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ORIGINAL ARTICLE

Clinical characteristics of the mixed form of neuroendocrine tumor in the lung: A retrospective study in 2501 lung cancer cases

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Abstract

Background: A neuroendocrine tumor (NET) is a special kind of epithelial tumor with predominant neuroendocrine differentiation, which arises throughout the body, including the lung. A subpopulation of lung cancer patients suffer from the mixed (combined) form of NET with components of non-neuroendocrine carcinoma. However, the clinical characteristics of the mixed form of NET are not well established.

Methods: We analyzed 2501 consecutive cases of primary lung cancer from 2009 to 2011. The diagnosis, histology, therapy, and outcome were collected.

Results: A total of 22 patients were enrolled. The occurrence rate of lung cancer was 0.9%. Neither gender (1.2% and 0.3% for male and female, respectively, $P = 0.35$) nor age (0.6% and 1.3% for patients aged ≤60 and >60, respectively, $P = 0.13$) was associated with the onset of this disease; however it has become more frequent in recent years (0.6% and 1.6% at the time ≤ and >2010 respectively, $P = 0.03$). This cohort of 22 patients had a median survival of 60.0 months (95% confidence interval: 14.3–105.6 months). Patients with metastatic disease (60 months and not reached [NR], $P = 0.18$) or a small-cell lung cancer component tended to have a shorter survival (35 months and NR, $P = 0.16$). Patients who underwent surgery had a significantly longer survival period (NR and 17.0 months, $P = 0.001$).

Conclusions: A mixed form of NET in the lung is a rare disease. While stage and histology might influence prognosis, surgery is the critical factor for long-term survival.

Introduction

Neuroendocrine tumors (NETs) are a special kind of epithelial tumor with predominant neuroendocrine differentiation.[1] They are considered an uncommon disease, with incidence estimated at 2.5 to five per 100 000 people per year. A common feature of NETs is that they produce and often release biogenic amines and polypeptide hormones.[2] NETs comprise a broad family of tumors, the most common of which are carcinoids and pancreatic NETs. They can be found throughout the body, including the lung, but usually occur in the gastrointestinal tract.[3,4]

Lung NETs comprise a special subgroup of lung cancer. From a pathological point of view, a lung NET is further divided into carcinoid, atypical carcinoid, large cell neuroendocrine cancer, and small-cell lung cancer (SCLC). A mixed (combined) form of NET with components of non-neuroendocrine carcinoma is also recognized. The most prominent form is combined SCLC, where components of SCLC and other pathological types are observed in the same tumor tissue.[5]

Ample reports on NETs are available in the literature, however, the majority detail pancreatic or gastrointestinal NETs.[2,3] Although lung NETs constitute approximately 30% of NETs,[4] they are generally overlooked. The mixed form of NET in the lung is rarely discussed, and to the best of our knowledge, mere case reports are available.[6,7] In this report, we conducted a retrospective study to analyze the clinical

features, occurrence, treatment, and prognosis of these patients.

Methods

Patients

From 1 January 2009 to 31 December 2011, data from all inpatients with lung cancer seen in the West China Hospital were reviewed and screened via the Hospital Information System. All demographic baselines and treatments were recorded in a pre-established lung cancer database, an infrastructure of the National Major Project of China (2011ZX09302-001-01). During this period, all patients with a mixed form of NET in the lung were enrolled, including both newly diagnosed and recurrent patients. A designated member followed eligible patients every six months. The ethical committee of Sichuan University reviewed the study concept. The study complied with the Declaration of Helsinki.

Pathological and treatment definition

A pathological classification of lung cancer was made according to the World Health Organization 2004 revision. Diagnoses involving adenocarcinoma were made according to the International Multidisciplinary Classification.[8] Tumor staging was performed according to the 7th edition of the Tumor Node Metastasis (TNM) classification of malignant tumors.[9]

There is currently no consensus on the criteria of the mixed form of NET in the lung. We adapted our criteria from the definition of the mixed form of NET, that is, NET with components of non-NET carcinoma. If the main component (the principle pathological diagnosis) is non-NET, the tumor must have an NET fraction. If the main component is NET, the tumor must contain a non-NET component. Combined SCLC is exemplified as a special subgroup because it is more frequently seen in clinical practice. Patients were considered to be eligible if they belonged to one of the following categories: (i) any pathological type of NSCLC excluding carcinoid, atypical carcinoid, or large-cell neuroendocrine carcinoma, either intermingled with neuroendocrine components, or with partial neuroendocrine differentiation; (ii) pathological types of carcinoid, atypical carcinoid, or large-cell neuroendocrine carcinoma, mixed with other types of NSCLC, such as squamous carcinoma or adenocarcinoma; or (iii) combined SCLC.

The clinician who cared for the patient assessed the objective response. The assessment was based on the Response Evaluation Criteria of Solid Tumors version 1.0 at the time of evaluation.[10] Overall survival (OS) was defined as the time interval between diagnosis and death from any cause.

Statistical analysis

The chi-square test was used for statistical analysis of categorized data. For survival comparison, a Kaplan-Meier analysis was used. For quantitative data, *t* tests were used. All statistical analyses were performed using SPSS 19.0 software (IBM inc., Chicago, IL), and statistical significance was defined as a *P*-value <0.05.

Results

Rate of the mixed form of neuroendocrine tumors (NETs) in the lung

From 1 January 2009 to 31 December 2011, the records of 2501 consecutive lung cancer inpatients were screened. A retrieving strategy, as depicted in Figure 1, was adopted and a total of 22 patients (0.9%) were enrolled. The patient list and demographic features are provided in Table 1 and in the supplementary material (Table S1). A pathologist confirmed the diagnoses of all eligible patients. A typical pathological view of the mixed form of NET is provided in Figure 2.

Onset of the mixed form NET

The rates of the mixed form of NET in men (1.2%) and women (0.3%) with lung cancer were similar ($P = 0.35$). There was no significant difference in the rates between patients aged ≤ (0.6%) and > (1.3%) 60 years (*P* 0.13). The only factor that had significance was the time of diagnosis. There were fewer patients diagnosed (0.6%) during the period of 2009 to 2010 than in 2011 (1.6%, $P = 0.03$, Table 2).

Treatments

Patients received surgery (68.2%, 15/22) and chemotherapy (95.5%, 21/22). Additionally, 27.2% (6/22) patients received palliative ($n = 3$) or definitive ($n = 3$) radiotherapy. The dose for the definitive radiotherapy varied from 15 Gy/5f, 50 Gy/25f, and 56 Gy/28. SCLC (etoposide with platinum, $n = 5$) and NSCLC regimens (the third-generation of cytotoxic agents either alone or in combination with platinum, $n = 16$) of chemotherapy were used.

Patient Survival

The whole cohort of patients had a median survival of 60.0 months (95% confidence interval [CI]: 14.3–105.6 months, Fig 3a) and 31.8% (7/22) of patients died. Patients with metastatic diseases ($n = 12$) had a shorter survival (60 months, 95%: 25.4–94.5 months) than those with phase I-III diseases ($n = 10$, OS not reached [NR]), but there was no statistical significance in the difference ($P = 0.18$, Fig 3b). Patients

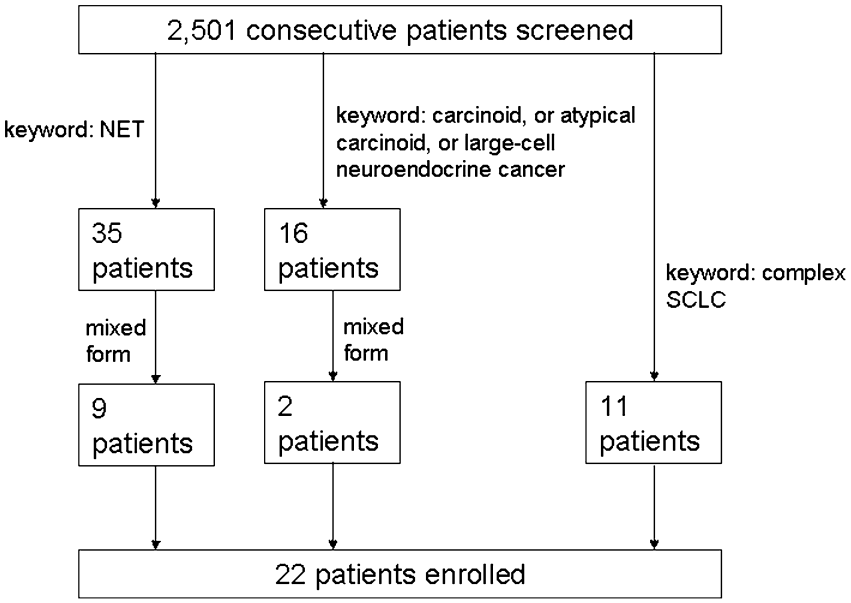

Figure 1 Schematic depiction of retrieval strategy. Among 35 patients who were found using the key words "neuroendocrine tumor," nine had a mixed form of neuroendocrine tumor (NET). Another cohort of 16 patients was obtained by searching the database with the key words "carcinoid," "atypical carcinoid," or "large-cell neuroendocrine carcinoma," and two were found to suffer from a mixed form of NET. Finally, 11 patients with combined small cell lung cancer (SCLC) were found by manually searching the database. A total of 22 patients were enrolled in the current study.

harboring SCLC ($n = 11$) components lived for shorter period (35 months, 95%: 1.2–68.7 months) than those harboring non-SCLC neuroendocrine components ($n = 11$, OS NR), but again the difference did not reach any statistical significance ($P = 0.16$, Fig 3c). Patients receiving surgery ($n = 15$) had a significantly longer survival period (NR) than those without surgery ($n = 7$, 17.0 months, 95% CI: 14.9–19.1 months, $P = 0.001$, Fig 3d).

Table 1 List of enrolled patients

No.	Gender	Age	Location	Diagnosis	Stage
1	M	53	R	Carcinoid with adenocarcinoma component	IV
2	M	65	L	SCLC with squamous carcinoma	II
3	M	70	R	NET mixed with squamous carcinoma	II
4	M	70	R	SCLC with adenocarcinoma	II
5	M	59	L	SCLC with adenosquamous carcinoma	IV
6	M	60	R	SCLC with squamous carcinoma	IV
7	M	60	L	Adenocarcinoma with SCLC component	III
8	M	52	R	Adenocarcinoma combined with NET	I
9	M	71	L	SCLC with squamous carcinoma	IV
10	M	72	R	Large-cell NET with squamous carcinoma	IV
11	M	57	R	Squamous carcinoma mixed with NET	II
12	M	61	L	NET mixed with squamous carcinoma	IV
13	M	56	R	SCLC with adenocarcinoma	IV
14	M	78	R	SCLC with adenocarcinoma	III
15	M	58	R	SCLC with adenocarcinoma	II
16	M	48	R	Adenocarcinoma with SCLC	IV
17	M	42	R	SCLC with squamous carcinoma	IV
18	M	63	R	Squamous carcinoma with NET	II
19	M	64	R	Mixed form of adenocarcinoma, squamous carcinoma, and NET	IV
20	M	69	L	Large-cell NET with adenocarcinoma	II
21	F	61	R	NET with adenocarcinoma	IV
22	M	71	R	Large-cell NET with squamous carcinoma	IV

L, left; NET, neuroendocrine tumor; R, right; SCLC, small cell lung cancer.

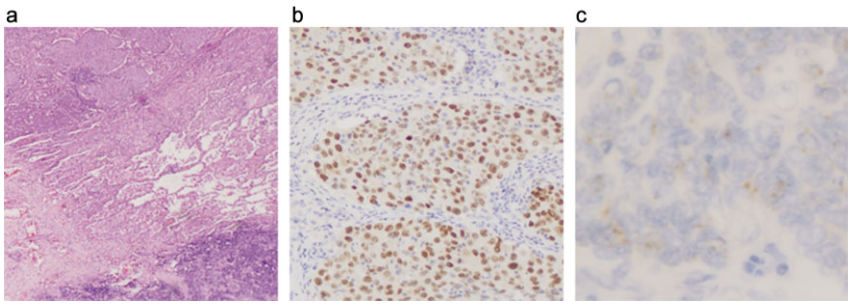

Figure 2 One example of a combined form of small cell lung cancer (SCLC). (**a**) In this case, the components of SCLC were mixed with that of squamous carcinoma (20×). (**b**) The squamous carcinoma was confirmed by immunohistochemistry of P63 (100×). (**c**) In the same patient, scattered chromogranin **a**-positive dots were observed (400×).

Discussion

Heterogeneity in lung cancer has been noted previously. Mixed histological phenotypes were observed in 59 cases from 1158 lung cancer patients.[11] With the advent of targeted therapy, the prevalence and importance of heterogeneity are recognized more than ever before.[12] Therefore, research such as the current study focusing on tumor heterogeneity, has merit for future exploration.

In this study, the risk factor of the mixed form of NET was explored. Although 95% (21/22) of patients were male, the occurrence of the disease in men with lung cancer did not differ significantly from that in women (P = 0.35). Also, occurrence in young patients (≤60 years) was similar to that in the elderly (P = 0.13). From these results, one would speculate that neither gender nor age is associated with the onset of the mixed form of NET. However, occurrence has increased in recent years. The occurrence of NET before 2011 was significantly lower than in 2011 (P = 0.03). This increase cannot be fully explained at this time. However, we posit that the wide application of histological diagnostic tools, such as immunohistochemistry (IHC), have greatly elevated the awareness of NETs. Indeed, NETs in the lung represented about 30% of all NETs, three percent of all lung cancer cases in the United States.[13]

Table 2 Occurrence of the mixed form of NET in lung cancer

Risk factors	Total (n = 2501)	Mixed form of NET (n = 22)	Rate (%)	P-value
Gender				
Male	2149	21	1.2	
Female	352	1	0.3	0.35
Age (42–78)				
≤60	1548	10	0.6	
>60	953	12	1.3	0.13
Time				
≤2010	1814	11	0.6	
>2010	687	11	1.6	0.03

NET, neuroendocrine tumor.

The incidence of the mixed form of NET in the lung remains largely unknown. Previously, an incidence of 5.9% (59/1158) of the mixed histological form of lung cancer was reported.[11] In this report, three categories were defined: adenosquamous carcinoma, combined neuroendocrine with non-neuroendocrine carcinoma, and biphasic tumors (epithelial with mesenchymal malignant components). The study found an incidence of 1.8% (21/1158) of combined neuroendocrine with non-neuroendocrine carcinoma, which was similar to our results (0.9%, 22/2501). Therefore, it could be reasoned that the mixed form of NET in the lung is extremely rare. In support of this, mere case reports exist in the literature.[6,7] Given the lack of any large series of reports, our study represents a good resource for the study of this rare disease.

Because of the rarity of this disease, the optimal management approach has not yet been determined. Treatment is based on the grade of the NET and extension of the disease. For localized disease surgery is the mainstay of treatment, while for advanced stage chemotherapy is most widely used. However, the preferred regimen remains unknown. In our study, 68.2% (15/22) and 95.5% (21/22) of patients received surgery and chemotherapy, respectively. Patients administered SCLC (n = 5) and NSCLC regimens (n = 16) experienced similar survival periods (supplementary material, Figure S1). Our data suggested that neither regimen was superior to the other.

Targeted therapy is recognized for the treatment of NSCLC and is considered a future development direction. For NET of the lung, several targeted therapies were tested. The mammalian target of rapamycin (mTOR) inhibitor, everolimus,[14] and the angiogenesis inhibitor, sunitinib,[15] were proposed. However, because of the inaccessibility of these drugs in China, none of our patients was prescribed these. Our data, therefore, cannot provide evidence of the potential benefit of these drugs for the mixed form of NET in the lung.

Whether the mixture of neuroendocrine fraction indicated a better prognosis remains an interesting question. A previous report found that neuroendocrine differentiation was associated with a favorable outcome in 116 cases with

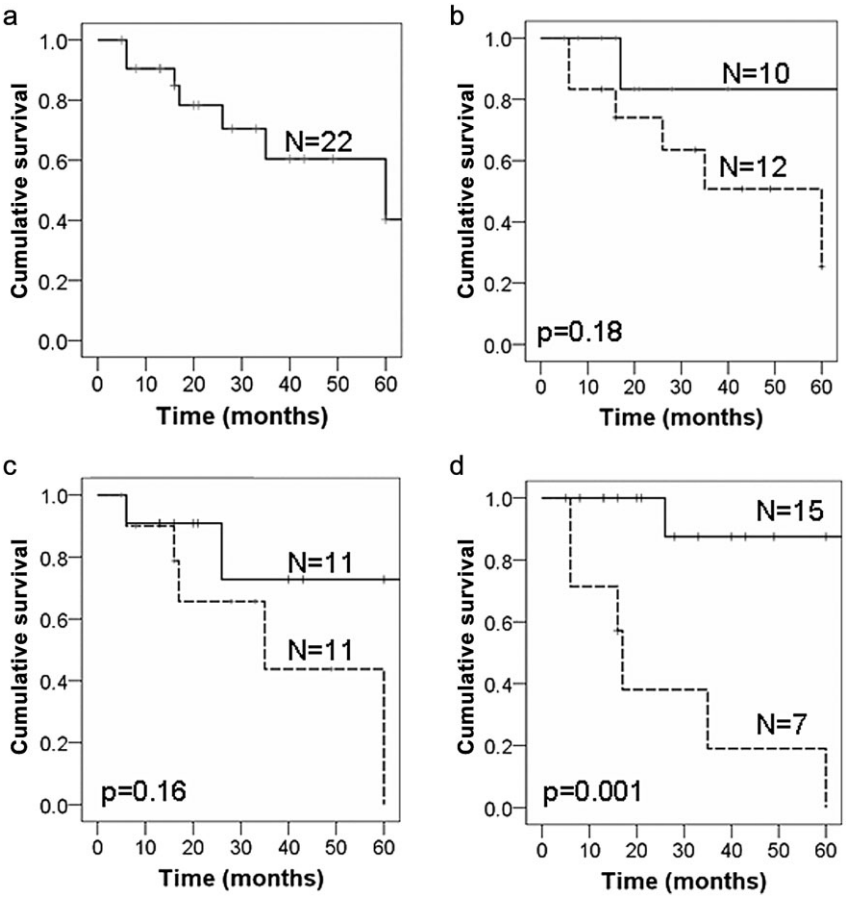

Figure 3 (**a**) Long-term survival of enrolled patients. (**b**) Patients with metastatic diseases (dash line) had shorter survival than those with earlier phases (solid line). (**c**) Patients harboring small cell lung cancer (SCLC) components (dash line) had shorter survival than those harboring non-SCLC neuroendocrine components (solid line). (**d**) Patients receiving surgery (solid line) had significantly longer survival than those without surgery (dash line).

advanced NSCLC.[16] In our study, the whole cohort had a median survival of 60 months. Even those with metastatic diseases had a median survival of 60 months (25.4–94.5 months), which was longer than the advanced stage of NSCLC (10 months) or extensive-stage SCLC (8 months).[17,18] Our results support the proposal that a mixture of neuroendocrine fraction indicates a better prognosis and future large-scale prospective trials are warranted to make a definitive conclusion.

Conclusion

In summary, this retrospective study analyzed 22 patients with the mixed form of NET in the lung from a cohort of 2501 cases with primary lung cancer. The onset of the mixed form of NET was not associated with gender or age, however the rate of this rare disease has recently increased, possibly as a result of the wider application of IHC. Patients with the mixed form of NET had a better prognosis than those without an NET component. Patients with metastatic disease or an SCLC component had a poor prognosis. Surgery is critical for long-term survival. Patients with their tumors resected lived much longer than those without surgery. This was a retrospective study conducted in one institute, therefore, all conclusions should be interpreted with caution because of inevitable selection bias. In order to confirm current results, large-scale prospective clinical studies are warranted in the future.

Acknowledgment

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Disclosure

The preliminary data of this study was submitted to the American Society of Clinical Oncology 2013 Annual Meeting. No authors report any conflict of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 The survival of patients receiving a non-small cell lung cancer (NSCLC) regimen (solid line) or an etoposide and cisplatin (EP) chemotherapy regimen (dash line) was similar.

Table S1 Demographic features of enrolled patients

