RESEARCH ARTICLE

Analysis on the Characteristics and Prognosis of Pulmonary Neuroendocrine Tumors

Bai-Shou Wu[1], Yi Hu[1]*, Jing Sun[1], Jin-Liang Wang[1], Peng Wang[2], Wei-Wei Dong[1], Hai-Tao Tao[1], Wen-Juan Gao[1]

Abstract

Objective: To retrospectively review the clinical characteristics and analyze the prognostic factors of Chinese patients with pulmonary neuroendocrine tumors. Materials and Methods: The clinical data of 176 patients with pulmonary neuroendocrine tumors in Chinese PLA General Hospital from Mar., 2000 to Oct., 2012 were retrospectively analyzed. The parameters were evaluated by univariate and multivariate analysis, including the gender, age, smoking history, family history, TNM staging, localization (central or peripheral), tumor size, nodal status, histological subtype and treatment (operation or non-operation). Results: There were 23 patients with typical carcinoids (TC) (13.1%), 41 with atypical carcinoids (AC) (23.3%), 10 with large cell neuroendocrine carcinoma (LCNEC) (5.7%) and 102 with small cell lung cancer (SCLC) (57.9%). The median follow-up time was 64.5 months for AC, 38 months for LCNEC and 27 months for SCLC. The typical carcinoid censored data was 18 (more than 50% of the patients), so the median follow-up time was not obtained, and actuarial 5-year survivals for TC, AC, LCNEC and SCLC were 75.1%, 51.7%, 26.7% and 38.8%, respectively. COX univariate analysis revealed that the age (*P*=0.001), histological subtype (*P*=0.005), nodal status (*P*=0.000), treatment (*P*=0.000) and TNM staging (*P*=0.000) were the prognostic factors of the patients with pulmonary neuroendocrine tumors, whereas its multivariate analysis showed that only the age(*P*=0.001), TNM staging (*P*=0.002) and treatment (*P*=0.000) were independent prognostic factors. Conclusions: Radical surgery remains the treatment of choice, and is the only curative option. The age, TNM staging and treatment are confirmed to be the independent prognostic factors in multivariable models for pulmonary neuroendocrine tumors.

Keywords: Neuroendocrine tumors - carcinoid - prognosis - small cell lung cancer - large cell neuroendocrine carcinoma

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Introduction

Pulmonary neuroendocrine tumors (NET) arise from Kulchitzky cells that are normally present in the bronchial mucosa, which share morphological, ultrastructural, immunohistochemical and molecular characteristics. NET account for 25% of primary lung neoplasms, with the remaining 75% of non-small cell lung cancer (NSCLC) and a few rare tumors (Bertino et al., 2009; Rekhtman 2010; Travis 2010). The clinical behavior of these neoplasms greatly depends on their histological differentiation. Classification of pulmonary NET is a difficult problem due to many different terms and criteria which have been used over the years. The classification on pulmonary NEC made by World Health Organization (WHO) in 2004 mainly includes typical carcinoids (TC), atypical carcinoids (AC), large cell neuroendocrine carcinoma (LCNEC) and small cell lung cancer (SCLC) (Travis et al., 2004), in which SCLC (20%) is the most commonly one, then LCNEC (3%), TC (2%) and AC (0.2%).

According to the grades of biological aggressiveness (G1-G3) and differentiated degrees (well-differentiated or poorly-differentiated), both TC (G1) and AC (G2) belong to well-differentiated neoplasms, while LCNEC and SCLC (G3) to poorly-differentiated ones (Gridelli et al., 2013). Some scholars reported that the 5-year survival rate for TC was more than 87% (Thomas et al., 2001; Travis et al., 1998). Likewise, the 5-year survival for AC was about 60% (Beasley et al., 2000). It is well known that the prognosis for SCLC is very poor. Typical survival is still measured in months, and the 5-year survival is less than 5% (Merrill et al., 1999). The prognosis associated with LCNEC is less well defined. LCNEC is a highly aggressive disease, but the 5-year survival rate has been reported to be 15%~57% (Lyoda et al., 2007). TC has been considered to be a sort of 'benign' tumor for several decades (Detterbeck 2010), but they may actually present with lymph node metastasis or spread, even if rarely. It still exists controversy regarding the independent prognostic factors for overall survival (OS). Several authors pointed out that lymph node involvement, histology and tumor size

*[1]First Department of Medical Oncology, Chinese PLA General Hospital, Beijing, [2]Department of Oncology, Qufu People's Hospital, Qufu, China *For correspondence: huyi040@aliyun.com*

Table 1. The Baseline Characteristics of Patients [n(%)]

Histological subtype	Total (n=176)	TC 23 (13.1)	AC 41 (23.3)	LCNEC 10(5.7)	SCLC 102(57.9)
Gender					
Male	133(75.6)	12(52.2)	33(80.5)	10(100)	78(76.5)
Female	43(24.4)	11(47.8)	8(19.5)	0(0)	24(23.5)
Age (median, IQR)	(56, 14)	(47, 12)	(59, 17)	(54.5, 17.5)	(55.5, 12.5)
Range	26~79	26~74	35~75	48~79	39~79
Smoking history					
Smoking	105(59.7)	9(39.1)	28(68.3)	6(60.0)	62(60.8)
No smoking	71(40.3)	14(60.9)	13(31.7)	4(40.0)	40(39.2)
Family history					
Yes	18(10.2)	1(4.3)	6(14.6)	1(10.0)	10(9.8)
No	158(89.8)	22(95.7)	35(85.4)	9(90.0)	92(90.2)
Localization					
Central	89(50.6)	11(47.8)	14(34.1)	2(20.0)	62(60.8)
Peripheral	87(49.4)	12(52.2)	27(65.9)	8(80.0)	40(39.2)
Tumor size					
>3cm	94(53.4)	3(13.0)	24(58.5)	7(70.0)	61(59.8)
≤3cm	82(46.6)	20(87.0)	17(41.5)	3(30.0)	41(40.2)
Nodal status					
N0	82(46.6)	22(95.7)	29(70.7)	4(40.0)	27(26.5)
N1-3	94(53.4)	1(4.3)	12(29.3)	6(60.0)	75(73.5)
Treatment					
Operation	111(63.1)	20(87.0)	37(90.2)	7(70.0)	47(46.1)
Non-operation	65(36.9)	3(13.0)	4(9.8)	3(30.0)	55(53.9)
7th AJCC staging					
I	53(30.1)	17(73.9)	21(51.2)	2(20.0)	13(12.8)
II	45(25.5)	4(17.4)	13(31.7)	3(30.0)	25(24.5)
III	58(33.0)	0(0.0)	5(12.2)	4(40.0)	49(48.0)
IV	20(11.4)	2(8.7)	2(4.9)	1(10.0)	15(14.7)

were the important and independent factors influencing the prognosis (Lim et al., 2005; Asamura et al., 2006; Filosso et al., 2013). The aim of this study was to describe the clinical characteristics and independent prognostic factors of Chinese patients with pulmonary NET.

Materials and Methods

Patients

The clinical data of 176 patients with pulmonary NET in Chinese PLA General Hospital from Mar., 2000 to Oct., 2012 were retrospectively analyzed. Inclusion criteria: All the patients were diagnosed and treated for the first time; Pathologic diagnosis was confirmed by different methods, such as flexible fiberoptic bronchoscopy, CT-guided percutaneous transthoracic needle biopsy, ultrasound-guided lung biopsy, thoracotomy biopsy, ultrasound-guided lymph biopsy, mediastinoscopy-guided lymph node biopsy and surgical specimens; Clinical and pathological data were detailed; All patients received electrocardiogram, lung functional test, chest X-ray, CT, magnetic resonance and positron emission tomography (PET) if clinically required at the time of diagnosis; Outcome data could be obtained from hospital records, ambulatory controls or telephone interviews. Exclusion criteria: presence of cardiovascular and cerebrovascular diseases; combined with other types of malignant tumors, or mixed (neuroendocrine and nonneuroendocrine) histology and other life-threatening diseases like severe liver failure.

All the enrolled patients signed a informed consent and the experimental protocol was approved by the ethical committee of PLA General Hospital.

Table 2. Present Symptoms [n(%)]

Cough	111(63.1)
Hemoptysis	47(26.7)
Chest Pain	24(13.6)
Dyspnea	28(15.9)
Fever	11(6.3)
Headache	4(2.3)
Lambert-Eaton myasthenic syndrome	1(0.6)

Diagnosis and staging

For the present study, at least two expert pathologists reviewed all the hematoxylin-eosin stained slides of formalin-fixed and paraffin-embedded tissue sections and achieved a definitive diagnosis of NET, including its differentiation in TC, AC, LCNEC and SCLC. The histological diagnosis was established according to the criteria proposed by Arrigoni and modified by Travis (Travis, 2010). In this study, in order to compare the clinical, pathological and prognostic differences between different types of pulmonary NET, we used the 7th edition of American Joint Committee On Cancer/Union For International Cancer Control (AJCC/UICC) TNM staging system (Edge et al., 2010). The reason for applying the TNM staging system was chiefly on the basis of two large-scale surveys on carcinoid tumors and SCLC from International Associational Association for the Study of Lung Cancer (IASLC) database (Travis et al., 2008; Vallieres et al., 2009). OS was the main endpoint of this study. The starting point was defined as the pathological diagnosis data and the endpoint was defined as the data of death. Patients alive at the last follow-up were censored.

Statistical analysis

Data was analyzed statistically using SPSS13. 0 (IBM, Armonk, NY, USA). Categorical data was presented as frequency (%) and continuous data as median inter-quartile rang (IQR)). Survival was estimated according to the Kaplan-Meier method. The log-rank test was used to compare the difference between the survival curves. Univariable and multivariable analyses were performed by Cox proportional hazard model to investigate the relative importance of different prognostic factors. The parameters evaluated included the gender, age, smoking history, family history, TNM staging, localization (central or peripheral), tumor size, nodal status, histological subtype and treatment. A *P*-value lower than 0.05 was considered statistically significant.

Results

Clinical features and histological classification

Of the 176 consecutive patients, there were 133 males (75.6%) and 43 (24.4%) females with a median age of 56 (rang 26~79). The characteristics of patients in this group were listed (Table 1). There were 89 patients centrally located as well as 87 ones were classified as peripheral according to fiberoptic bronchoscopy and/or radiological evaluation. The major symptoms were cough, hemoptysis, chest pain and dyspnea (Table 2). The median duration of presenting symptoms to diagnosis was 1.5 months (range 0.5~84).

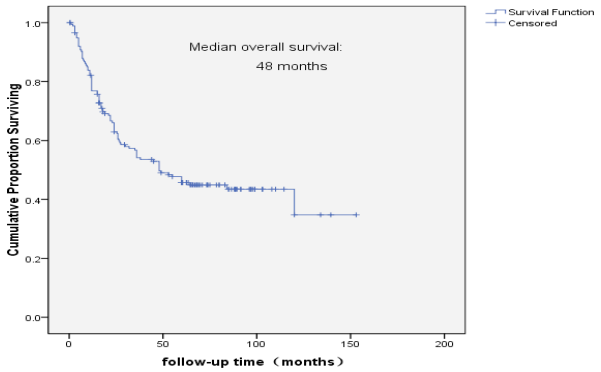

Figure 1. OS of the 176 Patients

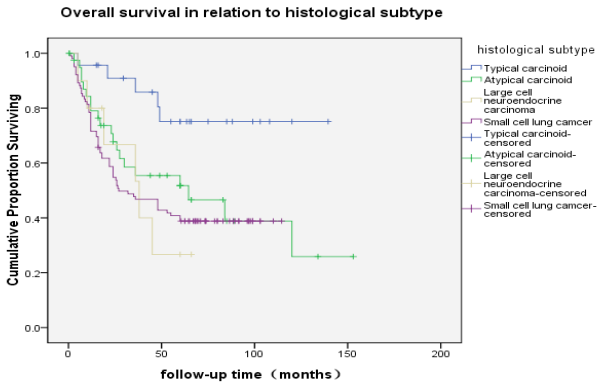

Figure 2. Survival Curves of Different Histologic Groups by Kaplan-Meier Survival and Log-rank Test

All patients were divided into TC (n=23), AC (n=41), LCNEC (n=10) and SCLC (n=102) according to WHO classification in 2004. The median age for TC, AC, LCNEC and SCLC were 47, 59, 54 and 55.5, respectively. There were 12 males and 11 females for TC (M:F=1.1:1). However, AC, LCNEC and SCLC occurred mainly in males (M:F=4.1:1, 10:0 and 3.3:1). The smoking rates were 68.3%, 60.0% and 60.8 for AC, LCNEC and SCLC. On the contrary, only 39.1% of the patients with TC were smokers. The median tumor size was 3.48 cm in this group. There were 94 cases with tumor size greater than 3 cm. The cut-off of 3 cm in tumor size was adopted on the basis of the reports by other authors (Costes et al., 1995; Carretta et al., 2000). Only one paraneoplastic syndrome was observed (Lambert-Eaton myasthenic syndrome). Finally, 11 patients were diagnosed by CT-guided percutaneous transthoracic needle biopsy, 38 by flexible fiberoptic bronchoscopy, 3 by ultrasound guided lung biopsy, 3 by thoracotomy biopsy, 7 by ultrasound-guided lymph biopsy, 3 by mediastinoscopy-guided lymph node biopsy and 111 by surgical specimens.

Surgical and conservative treatment

There were 111 patients undergoing surgical treatment. Surgical types included lobectomy (n=85, 76.6%), pneumonectomy (n=19, 17.1%), segmentectomy (n=3, 2.7%) and wedge resection (n=4, 3.6%). Sixty-one patients received conservative treatment, such as chemotherapy and/or radiotherapy. The other 4 patients did not reveive any treatment.

OS analysis

At the final cutoff date (Nov. 27, 2013), 93 patients died (5 TC, 20 AC, 6 LCNEC and 62 SCLCs). The median follow-up time was 48 months (Figure 1).

Table 3. Univariable Analysis on Prognostic Factors of Patients

Covariates	RR	95%CI	*P*
Sex (male vs. female)	1.41	0.85~2.34	0.180
Age (≥56 vs.<56)	2.12	1.39~3.23	0.001
Smoking history	1.36	0.88~2.08	0.164
Family history (yes vs no)	0.89	0.43~1.84	0.749
(smoking vs. non-smoking)			
Localization (central vs. peripheral)	0.99	0.66~1.50	0.989
Tumor size (>3cm vs. ≤3 cm)	1.45	0.95~2.20	0.082
Nodal status (N0 vs. N1-3)	2.47	1.60~3.82	0.000
Treatment (operation vs. non-operation)	0.22	0.15~0.34	0.000
7th AJCC staging (I vs. II+III+IV)	3.83	2.13~6.89	0.000
Histological subtype	3.61	1.47~8.91	0.005
(TC vs. AC+LCNEC+SCLC)			

The median follow-up time in 41 patients treated for AC was 64.5 months, in which most of them (n=37, 90.2%) received the operation, and the median survival time was 84 months. Four cases in this group diagnosed with AC received chemotherapy and/or radiotherapy, whose median survival time was only 8 months. The difference showed statistical significance (*P*=0.004). As to LCNEC, the median survival time was 38 months, in which 7 patients were operated, and the median survival time was 45 months. The other 3 received chemotherapy and/or radiotherapy, and their median survival time was 10 months. Similarly, the prognosis was showed significant difference (*P*=0.011). There were 111 cases diagnosed with SCLC, the median survival time was 27 months, in which 47 were treated by operation. However, 31 surgical patients (66%) were censored. The mean survival time was 83 months. The majority of 55 patients with SCLCs received conservative treatment, in which 52 received chemotherapy and/or radiotherapy, and 3 did not receive any treatment. Their mean survival time was 29 months. The difference had statistical significance regarding the prognosis between the operation and non-operation groups (*P*=0.000). The majority of patients with TC were censored, so the median follow-up time was not obtained. The mean survival time was 113 months. Twenty patients in this group underwent the operation, and the mean survival time was 128 months. Two patients received chemotherapy and the remaining one underwent no treatment. The mean follow-up time of 3 cases was 21 months. The overall 5-year survival rate was 45.7%. The 5-year survival rates for TC, AC, LCNEC and SCLC were 75.1%, 51.7%, 26.7% and 38.8%, respectively. The survival curve relevant to the histological subtype was shown in Figure 2. The prognosis of patients with TC was significantly better than those with AC (*P*=0.017), LCNEC (*P*=0.006) and SCLC (*P*=0.003). However, there was no significant difference between the survival of patients with LCNEC and SCLC (*P*=0.865).

Analysis on the prognostic factors

In order to investigate the prognostic factors of deaths, the impacts of gender, age, smoking history, family history, TNM staging, localization (central or peripheral), tumor size, nodal status, histological subtype and treatment (operation or non-operation) were analyzed. The

Table 4. Multivariable Analysis on Prognostic Factors of Patients

Covariates	RR	95%CI	*P*
Age (≥56 vs.<56)	2.12	1.39~3.23	0.001
Treatment (operation vs. non-operation)	0.22	0.15~0.34	0.000
7th AJCC staging (I vs. II+III+IV)	3.83	2.13~6.89	0.000

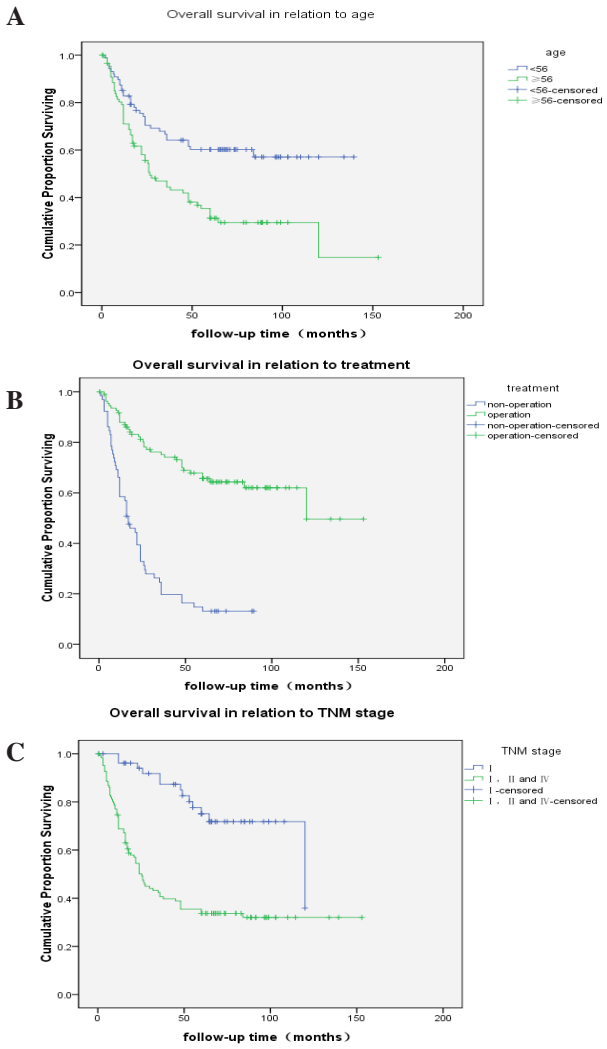

Figure 3. Kaplan-Meier Survival and Log-rank Test According to (A) Age, (B) Treatment and (C) TNM Staging

univariable analysis emphasized that nodal status (N1-3, *P*=0.000), increasing age (*P*=0.001), histological subtype (AC, LCNEC and SCLC vs. TC, *P*=0.005), treatment (non-operation, *P*=0.000) and TNM staging (II, III and IV vs. I, *P*=0.000) were negatively associated with prognosric factors (Table 3).

The multivariable analysis showed that the age, TNM staging and treatment were confirmed to be the independent prognostic factors. The specific statistical results were as follows: age (≥56 vs. <56, RR 1.99; 95% CI: 1.30~3.05, *P*=0.001), TNM staging (II, III and IV vs.I, RR 2.55; 95% CI: 1.39~4.67, *P*=0.002), treatment (operation vs. non-operation, RR 0.268; 95% CI: 0.17~0.42, *P*=0.000) (Table 4). The survival curves relevant to each independent prognostic factor was shown in Figure 3 (A~C).

Discussion

Pulmonary NET could be clinically, radiologically, and pathologically classified into four subtypes: TC, AC, LCNEC and SCLC (Haghighi et al., 2012; Liu et al., 2013; Yucel et al., 2013; Zahir et al., 2013; Zeng et al., 2013). They represent a specific group of tumors with heterogeneous histological patterns and clinical behaviors. TC belongs to relatively indolent well-differentiated tumors, with locally invasion but seldom distant metastases. Contrary to TC, AC, LCNEC and SCLC are highly aggressive and may frequently develop metastases.

In this study, the data of 176 patients with pulmonary NET from Chinese PLA General Hospital were retrospectively analyzed. The results showed that there were significant differences in patient characteristics between low and intermediate-grade (TC and AC) and high-grade (LCNEC and SCLC) NET. In fact, TC showed a very favorable clinical behavior and survival; AC was more aggressive compared with TC; By contrast, LCNEC and SCLC were poorly differentiated and highly aggressive neoplasms.

TC tends to occur in the young, with the median age of 47. In contrast, AC, LCNEC and SCLC tend to occur in older patients, with the respective median age of 59, 54.5 and 55.5. Only 39.1% of the patients with TC were smokers. The smoking rates of AC, LCNEC and SCLC were 68.3%, 60% and 60.8%, respectively. As far as 176 cases were concerned, they tended to occur in the males. For TC, AC, LCNEC and SCLC, the male proportions were 52.2%, 80.5%, 100% and 76.5%. These results were fairly comparable to the results of a recent large-scale multi-institute study by Asamura et al (Asamura et al., 2006). The general present symptoms of these patients included cough (63.1%), hemoptysis (26.7%), dyspnea (15.9%), chest pain (13.6%), fever (6.3%) and headache (2.3%). However, 45 ones were asymptomatic, which was described in the literature (Chong et al., 2006). Some scholars reported that less than 2% of patients with lung carcinoids were associated with hypersecretion, such as carcinoid syndrome (McCaughan et al., 1985). On the other hand, ectopic hormone production and paraneoplastic syndromes were frequent in SCLC (Rekhtman et al., 2010). In this study, paraneoplastic syndrome (Lambert-Eaton myasthenic syndrome) was observed only in one case diagnosed with SCLC.

Survival analysis revealed that the survival of patients with TC was generally good, significantly better than that of AC (*P*=0.017), LCNEC (*P*=0.006) and SCLC (*P*=0.003). The survival curve of AC was between those of TC and high-grade NET (LCNEC and SCLC). However, no significant difference was observed in survivals between LCNEC and SCLC (*P*=0.865). In this study, actuarial 5-year survivals for TC, AC, LCNEC and SCLC were 75.1%, 51.7%, 26.7% and 38.8%, respectively, very similar to the data reported in the literature (Asamura et al., 2006; Yeh et al., 2014). Garcia-Yuste had reported that the 5-year survival rate for LCNEC and SCLC were 21% and 14% (Garcia-Yuste et al., 2000), while Travis had observed that it was 27% and 9% for LCNEC and SCLC (Travis et al., 1998). Hence, it can been seen that the survivals

of patients with LCNEC and SCLC were slightly better.

Different from the previous reports (Fink et al., 2001; Ferguson et al., 2002; Filosso et al., 2002; Cardillo et al., 2004), the histological subtype did not provide the accurate prediction of prognosis according to multivariate analysis. The results in this study revealed that age, TNM staging and treatment were confirmed to be independent prognostic factors that conditioned the long-term survival. To our knowledge, only a few articles reported that age was the independent prognostic factors for pulmonary NET (Filosso et al., 2014), which was likely attributable to the good immunity and resistance to the illness of young patients. TNM staging was also effective in predicting the outcome of pulmonary NET, similar to what Vallieres E reported (Vallieres et al., 2009) However, it was strange that nodal status did not predict the prognosis. A previous report showed that lymph node sampling might be inaccurate in evaluating the nodal status (Massard et al., 2006). Only 63.1% of patients in this study underwent the systemic nodal dissection, so it might underestimate the N stage. As expected, the treatment (operation or non-operation) was an independent prognostic factor that influenced the survival of patients. Until now, only a few articles discussed the clinical treatment outcomes of NET (Lim et al., 2005; Asamura et al., 2006), and many scholars just cared about TC outcomes alone (Ferolla et al., 2009; Naalsund et al., 2011). In this study, there were 111 patients undergoing the surgical treatment, and the survival in operation group was significantly better than in non-operation group (P=0.000), suggesting that surgery is the cornerstone in the treatment of pulmonary NET.

In conclusion, radical surgery remains the treatment of choice, and is the only curative option for patients with pulmonary NET. The age, TNM staging and treatment are confirmed to be the independent prognostic factors in the multivariable models for pulmonary NET. Until now, there still lacks of information about pulmonary NET, and the majority of studies are based on single-center experiences. Hence, more evidence-based guidelines for the treatment need to be further substantiated in large-scale multicenter trials.

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