Research Square

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Clinical Features And Prognosis of Advanced Intra- And Extra-Pulmonary Neuroendocrine Carcinomas

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Research

Keywords: Neuroendocrine carcinomas (NECs), clinical features, survival prognosis, small-cell lung cancer (SCLC)

Posted Date: November 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1089101/v1

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Abstract

Objective: We analyzed the clinical features and prognosis of advanced intra- and extra-pulmonary neuroendocrine carcinomas (NECs) in order to provide further guidance for the clinical treatment of small-cell lung cancer, which is a type of advanced intrapulmonary NECs.

Methods: The clinical data and survival of 123 patients with advanced intra- and extra-pulmonary NECs in the Fujian Medical University Union Hospital, Fujian Province, China, between January 2013 to November 2019 were collected. We retrospectively analyzed the corresponding clinical diagnosis and treatment, and explored the relevant factors affecting the survival prognosis of patients with intra- and extra-pulmonary NECs.

Results: The data of 123 patients were collected. There were 90 cases of intra-pulmonary NECS (including 81 cases of small-cell lung cancer, SCLC), 25 cases of extra-pulmonary NECs involving in the gastrointestinal tract, and 8 cases of extra-pulmonary NECs in other regions. The median overall survival (OS) of intra-pulmonary NECs was 13.53 months, of which the median OS of SCLC was 12.97 months, and the median OS of other intra-pulmonary NECs was 27.07 months. The median OS of extra-pulmonary NECs in the gastrointestinal tract was 9.42 months, and the OS of extra-pulmonary NECs in the other regions was 8.69 months. The median OS of intra-pulmonary NECs was significantly longer than that of the extra-pulmonary NECs in the gastrointestinal tract and in the other regions ($P < 0.05$). Multivariate analysis showed that age, liver metastasis, number of cycles of first-line chemotherapy, and chest radiotherapy were risk factors affecting OS in patients with NECs ($P < 0.05$).

Conclusions: The survival of intra-pulmonary NECs was significantly longer than that of extra-pulmonary NECs of the gastrointestinal tract and in other regions. However, patients with advanced intra- and extra-pulmonary NECs who were older and had liver metastases had a poorer prognosis. Multi-disciplinary treatments such as multi-cycle chemotherapy and combination of chemotherapy and radiotherapy should play an important role in prolonging the survival of NECs.

Introduction

Neuroendocrine neoplasms (NENs) refer to heterogeneous tumors of neuroendocrine cells and peptidergic neurons. In 2010, the World Health Organization (WHO) classified gastrointestinal NENs into three tissue categories based on the level of mitotic count and Ki-67 index, namely, low grade (G1, mitotic count: 1 per 10 high power fields (HPF) and Ki-67 index ≤ 2%), medium grade (G2, mitotic count: 2–20 per 10 HPF and Ki-67 index 3–20%) and high grade (G3, mitosis count > 20 per 10 HPF and Ki-67 index > 20%). Patients at G1 and G2 have good tissue differentiation where patients at G3 have poor tissue differentiation, namely neuroendocrine carcinomas (NECs). NECs can be divided into two categories: large-cell NEC (LCNEC) and small-cell NEC (SCNEC) [2]. According to the 2015 WHO standard, pulmonary NECs usually include four subtypes: LCNEC, small-cell lung cancer (SCLC), typical carcinoid (TC), and atypical carcinoid (AC) [3]. Among them, SCLC is the main pathological type.

The incidence of NENs was previously considered to be low. However, the number of NEC cases in Western countries has increased steadily from 1973 to 2012. The incidence in the United States in 2012 reached 6.98 per 100,000 people, compared to only 1.09 per 100,000 people in 1973, indicating that the incidence increased six-fold. Among 45,318 patients with NENs and a clear histological grade, the proportion of patients with NECs is as high as 32.6% (14,766/45,318) [4]. Studies have shown that 50% of patients with NECs have distant metastases at the time of diagnosis, and the median overall survival (OS) is only 5.8 months [4]. Treatments for advanced pulmonary NECs are mainly based on systemic therapies including chemotherapy, targeted therapy, and immunotherapy.

Advanced pulmonary NECs have a high degree of malignancy, relatively few diagnosis and treatment measures, and a poor prognosis. SCLC, which is the most common form, is still mainly treated with chemotherapy. Hence, this study analyzed the clinicopathological data and survival data of 123 patients with advanced intra- and extra-pulmonary NECs and summarized the clinical experience with the goal of providing guidance for the clinical treatment of SCLC.

Materials And Methods

Patients

One hundred-twenty-three patients with advanced intra- and extra-pulmonary NECs seen at the Fujian Medical University Union Hospital, Fujian Province, China, from January 2013 to November 2019 were included in this study. Data from the relevant cases were obtained from the case retrieval system of the medical record room of the Fujian Medical University Union Hospital. The inclusion criteria included: (1) diagnosed with NECs through histopathological examination of biopsy and dissected tumors. Patients had not received any prior chemotherapy, radiotherapy, and other treatments; and (2) with complete clinicopathological data. The exclusion criteria included: (1) combined with other types of malignant tumors; and (2) with medullary thyroid carcinoma, paraganglioma, or Merkel cell carcinoma.

Research methods

Data collection

Clinical data meeting the inclusion criteria, such as the primary site of the tumor, age, gender, clinical symptoms, and treatment status were collected from pathological and clinical electronic medical records and subjected to statistical analysis.

Follow up

The survival and disease conditions of the 123 patients were followed up by case review and telephone follow-up. The deadline for follow-up was November 30, 2020. The survival of patients was presented in months and defined as the duration from the date of diagnosis to the date of death or the end of follow-up. The observation endpoint of this study was the death of the patient and the observation index was

OS. All surviving patients and patients lost to follow-up as of the last follow-up date were treated as censored data.

Statistical analyses

This study used the SPSS22.0 software package (IBM, Armonk, NY) for statistical analysis. The count data are presented as number of cases, and percentages and were compared by Chi-square test. Kaplan-Meier method and log-rank test were used for univariate survival analysis to calculate and compare survival rates. Significant variables in the univariate analysis were subjected to multivariate analysis using the Cox risk regression model. The level of effectiveness was $\alpha = 0.05$.

Results

Clinical data

Among the 123 patients with advanced pulmonary NECs, the primary lesion was located in the lung in 90 cases (73.2%), esophagus in eight cases (6.5%), stomach in 6 cases (4.9%), pancreas in five cases (4.1%), mediastinum in three cases (2.4%), liver in two cases (1.6%), rectum in two cases (1.6%), duodenum in one case (0.8%), gallbladder in one case (0.8%), sinuses in one case (0.8%), ovary in one case (0.8%), cervix in one case (0.8%), prostate in one case (0.8%), and bladder in one case (0.8%).

Age

The median age of onset of patients with advanced pulmonary NECs was 59 years (ranging from 27 to 88 years), and the proportion of patients < 60 years old and ≥ 60 years old was 53.7% (66/123) and 46.3% (57/123), respectively. The median age of onset of intra-pulmonary NECs was 59 years (ranging from 27 to 88 years), and the proportion of patients < 60 years old and ≥ 60 years old was 52.2% (47/90) and 47.8% (43/90), respectively. The median age of onset of SCLC was 60 years (ranging from 27 to 88 years), and the proportion of patients < 60 years old and ≥ 60 years old was 48.1% (39/81) and 51.9% (42/81), respectively. The median age of onset for intra-pulmonary NECs other than SCLC (other intra-pulmonary NECs) was 55 years (ranging from 41 to 59 years), and the proportion of patients < 60 years old and ≥ 60 years old was 100.0% (5/5) and 0.0% (0/5), respectively. The median age of onset in the extra-pulmonary NECs group was 58 years (ranging from 31 to 78 years), and the proportion of patients < 60 years old and ≥ 60 years old was 57.6% (19/33) and 42.4% (14/33), respectively. The median age of onset of extra-pulmonary NECs in the gastrointestinal tract was 59 years (ranging from 32 to 74 years), and the proportion of patients < 60 years old and ≥ 60 years old was 56.0% (14/25) and 44.0% (11/25), respectively. The median age of onset of extra-pulmonary NECs in other regions was 57 years (ranging from 31 to 78 years), and the proportion of patients < 60 years old and ≥ 60 years old was 62.5% (5/8) and 37.5% (3/8), respectively (Table 1, Figure 1).

Table 1
Clinical characteristics of patients with intra- and extra-pulmonary NECs

Clinical parameters		Intra-pulmonary NECs (90 cases)	Extra-pulmonary NECs (33 cases)	Total (123 cases)	p
Age (year)	Median	59	58	59	/
	Range	27-88	31-78	27-88	/
	< 60 years	47	19	66	0.598
	≥ 60 years	43	14	57	
Sex	Male	73	25	98	0.614
	Female	17	8	25	

No significant difference in patient age was found between the intra-pulmonary NEC and the extra-pulmonary NEC groups (P > 0.05), between the other intra-pulmonary NEC and the SCLC groups (P > 0.05), and between the extra-pulmonary NECs in the gastrointestinal tract and the extra-pulmonary NECs in the other region groups (P > 0.05).

Sex

Among all patients with advanced pulmonary NECs, there were 98 males and 25 females, accounting for 79.7% (98/123) and 20.3% (25/123), respectively. The percentage of male and female patients with intra-pulmonary NECs was 81.1% (73/90) and 18.9% (17/90), respectively. Among the patients with intra-pulmonary NECs, there were 81.5% (66/81) males and 18.5% (15/81) females with SCLC, and 60.0% (3/5) males and 40.0% (2/5) females with other intra-pulmonary NECs. Among the patients with extra-pulmonary NECs, there were 75.8% (25/33) males and 24.2% (8/33) females, including 80.0% (20/25) males and 20.0% (5/25) females with extra-pulmonary NECs of the gastrointestinal tract and 62.5% (5/8) males and 37.5% (3/8) females with extra-pulmonary NECs in the other regions (Table 1).

No significant differences in sex were found between the patients in the intra-pulmonary NEC and the extra-pulmonary NEC groups (P > 0.05), between the patients in the SCLC and the other intra-pulmonary NEC groups (P > 0.05), and between the patients in the extra-pulmonary NECs in the gastrointestinal tract group and the extra-pulmonary NECs in the other regions group (P > 0.05).

Treatment

Of the 123 patients with advanced pulmonary NECs, 85 patients received chemotherapy alone, accounting for 69.1% (85/123), and 15 patients received chemotherapy combined with thoracic radiotherapy (all SCLC), accounting for 12.2% (15/123). The first-line chemotherapy regimen used in this study was etoposide/irinotecan combined with platinum. The patients underwent nine chemotherapy cycles with a total of 401 cycles adopted overall, and a median number of three cycles. The median

number of cycles of chemotherapy for all patients with intra-pulmonary NECs was three, the median number of cycles of chemotherapy for SCLC was also three, and the median number of cycles of chemotherapy for other intra-pulmonary NECs was four. The median number of cycles of chemotherapy for extra-pulmonary NECs in the gastrointestinal tract was two, and the number of cycles of chemotherapy for extra-pulmonary NECs in the other regions was three.

Analysis of survival prognosis

As noted, the deadline for follow-up was November 30, 2020. Of the 90 patients with intra-pulmonary NECs, there were 10 cases lost to follow-up and 57 deaths, accounting for 71.25% of the total. In addition, of the 33 patients with extra-pulmonary NECs, seven patients were lost to follow-up and there were 19 deaths, with a mortality of 73.1%. A total of 30 patients with advanced pulmonary NECs survived until the end of follow-up, and the survival period was determined according to the end of the follow-up time. In this study, the median OS of all 123 patients with advanced pulmonary NECs after chemotherapy was 11.37 months. The median OS of all patients with intra-pulmonary NECs after chemotherapy was 13.53 months, the median OS of SCLC patients after chemotherapy was 12.97 months, and the median OS of patients with other intra-pulmonary NECs after chemotherapy was 27.07 months. The median OS of patients with extra-pulmonary NECs in the gastrointestinal tract was 9.42 months, and the median OS of extra-pulmonary NECs in the other regions after chemotherapy was 8.69 months. The median OS of patients with intra-pulmonary NECs was significantly longer than that of patients with extra-pulmonary NECs in the gastrointestinal tract and with extra-pulmonary NECs in other regions ($P < 0.05$). The median OS of patients with other intra-pulmonary NECs was longer than that of patients with SCLC ($P > 0.05$). Compared with the SCLC patients who received chemotherapy alone, the median OS of SCLC patients who received combined chemotherapy and radiotherapy was significantly prolonged ($P < 0.05$). The median OS of patients that received ≥ 4 cycles of first-line chemotherapy was significantly higher than patients that received < 4 cycles of first-line chemotherapy ($P < 0.05$, Table 2).

Table 2
Univariate analysis of prognosis in 123 patients with NECs

Factor		Median OS (month)	95% CI	χ^2	p
Age (year)	< 60	14.80	10.433–19.167	7.280	0.007**
	≥ 60	9.42	7.874–10.966		
Sex	Male	11.37	8.738–14.002	1.184	0.277
	Female	12.33	3.238–21.422		
Primary tumor site	Intra-pulmonary NECs	13.53	10.238–16.822	7.696	0.021*
	Extra-pulmonary NECs in the gastrointestinal tract	9.42	7.111–11.729		
	Extra-pulmonary NECs in other regions	8.69	2.667–14.713		
Albumin (g/L)	< 35	10.65	7.574–13.726	0.072	0.788
	≥ 35	12.33	9.316–15.344		
Hemoglobin (g/L)	< 120	9.93	8.455–11.405	1.210	0.271
	≥ 120	12.53	8.909–16.151		
ALP (U/L)	< 104	12.33	9.038–15.622	4.963	0.026*
	≥ 104	9.50	6.293–12.707		
LDH (U/L)	< 245	13.53	10.048–17.012	5.080	0.024*
	≥ 245	9.50	6.911–12.089		
Liver metastasis	With	9.23	7.086–11.374	13.417	< 0.001***
	Without	15.80	10.056–21.544		

Factor		Median OS (month)	95% CI	χ^2	p
Bone metastasis	With	10.67	5.557–15.783	0.303	0.582
	Without	11.83	9.147–14.513		
Brain metastasis	With	10.03	8.254–11.806	4.869	0.027*
	Without	17.93	12.669–23.191		
Tumor proliferation index	Ki-67 < 55%	11.40	7.792–15.008	2.571	0.109
	Ki-67 ≥ 55%	7.95	6.118–9.782		
Tissue morphology	SCLC	12.97	8.931–17.009	1.229	0.268
	Other intra-pulmonary NECs	27.07	/		
Number of cycles of first-line chemotherapy	< 4	8.60	6.704–10.496	20.704	< 0.001***
	≥ 4	19.83	14.463–25.197		
Chest radiotherapy	With	19.83	0.000–43.557	6.178	0.013*
	Without	9.93	7.718–12.142		

Results of univariate analysis affecting prognosis

Univariate analysis of age, primary tumor site, albumin, hemoglobin, alkaline phosphatase (ALP), lactate dehydrogenase (LDH), liver metastasis, bone metastasis, brain metastasis, tumor proliferation index, tissue morphology, number of cycles of first-line chemotherapy, and chest radiotherapy showed that age, primary tumor site, ALP, LDH, liver metastasis, brain metastasis, number of cycles of first-line chemotherapy, and chest radiotherapy were significantly correlated with the OS of patients with NECs ($P < 0.05$). Alternatively, sex, albumin, hemoglobin, bone metastasis, tumor proliferation index, and histological morphology were not significantly correlated with the OS of patients with NECs ($P > 0.05$, Table 2).

Results of multivariate analysis affecting prognosis

Cox regression analysis of eight variables including age, tumor primary site, ALP, LDH, liver metastasis, brain metastasis, number of cycles of first-line chemotherapy, and chest radiotherapy showed that age, liver metastasis, number of cycles of first-line chemotherapy, and chest radiotherapy were significantly correlated with the OS of patients with NECs ($P < 0.05$, Table 3, Figure 2).

Table 3
Multivariate analysis of 123 NECs patients

Variable	HR	95% CI	P
Age (< 60 years vs. ≥ 60 years)	1.637	1.033–2.592	0.036
Liver metastasis (with *vs.* without)	1.821	1.119–2.962	0.016
Number of cycles of first-line chemotherapy (< 4 *vs.* ≥ 4)	0.393	0.242–0.638	< 0.001
Chest radiotherapy (with *vs.* without)	0.450	0.204–0.991	0.047

Discussion

NENs originated from the concepts of “carcinoid” or “carcinoid tumor” proposed by Oberndorfer in 1907, i.e., a new class of organisms derived from argyrophil cells of organs, such as the organs in the gastrointestinal tract, showing different biochemical, histological, and clinical characteristics in different regions. In November 2017, the International Agency for Research on Cancer (IARC) meeting reached a consensus on the classification of all NENs, dividing NENs into 2 categories: differentiated neuroendocrine tumors (NETs), which is the carcinoid named in some classification standards; and poorly differentiated NECs [9]. NECs are defined as high-grade tumors with high malignancy, poor prognosis, and lack of specific clinical features.

To date, the common locations of NECs in the Asian population are the lung, unknown primary site, cervix, pancreas, rectum, stomach, and bladder, according to the evidence-based medicine data of the Surveillance, Epidemiology, and End Results (SEER) database in the United States [5]. According to the statistical data of this study, the lung was the site with the highest incidence of NECs, followed by the esophagus, stomach, pancreas, mediastinum, liver, and rectum, which is different from reports from other countries. We speculate that this may be due to the small sample size in this study, which failed to fully summarize the features of the primary site of NECs in China. The median age of NECs in this study was 59 years old, which is consistent with the conclusions of other studies in China [10, 11], while a foreign study showed that the median age of patients with NECs was 67 years old [5]. The differences in patient median age may be due to racial differences. Previous studies have shown that the incidence of NECs in both men and women is equal [5, 12], while in this study, the incidence of NECs in males was higher than that of females. In addition, the incidence of intra-pulmonary NECs in males was also higher than in females, which is consistent with the findings reported by Ichiki et al. [13]. Leone et al. showed that lung cancer is associated with smoking [14], and a study by Bernhardt et al. showed that SCLC was significantly correlated with smoking [15]. A study on smoking in China showed that the smoking rate in

Chinese males was significantly higher than that of Chinese females [16]. Therefore, smoking may be an important factor leading to the high incidence of intra-pulmonary NECs in males in this study.

Currently, there is no uniform treatment standard or norms for NECs, and the treatment principles are mainly based on the primary site of the tumor [19, 20]. The main pathological types of NECs in the advanced lung are SCLC and LCNEC. The treatment for advanced SCLC remains chemotherapy. According to the NCCN Guidelines for cancer diagnosis and treatment, the first-line chemotherapy for advanced SCLC is 4–6 cycles of etoposide combined with cisplatin (EP). There is debate on the therapeutic outcomes between irinotecan with combined cisplatin (IP) and EP regimens. In 2002, Japanese researchers used the IP regimen for treatment of patients with extensive SCLC and showed an improved total effective rate (65% *vs.* 52%, P = 0.02) and survival rate (12.8 months *vs.* 9.4 months, P = 0.002) [21]. According to the S0124 randomized phase III clinical trial published by the American Society of Clinical Oncology, no significant differences in OS, progression-free survival (PFS), or effective rate were found between the EP and IP regimens. The S0124 trial did not confirm the results reported by the above Japanese group. In the clinical treatment of advanced SCLC, programmed cell death-1 (PD-1) and T lymphocyte programmed death-ligand 1 (PD-L1) checkpoint inhibitors showed high clinical activity. The IMpower133 study of the efficacy and safety of Atezolizumab combined with chemotherapy for extensive-stage SCLC showed that patients receiving Atezolizumab combined with chemotherapy had a significantly longer median OS (P = 0.0154) than patients receiving standard treatment. In addition, the median PFS of the patients that received Atezolizumab combined with chemotherapy was extended from 4.3 months to 5.2 months, suggesting that the combination of Atezolizumab and chemotherapy as a first-line treatment achieved significant improvement in the survival of patients with extensive-stage SCLC [22, 23]. The CASPIAN study used the PD-L1 inhibitor Durvalumab combined with chemotherapy as the first-line treatment of extensive-stage SCLC and showed that this combination therapy significantly increased the median OS (P = 0.0047) and lowered the mortality of the patients compared with the patients receiving standard treatments [24].

The univariate analysis in this study showed that tissue morphology was not correlated with the OS of patients with NECs. Previous studies have shown that patients with pulmonary LCNEC have better prognosis than those with SCLC. In our study, the median OS of patients with other intra-pulmonary NECs was 27.07 months, which was longer than that of patients with SCLC (12.97 months), although no significant difference was found between the two groups of patients. This is possibly related to the small sample size of the other intrapulmonary NECs. According to statistics from the US SEER database, the median OS of advanced intra-pulmonary NECs is 5.8 months, the median OS of extra-pulmonary NECs in the gastrointestinal tract is 5.2 months, the median OS of extra-pulmonary NECs in other regions is 7.5 months, and the median OS of extra-pulmonary NECs in other regions is longer than that of intra-pulmonary NECs [5]. In addition, a study by Lokesh et al. showed that the median OS of extra-pulmonary NECs was longer than that of intra-pulmonary NECs (13 months *vs.* 8 months) [40]. In our study, however, the median OS of intra-pulmonary NECs (13.53 months) was significantly longer than that of extra-pulmonary NECs in the gastrointestinal tract (9.42 months) and extra-pulmonary NECs in the other

regions (8.69 months). The difference between our study and the other studies may be due to the different populations. In addition, compared with extra-pulmonary NECs, intra-pulmonary NECs have been studied more extensively, and their diagnosis and treatment are more systematic and standardized.

Multivariate analysis in this study showed that age, liver metastasis, the number of cycles of first-line chemotherapy, and chest radiotherapy were risk factors affecting median OS in patients with NECs. In terms of age, the data from this study suggests that young patients are more likely to benefit from treatment than older patients. Previous studies by Yao et al. and Yucel et al. also showed a correlation between survival and patient age in patients with NECs [12, 41]. The liver is the most common metastasis site in patients with NECs. After liver metastasis occurs, tumor progression increases, which has an enormous impact on the quality of life and prognosis of the patient. In this study, results of multivariate analysis indicated that liver metastasis as an independent prognostic factor affecting the median OS of NECs patients, which is consistent with the findings of many previous studies [42–45]. Studies have shown no statistical difference in improvement in prognosis or survival rate between a regimen of 4–6 cycles of chemotherapy and > 6-cycle chemotherapy. A larger number of chemotherapy cycles increases toxicity. Therefore, 4–6 cycles are generally used during platinum-based chemotherapy for NECs. In this study, patients receiving ≥ 4 cycles of chemotherapy had a significantly improved median OS compared with those receiving < 4 cycles of chemotherapy, which is consistent with the findings of a previous study [46]. The more cycles of first-line chemotherapy, the longer the disease progression-free time, which is equivalent to prolonging OS. Although the survival of patients with SCLC is significantly improved by chemotherapy, 80% of these patients are prone to intrathoracic recurrence. One study showed that after three cycles of EP treatment in advanced SCLC patients, patients with complete remission of chest lesions and patients with complete or partial remission of intrathoracic lesions had a significant increase in survival after receiving thoracic radiotherapy [47]. In this study, 15 patients with SCLC received combined radiotherapy and chemotherapy, and the survival benefit was significantly increased compared with patients receiving chemotherapy alone (19.83 months *vs.* 9.93 months), which is consistent with previous reports.

In conclusion, the prognosis of advanced intra- and extra-pulmonary NECs is poor, especially for SCLC, which is the dominant intra-pulmonary NEC and commonly requires chemotherapy. Comprehensively integrating age, presence or absence of liver metastasis, and other aspects of patient information is necessary to diagnosis and treatment. In addition, following the principle of individualization and providing the best or most appropriate diagnosis and treatment is required under the standardized framework. Given the unique heterogeneity of SCLC, scholars have found that there are still many questions to be answered in the field of drug therapy, and more basic research and clinical research are needed to provide answers.

Declarations

Acknowledgements

None

Authors' contributions

Chen Xiaoyun designed the study and drafted the manuscript. Guo

Peilin contributed to the data collection and the analysis of the data. Yang Fan helped in data analysis. Chen Xiangqi and Yang Sheng revised the

manuscript and approved the final version for publication. All authors have

read and approved the final manuscript.

Funding

This work was supported by the Fujian Provincial Health Technology Project(2020CXB016).

Availability of data and materials

The datasets used and/or analyzed during the current study are available

from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing/conflict of interest.

References

1. CSCO Neuroendocrine Tumor Expert Committee. Expert consensus on gastrointestinal pancreatic neuroendocrine tumors in China. Chinese Clinical Oncology, 2013, 18(09): 815–832.
2. Li Z S, Li Q. [The latest 2010 WHO classification of tumors of digestive system]. Zhonghua Bing Li Xue Za Zhi, 2011, 40(5): 351–354.
3. Fang San Gao, Li Sheng Lei, Chen Gang. Interpretation of the 2015 WHO classification of lung, pleura, thymus and heart tumors (thymus). Chongqing Medicine, 2015, 44(36): 5041–5053.
4. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, Shih T, Yao J C. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States.

JAMA Oncol, 2017, 3(10): 1335–1342.

5. Dasari A, Mehta K, Byers L A, Sorbye H, Yao J C. Comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas: A SEER database analysis of 162,983 cases. Cancer, 2018, 124(4): 807–815.
6. Ke Ni, Shuo. Classification and staging of neuroendocrine tumors. Cancer Frontier, 2017(04): 15–18.
7. YU Hai-feng, WANG Wei-qiang. Progress in diagnosis and treatment of gastrointestinal and pancreatic neuroendocrine tumors. Chinese Journal of Urban and Rural Enterprise Hygiene, 2021, 36(01): 46–48.
8. Zhu Xiong-zeng. The evolution and clinical significance of some diagnostic terms for tumors of the digestive system. Chinese Journal of Gastrointestinal Surgery, 2011(01): 21–23.
9. 2020 China Consensus Expert Group on Pathological Diagnosis of Gastrointestinal Pancreatic Neuroendocrine Tumors. Chinese consensus on pathological diagnosis of gastrointestinal pancreatic neuroendocrine tumors (2020 edition). Chinese Journal of Pathology, 2021, 50(01): 14–20.
10. Tang Chengwei, Guo Linjie. Current clinical practice of gastroenteropancreatic neuroendocrine neoplasm in China. Chinese Journal of Practical Surgery, 2014, 34(06): 490–492.
11. Zhang Ping, Meng Xianyu, Guo Mei. Analysis of Clinicopathological Features of 43 Patients with Small Cell Lung Carcinoma. Journal of Basic and Clinical Oncology, 2015, 28(02): 146–148.
12. Yao J C, Hassan M, Phan A, Dagohoy C, Leary C, Mares J E, Abdalla E K, Fleming J B, Vauthey J N, Rashid A, Evans D B. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol, 2008, 26(18): 3063–3072.
13. Ichiki Y, Matsumiya H, Mori M, Kanayama M, Nabe Y, Taira A, Shinohara S, Kuwata T, Takenaka M, Hirai A, Imanishi N, Yoneda K, Noguchi H, Shimajiri S, Fujino Y, Nakayama T, Tanaka F. Predictive factors of postoperative survival among patients with pulmonary neuroendocrine tumor. J Thorac Dis, 2018, 10(12): 6912–6920.
14. Leone F T, Evers-Casey S, Toll B A, Vachani A. Treatment of tobacco use in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest, 2013, 143(5 Suppl): e61S-e77S.
15. Bernhardt E B, Jalal S I. Small Cell Lung Cancer. Cancer Treat Res, 2016, 170: 301–322.
16. Abdullah A S, Qiming F, Pun V, Stillman F A, Samet J M. A review of tobacco smoking and smoking cessation practices among physicians in China: 1987-2010. Tob Control, 2013, 22(1): 9–14.
17. Daskalakis K, Chatzelis E, Tsoli M, Papadopoulou-Marketou N, Dimitriadis G K, Tsolakis A V, Kaltsas G. Endocrine paraneoplastic syndromes in patients with neuroendocrine neoplasms. Endocrine, 2019, 64(2): 384–392.
18. Kalemkerian G P, Loo B W, Akerley W, Attia A, Bassetti M, Boumber Y, Decker R, Dobelbower M C, Dowlati A, Downey R J, Florsheim C, Ganti A, Grecula J C, Gubens M A, Hann C L, Hayman J A, Heist R S, Koczywas M, Merritt R E, Mohindra N, Molina J, Moran C A, Morgensztern D, Pokharel S, Portnoy D C, Rhodes D, Rusthoven C, Sands J, Santana-Davila R, Williams C C, Hoffmann K G, Hughes M.

NCCN Guidelines Insights: Small Cell Lung Cancer, Version 2.2018. J Natl Compr Canc Netw, 2018, 16(10): 1171–1182.

19. Shah M H, Goldner W S, Halfdanarson T R, Bergsland E, Berlin J D, Halperin D, Chan J, Kulke M H, Benson A B, Blaszkowsky L S, Eads J, Engstrom P F, Fanta P, Giordano T, He J, Heslin M J, Kalemkerian G P, Kandeel F, Khan S A, Kidwai W Z, Kunz P L, Kuvshinoff B W, Lieu C, Pillarisetty V G, Saltz L, Sosa J A, Strosberg J R, Sussman C A, Trikalinos N A, Uboha N A, Whisenant J, Wong T, Yao J C, Burns J L, Ogba N, Zuccarino-Catania G. NCCN Guidelines Insights: Neuroendocrine and Adrenal Tumors, Version 2.2018. J Natl Compr Canc Netw, 2018, 16(6): 693–702.
20. Kalemkerian G P, Loo B W, Akerley W, Attia A, Bassetti M, Boumber Y, Decker R, Dobelbower M C, Dowlati A, Downey R J, Florsheim C, Ganti A, Grecula J C, Gubens M A, Hann C L, Hayman J A, Heist R S, Koczywas M, Merritt R E, Mohindra N, Molina J, Moran C A, Morgensztern D, Pokharel S, Portnoy D C, Rhodes D, Rusthoven C, Sands J, Santana-Davila R, Williams C C, Hoffmann K G, Hughes M. NCCN Guidelines Insights: Small Cell Lung Cancer, Version 2.2018. J Natl Compr Canc Netw, 2018, 16(10): 1171–1182.
21. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S, Saijo N. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med, 2002, 346(2): 85–91.
22. Horn L, Mansfield A S, Szczesna A, Havel L, Krzakowski M, Hochmair M J, Huemer F, Losonczy G, Johnson M L, Nishio M, Reck M, Mok T, Lam S, Shames D S, Liu J, Ding B, Lopez-Chavez A, Kabbinavar F, Lin W, Sandler A, Liu S V. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med, 2018, 379(23): 2220–2229.
23. Liu S V, Reck M, Mansfield A S, Mok T, Scherpereel A, Reinmuth N, Garassino M C, De Castro C J, Califano R, Nishio M, Orlandi F, Alatorre-Alexander J, Leal T, Cheng Y, Lee J S, Lam S, McCleland M, Deng Y, Phan S, Horn L. Updated Overall Survival and PD-L1 Subgroup Analysis of Patients With Extensive-Stage Small-Cell Lung Cancer Treated With Atezolizumab, Carboplatin, and Etoposide (IMpower133). J Clin Oncol, 2021, 39(6): 619–630.
24. Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, Statsenko G, Hochmair M J, Ozguroglu M, Ji J H, Voitko O, Poltoratskiy A, Ponce S, Verderame F, Havel L, Bondarenko I, Kazarnowicz A, Losonczy G, Conev N V, Armstrong J, Byrne N, Shire N, Jiang H, Goldman J W. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet, 2019, 394(10212): 1929–1939.
25. Fasano M, Della C C, Papaccio F, Ciardiello F, Morgillo F. Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy. J Thorac Oncol, 2015, 10(8): 1133–1141.
26. Lo R G, Pusceddu S, Proto C, Macerelli M, Signorelli D, Vitali M, Ganzinelli M, Gallucci R, Zilembo N, Platania M, Buzzoni R, de Braud F, Garassino M C. Treatment of lung large cell neuroendocrine carcinoma. Tumour Biol, 2016, 37(6): 7047–7057.

27. Igawa S, Watanabe R, Ito I, Murakami H, Takahashi T, Nakamura Y, Tsuya A, Kaira K, Naito T, Endo M, Yamamoto N, Kameya T. Comparison of chemotherapy for unresectable pulmonary high-grade non-small cell neuroendocrine carcinoma and small-cell lung cancer. Lung Cancer, 2010, 68(3): 438–445.
28. Sun J M, Ahn M J, Ahn J S, Um S W, Kim H, Kim H K, Choi Y S, Han J, Kim J, Kwon O J, Shim Y M, Park K. Chemotherapy for pulmonary large cell neuroendocrine carcinoma: similar to that for small cell lung cancer or non-small cell lung cancer? Lung Cancer, 2012, 77(2): 365–370.
29. Masters G A, Johnson D H, Temin S. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Oncol Pract, 2016, 12(1): 90–93.
30. Komiya T, Ravindra N, Powell E. Role of Immunotherapy in Stage IV Large Cell Neuroendocrine Carcinoma of the Lung. Asian Pac J Cancer Prev, 2021, 22(2): 365–370.
31. De Pas T M, Giovannini M, Manzotti M, Trifiro G, Toffalorio F, Catania C, Spaggiari L, Labianca R, Barberis M. Large-cell neuroendocrine carcinoma of the lung harboring EGFR mutation and responding to gefitinib. J Clin Oncol, 2011, 29(34): e819-e822.
32. Fasano M, Della C C, Papaccio F, Ciardiello F, Morgillo F. Pulmonary Large-Cell Neuroendocrine Carcinoma: From Epidemiology to Therapy. J Thorac Oncol, 2015, 10(8): 1133–1141.
33. Lo R G, Pusceddu S, Proto C, Macerelli M, Signorelli D, Vitali M, Ganzinelli M, Gallucci R, Zilembo N, Platania M, Buzzoni R, de Braud F, Garassino M C. Treatment of lung large cell neuroendocrine carcinoma. Tumour Biol, 2016, 37(6): 7047–7057.
34. Naidoo J, Santos-Zabala M L, Iyriboz T, Woo K M, Sima C S, Fiore J J, Kris M G, Riely G J, Lito P, Iqbal A, Veach S, Smith-Marrone S, Sarkaria I S, Krug L M, Rudin C M, Travis W D, Rekhtman N, Pietanza M C. Large Cell Neuroendocrine Carcinoma of the Lung: Clinico-Pathologic Features, Treatment, and Outcomes. Clin Lung Cancer, 2016, 17(5): e121-e129.
35. Conte B, George B, Overman M, Estrella J, Jiang Z Q, Mehrvarz S A, Ferrarotto R, Hoff P M, Rashid A, Yao J C, Kopetz S, Dasari A. High-Grade Neuroendocrine Colorectal Carcinomas: A Retrospective Study of 100 Patients. Clin Colorectal Cancer, 2016, 15(2): e1-e7.
36. Smith J D, Reidy D L, Goodman K A, Shia J, Nash G M. A retrospective review of 126 high-grade neuroendocrine carcinomas of the colon and rectum. Ann Surg Oncol, 2014, 21(9): 2956–2962.
37. Heetfeld M, Chougnet C N, Olsen I H, Rinke A, Borbath I, Crespo G, Barriuso J, Pavel M, O'Toole D, Walter T. Characteristics and treatment of patients with G3 gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer, 2015, 22(4): 657–664.
38. Garcia-Carbonero R, Rinke A, Valle J W, Fazio N, Caplin M, Gorbounova V, O C J, Eriksson B, Sorbye H, Kulke M, Chen J, Falkerby J, Costa F, de Herder W, Lombard-Bohas C, Pavel M. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms. Systemic Therapy 2: Chemotherapy. Neuroendocrinology, 2017, 105(3): 281–294.
39. Galleberg R B, Knigge U, Tiensuu J E, Vestermark L W, Haugvik S P, Ladekarl M, Langer S W, Gronbaek H, Osterlund P, Hjortland G O, Assmus J, Tang L, Perren A, Sorbye H. Results after surgical treatment

of liver metastases in patients with high-grade gastroenteropancreatic neuroendocrine carcinomas. Eur J Surg Oncol, 2017, 43(9): 1682–1689.

40. Lokesh K N, Anand A, Lakshmaiah K C, Babu K G, Lokanatha D, Jacob L A, Babu M, Rudresha A H, Rajeev L K, Saldanha S C, Giri G V, Panwar D, Koppaka D, Patidar R. Clinical profile and treatment outcomes of metastatic neuroendocrine carcinoma: A single institution experience. South Asian J Cancer, 2018, 7(3): 207–209.
41. Yucel B, Babacan N A, Kacan T, Eren A A, Eren M F, Bahar S, Celasun M G, Seker M M, Hasbek Z. Survival analysis and prognostic factors for neuroendocrine tumors in Turkey. Asian Pac J Cancer Prev, 2014, 14(11): 6687–6692.
42. Janson E T, Holmberg L, Stridsberg M, Eriksson B, Theodorsson E, Wilander E, Oberg K. Carcinoid tumors: analysis of prognostic factors and survival in 301 patients from a referral center. Ann Oncol, 1997, 8(7): 685–690.
43. Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, Delle F G, Panzuto F, Scarpa A, Falconi M. Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. Ann Oncol, 2008, 19(5): 903–908.
44. Kouvaraki M A, Ajani J A, Hoff P, Wolff R, Evans D B, Lozano R, Yao J C. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol, 2004, 22(23): 4762–4771.
45. Madeira I, Terris B, Voss M, Denys A, Sauvanet A, Flejou J F, Vilgrain V, Belghiti J, Bernades P, Ruszniewski P. Prognostic factors in patients with endocrine tumours of the duodenopancreatic area. Gut, 1998, 43(3): 422–427.
46. Qi J, Xu L, Sun J, Wang X, Zhao L. Thoracic Radiotherapy Benefits Elderly Extensive-Stage Small Cell Lung Cancer Patients with Distant Metastasis. Cancer Manag Res, 2019, 11: 10767–10775.
47. Zhao D S, Valdivia A Y, Li Y, Blaufox M D. 18F-fluorodeoxyglucose positron emission tomography in small-cell lung cancer. Semin Nucl Med, 2002, 32(4): 272–275.

Figures

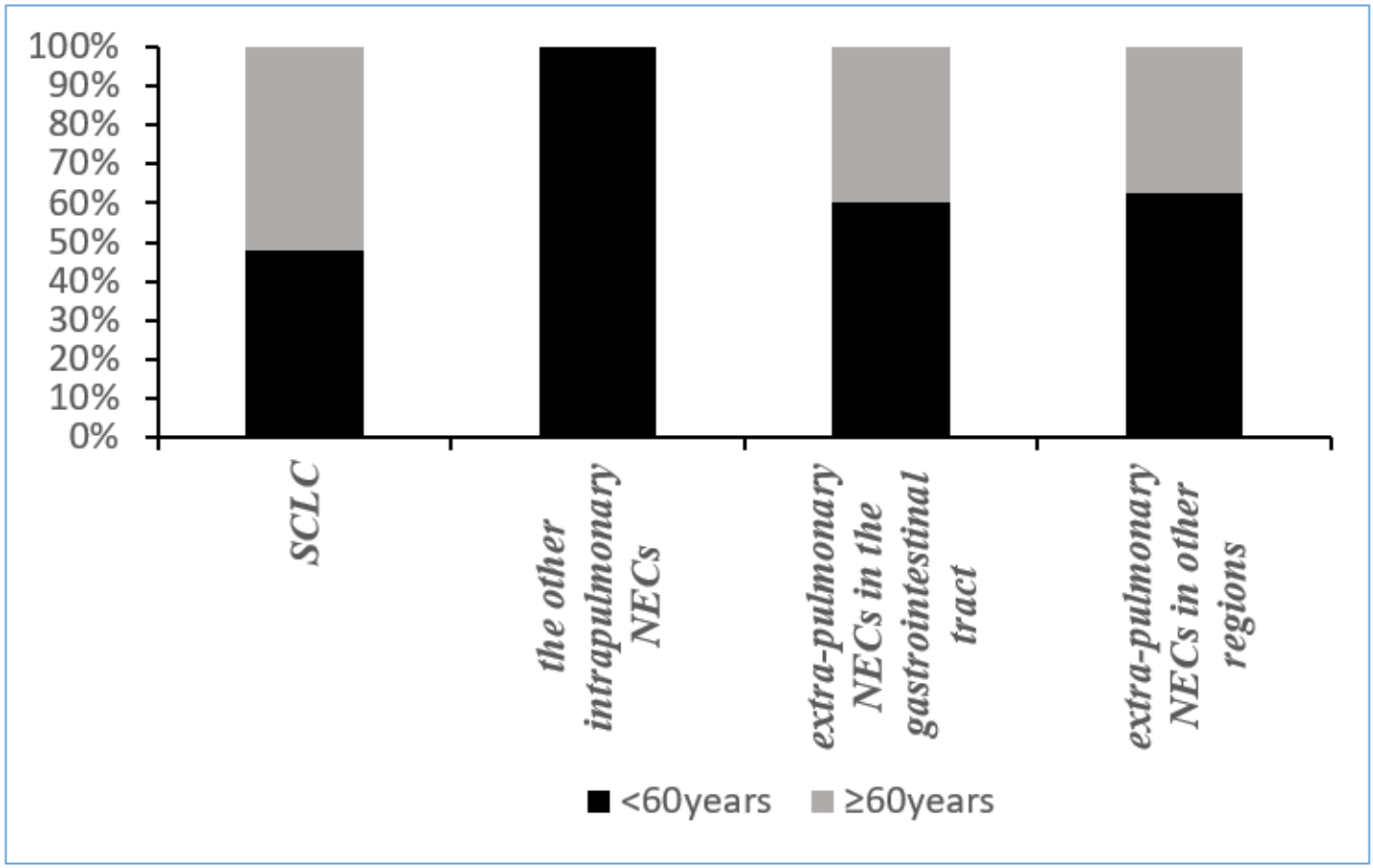

Figure 1

Distribution of 123 NECs patients < 60 years old and ≥ 60 years old

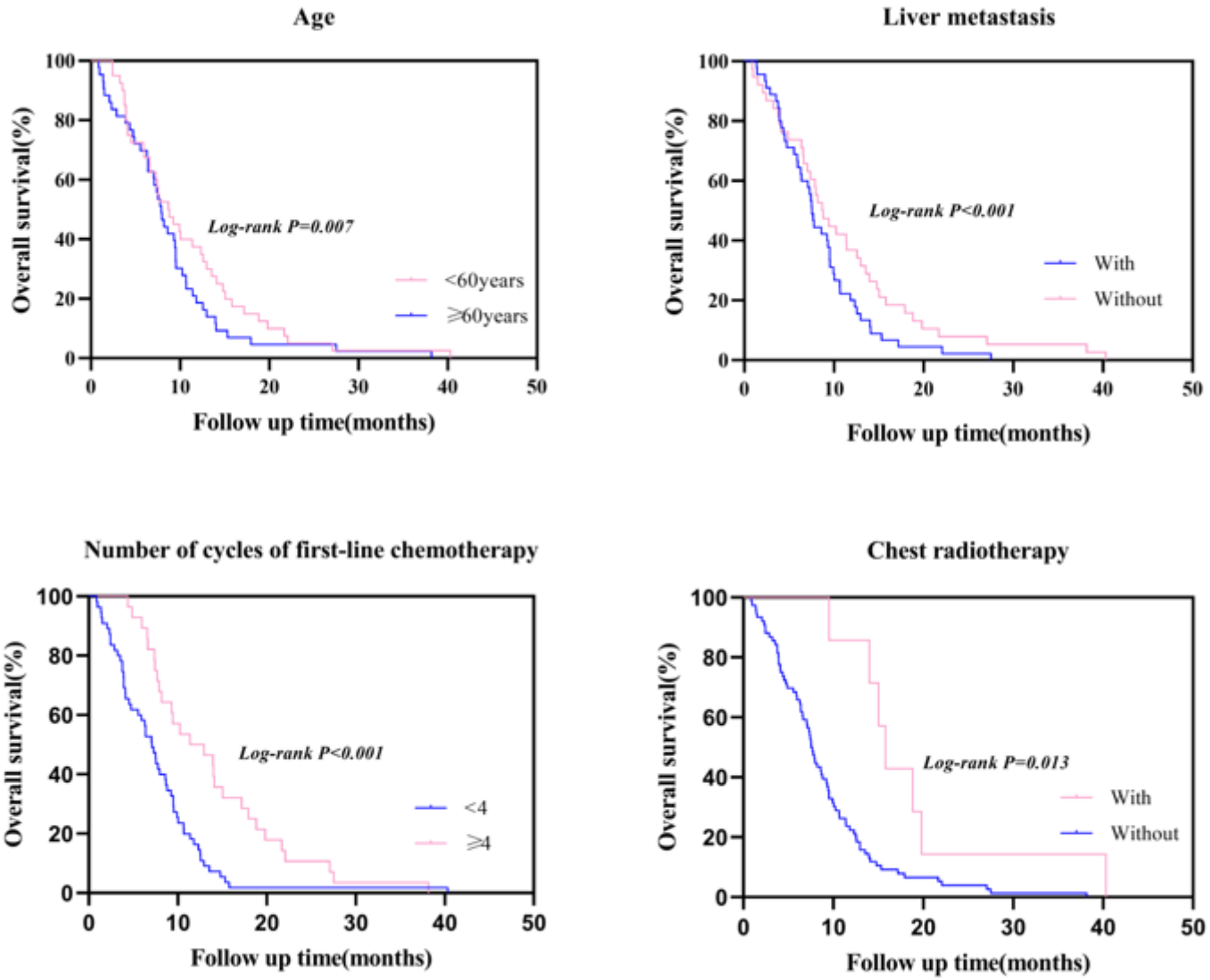

Figure 2

Effects of age, liver metastasis, number of cycles of first-line chemotherapy, and chest radiotherapy on OS in patients with NECs