/unknown	182 (57.59)	121,974 (64.60)	41,308 (58.05)		
Yes	134 (42.41)	66,849 (35.40)	29,846 (41.95)		
Chemotherapy				<0.01	<0.01
No/unknown	155 (49.05)	108,400 (57.41)	27,102 (38.09)		
Yes	161 (50.95)	80,423 (42.59)	44,052 (61.91)		

PSM, propensity score matching; ADE_ned, adenocarcinoma with neuroendocrine differentiation; ADE, adenocarcinoma; NEC, neuroendocrine carcinoma.

Table 2 Characteristics of patients after PSM

Variables	ADE_ned (n=316), n (%)	ADE (n=632), n (%)	NEC (n=632), n (%)	P value	
				ADE_ned *vs*. ADE	ADE_ned *vs*. NEC
Age (years)				>0.99	0.85
≤65	132 (41.77)	264 (41.77)	260 (41.14)		
>65	184 (58.23)	368 (58.23)	372 (58.86)		
Sex				>0.99	>0.99
Female	146 (46.20)	292 (46.20)	292 (46.20)		
Male	170 (53.80)	340 (53.80)	340 (53.80)		
T				>0.99	>0.99
T1	90 (28.48)	180 (28.48)	178 (28.16)		
T2	71 (22.47)	142 (22.47)	144 (22.78)		
T3	59 (18.67)	118 (18.67)	119 (18.83)		
T4	96 (30.38)	192 (30.38)	191 (30.22)		
N				>0.99	>0.99
N0	135 (42.72)	270 (42.72)	273 (43.20)		
N1	30 (9.49)	60 (9.49)	57 (9.02)		
N2	119 (37.66)	238 (37.66)	238 (37.66)		
N3	32 (10.13)	64 (10.13)	64 (10.13)		
M				>0.99	0.96
M0	170 (53.80)	340 (53.80)	339 (53.64)		
M1	146 (46.20)	292 (46.20)	293 (46.36)		
Stage				>0.99	>0.99
I	61 (19.30)	122 (19.30)	123 (19.46)		
II	30 (9.49)	60 (9.49)	59 (9.34)		
III	79 (25.00)	158 (25.00)	157 (24.84)		
IV	146 (46.20)	292 (46.20)	293 (46.36)		
Surgery				>0.99	>0.99
No	209 (66.14)	418 (66.14)	418 (66.14)		
Yes	107 (33.86)	214 (33.86)	214 (33.86)		
Radiotherapy				>0.99	0.93
No/unknown	182 (57.59)	364 (57.59)	366 (57.91)		
Yes	134 (42.41)	268 (42.41)	266 (42.09)		
Chemotherapy				>0.99	>0.99
No/unknown	155 (49.05)	310 (49.05)	310 (49.05)		
Yes	161 (50.95)	322 (50.95)	322 (50.95)		

PSM, propensity score matching; ADE_ned, adenocarcinoma with neuroendocrine differentiation; ADE, adenocarcinoma; NEC, neuroendocrine carcinoma.

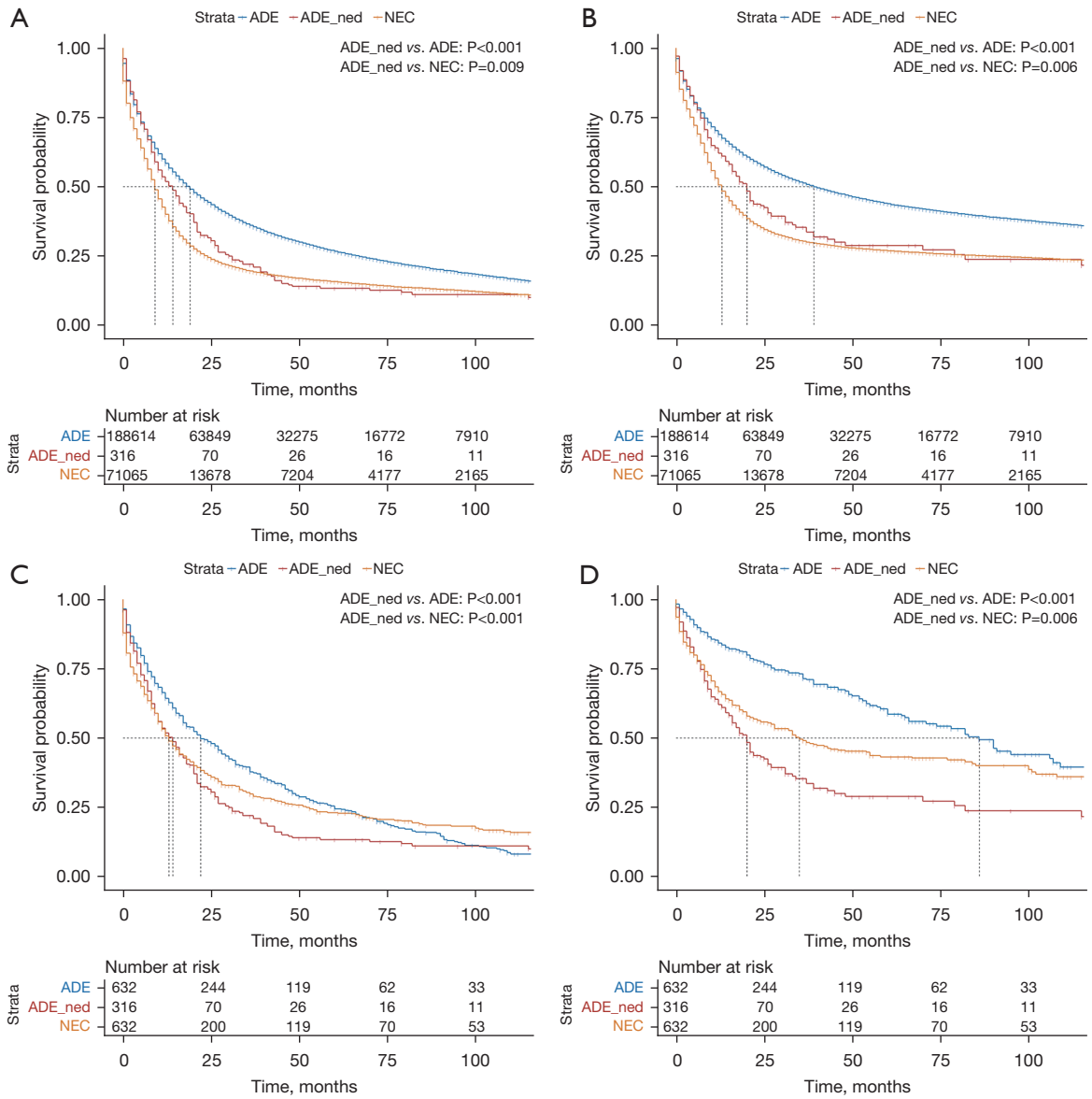

Figure 1 Comparison of OS (A) and CSS (B) before PSM and comparison of OS (C) CSS (D) after PSM. ADE, adenocarcinoma; ADE_ned, adenocarcinoma with neuroendocrine differentiation; NEC, neuroendocrine carcinoma; OS, overall survival; CSS, cancer-specific survival; PSM, propensity score matching.

was associated with improved patient outcomes (P<0.001; *Figure 2F*), while other clinical factors, including radiation (P=0.070; *Figure 2G*) and chemotherapy (P=0.791; *Figure 2H*) were not significantly correlated with the CSS of patients with lung ADE_ned (all P values >0.05).

The potential variables influencing CSS were further examined using Cox proportional hazards analysis, the findings of which are presented in *Table 3*. Factors with a P value <0.05 in univariate Cox regression were enrolled in the multivariate Cox regression analysis. Due to the fact that TNM staging was determined based on T stage, N stage, and M stage, it was not incorporated into the multivariate analysis. Ultimately, the results indicated that sex (P=0.036), T stage (P<0.001), N stage (P<0.001), M stage (P<0.001), and surgery (P<0.001) were independent prognostic indicators for lung ADE_ned.

Table 3 Univariate and multivariate competing risk regression analysis of CSS in patients with lung ADE_ned

Variables	ADE_ned (n=316), n (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	P value	HR (95% CI)	P value
Age (years)					
≤65	132 (41.77)	Reference			
>65	184 (58.23)	1.124 (0.819–1.543)	0.468		
Sex					
Female	146 (46.20)	Reference			
Male	170 (53.80)	1.485 (1.079–2.043)	0.015	1.412 (1.023–1.947)	0.036
T					
T1–2	161 (50.95)	Reference		Reference	
T3–4	155 (49.05)	1.998 (1.450–2.753)	<0.001	1.443 (1.033–2.016)	0.031
N					
N0	135 (42.72)	Reference		Reference	
N1–3	181 (57.28)	2.425 (1.734–3.391)	<0.001	1.554 (1.081–2.234)	0.017
M					
M0	170 (53.80)	Reference		Reference	
M1	146 (46.20)	4.668 (3.330–6.543)	<0.001	3.327 (2.276–4.863)	<0.001
Stage					
I	61 (19.30)	Reference			
II	30 (9.49)	1.221 (0.539–2.766)	0.632		
III	79 (25.00)	2.874 (1.603–5.152)	<0.001		
IV	146 (46.20)	8.356 (4.817–14.495)	<0.001		
Surgery					
No	209 (66.14)	Reference		Reference	
Yes	107 (33.86)	0.269 (0.186–0.390)	<0.001	0.598 (0.384–0.931)	0.023
Radiotherapy					
No/unknown	182 (57.59)	Reference			
Yes	134 (42.41)	1.338 (0.975–1.835)	0.071		
Chemotherapy					
No/unknown	155 (49.05)	Reference			
Yes	161 (50.95)	0.957 (0.699–1.311)	0.785		

CSS, cancer-specific survival; ADE_ned, adenocarcinoma with neuroendocrine differentiation; HR, hazard ratio; CI, confidence interval.

Discussion

Primary ADE_ned, a rare form of pulmonary malignancy, has not been extensively researched due to its low incidence. Consequently, the clinicopathological characteristics and outcomes of this pathological type remain uncertain. This investigation used data from the SEER database spanning from 2004 to 2015. First, the survival prognosis of patients with ADE, ADE_ned, or NEC was compared, which was

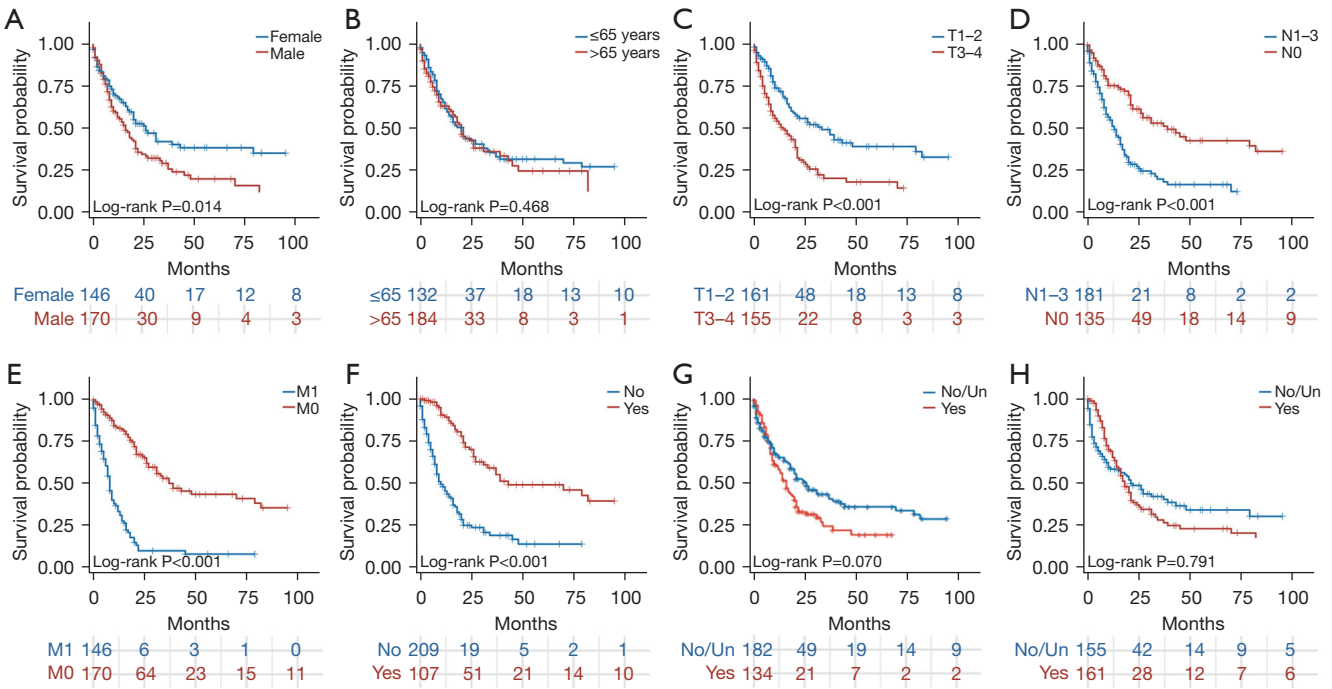

Figure 2 Comparative analysis of CSS of patients according to sex (A), age (B), T stage (C), N stage (D), M stage (E), surgery (F), radiation (G), and chemotherapy (H). Un, unknown; CSS, cancer-specific survival.

followed by a statistical analysis of variables influencing the outcomes of patients with ADE_ned. Our findings indicated that patients with ADE_ned had a poorer prognosis in terms of OS and CSS compared to patients with ADE and NEC. Furthermore, factors such as sex, TNM stage, and surgery were identified as notable prognostic indicators. Our results could provide important medical evidence for the development of follow-up and therapy for patients with ADE_ned.

Previous research has indicated that a minority of NSLCL cases (10–30%) exhibit neuroendocrine differentiation, with ADE being the most prevalent subtype (5,11,12). In the latest WHO classification, these tumors are classified as NSCLC with neuroendocrine differentiation (NSCLC-ND) (4), which denotes the presence of neuroendocrine differentiation in select tumor cells within the tissue, distinguishing them from ADE and NEC. NSCLC-ND represents a subtype of NSCLC lacking neuroendocrine morphological characteristics under light microscopy yet demonstrating neuroendocrine differentiation under immunohistochemistry and electron microscopy. Currently, a variety of biomarkers are being considered as indicators of neuroendocrine differentiation. However, in attempts to compare findings across various studies, the use of the different combinations of these biomarkers in practical is challenging. The markers commonly used to evaluate neuroendocrine differentiation encompass chromogranin A (CgA), synaptophysin, neuron-specific enolase (NSE), and neural cell adhesion molecule (NCAM; CD56) (13-15).

Due to its unique properties, neuroendocrine differentiation has been intensely examined to determine its association with the degree of malignancy, with the aim of informing prognosis and treatment. However, a systematic review of the available literature resulted in inconclusive findings (10). Although some researches have reported a negative impact of neuroendocrine differentiation on survival, others have reported that it has no meaningful correlation with patient outcomes (13,16).

Ionescu *et al.* (17) and Sterlacci *et al.* (9) conducted studies which found that the presence of neuroendocrine differentiation in NSCLC did not significantly impact prognosis and therefore did not warrant distinct consideration. This finding aligned with the results reported by Howe *et al.* (14). However, our own statistical analysis of patients with ADE involving characteristics of neuroendocrine differentiation revealed that the 5-year OS rates were 13.3% for ADE_ned, 26.6% for ADE, and

15.6% for NEC (ADE_ned *vs.* ADE, P<0.001 and ADE_ned *vs.* NSE, P=0.009, respectively). Following PSM, the prognosis of patients with ADE_ned remained inferior to that of the other two types, with 5-year OS rates of 13.3% for ADE_ned, 24.4% for ADE, and 23.0% for NEC (P<0.001 and P<0.001, respectively). Furthermore, several studies have also revealed the presence of neuroendocrine differentiation to be associated with unfavorable outcomes (18,19). Harada *et al.* (20) used surgical specimens of large-cell carcinoma to identify neuroendocrine markers and found a statistically meaningful association between neuroendocrine differentiation and outcome. We speculate that the variability in these studies can be attributed to the inclusion of different types of pathologies, case numbers, disease stages, treatment regimens, and the antibodies and techniques used for immunohistochemistry. Critically, it is worth noting that there is presently no universally accepted criterion for defining neuroendocrine differentiation.

In terms of prognostic factors, a previous study reported that the neuroendocrine proportion of tumor cells, vascular infiltration, and lymphatic invasion were significant adverse prognostic factors (21). Pelosi *et al.* further observed that stage I ADEs with ≥5% neuroendocrine tumor cells exhibited clinical aggressiveness comparable to large cell NEC (22). Additionally, Petrović *et al.* (23) discovered that patients diagnosed with NSCLC-ND had a significantly higher objective response rate of 68.0% compared to the remaining 37.4% (P=0.042), suggesting that the positive ratio of neuroendocrine differentiation may be a potential factor for predicting the efficacy of chemotherapy. However, other investigators have not demonstrated any correlation between neuroendocrine differentiation and prognosis or susceptibility to therapy (24-26). Our multivariate Cox regression indicated that sex (P=0.036), T stage (P=0.031), N stage (P=0.017), M stage (P<0.001), and surgery (P=0.023) were independent variables that significantly influenced patient survival outcomes. Additionally, chemotherapy and radiotherapy were not found to be significant prognostic factors for CSS. These discrepant results could be attributed to the absence of specific drug information within the SEER database and the inconsistent evaluation criteria for neuroendocrine differentiation.

There are several limitations that should be acknowledged in relation to this study. First, it is crucial to note that we employed a retrospective study, which has inherent disadvantages and biases. Second, the lack of comprehensive information pertaining to non-first-line treatments and gene expression may potentially influence the outcomes of patient survival. In order to address these concerns, it is imperative to conduct further investigations with larger sample sizes and with more detailed clinical feedback.

Conclusions

This study compared the prognosis of patients with ADE, NEC, or ADE_ned. We found that patients diagnosed with ADE_ned had significantly lower survival rates compared to patients with lung ADE or NEC. Additionally, factors such as sex, TNM stage, and surgical intervention emerged as potential independent prognostic indicators for individuals with lung ADE_ned.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1811/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1811/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1811/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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