

## Surgical management of large-cell neuroendocrine lung carcinoma: an analysis of 25 cases

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**Background/aim:** Large-cell neuroendocrine carcinoma (LCNEC) of the lung is a relatively uncommon and aggressive subset of pulmonary neuroendocrine tumors, which include typical and atypical carcinoid, and small-cell lung cancer. LCNEC of the lung accounts for no more than 1% of all lung cancers. LCNECs show features of high-grade neuroendocrine tumors and patients with LCNEC have a very poor prognosis.

**Materials and methods:** Twenty-five patients (22 males and 3 females; mean years 60.7; range 48 to 77 years) who underwent pulmonary resection for large-cell neuroendocrine carcinoma between January 2004 and December 2014 were investigated retrospectively.

**Results:** Type of surgery, pathologic TNM stage, adjuvant chemotherapy, time of recurrence, site of recurrence, response to treatment, and long-term results were evaluated. The longest patient follow-up period was 83 months. One-, two-, and three-year survival rates of these patients were, respectively, 80.95%, 76.47%, and 50%.

**Conclusion:** Complete surgical resection is the treatment of choice for early-stage LCNEC and chemotherapy after radical surgical treatment improves survival. Follow-up periods after surgery adjuvant chemotherapy will prevent recurrence and patients may survive for many years if complete surgical resection and adjuvant chemotherapy are possible.

**Key words:** Large-cell neuroendocrine carcinoma, resection, adjuvant chemotherapy, radiation therapy

### 1. Introduction

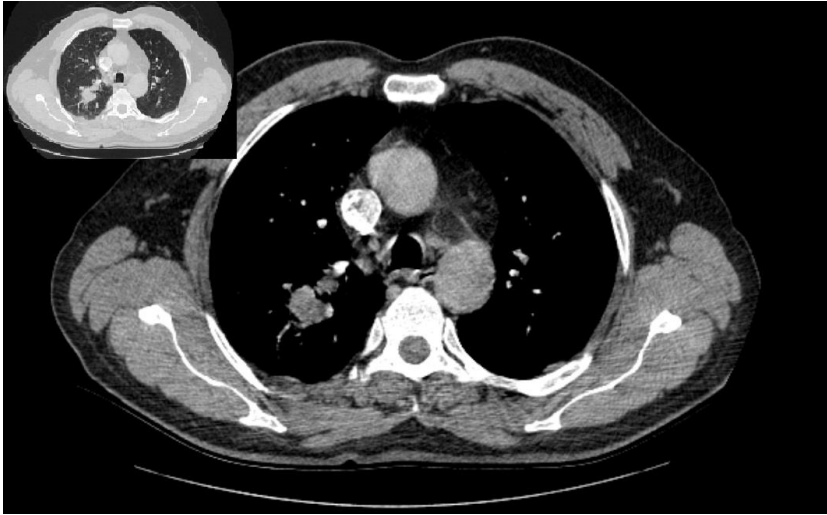
Large-cell neuroendocrine carcinoma (LCNEC) of the lung accounts for no more than 1% of all lung cancers. LCNEC shows features of high-grade neuroendocrine tumors. LCNECs are aggressive tumors and patients with LCNEC have a very poor prognosis. The typical histological features, first described in 1991 (1–3), include large cells with abundant cytoplasm, a high mitotic rate, extensive necrosis, and a neuroendocrine growth pattern. The World Health Organization classified LCNEC as a distinct subtype of pulmonary large-cell carcinoma in 2004 and therefore as a subtype of non-small-cell lung carcinoma (NSCLC). On the other hand, LCNEC was removed from the large cell carcinoma category and reclassified as a distinct subtype of neuroendocrine tumors by the WHO classification in 2015 (4). In addition, the clinical and biological characteristics of LCNEC are similar to those of small cell lung carcinoma (SCLC). Therefore, there is still no consensus on the treatment strategy for LCNEC (2). In the present study the clinicopathological data from 25 patients with LCNEC were

retrospectively analyzed with the aim of summarizing the specific clinicopathological features of LCNEC, and the results of surgical resection as a treatment and the follow-up period postoperatively were discussed.

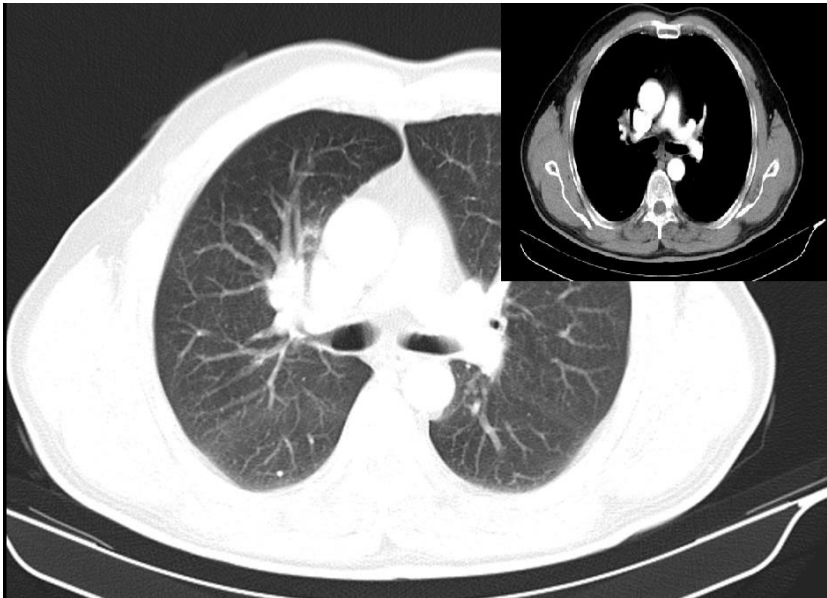
### 2. Materials and methods

Initially, 25 patients who underwent pulmonary resection for LCNEC are presented and discussed. The authors investigated the records of 25 patients who were operated on in the thoracic surgery clinic between January 2004 and December 2014 diagnosed with LCNEC. The mean age was 60.7 (range: 48–77); the male to female ratio was 22:3. All patients were evaluated based on their patient history, physical examinations, chest X-rays, chest and upper abdomen (including the liver and adrenal glands) computed tomography (CT), and positron emission tomography (PET)/CT (Figures 1 and 2). Twenty patients (80%) were smokers. Spirometry tests were routinely carried out in all of the patients, and preoperative fiberoptic bronchoscopy (FOB) was also performed. A malignant

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**Figure 1.** Lesion on the periphery of the right upper lobe, 4 × 3 × 3 cm in size.



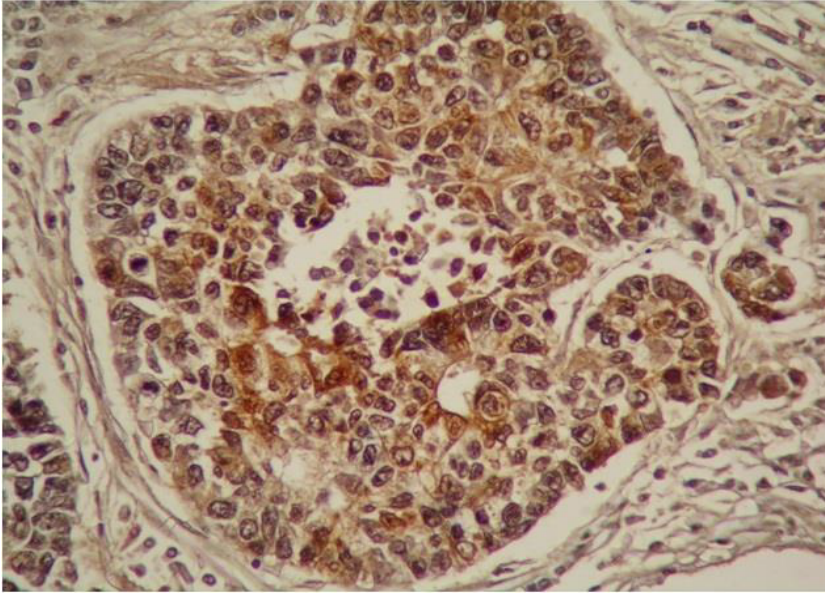
**Figure 2.** Lesion in the center of the right upper lobe, 2.5 × 2 × 2 cm in size.

tumor was confirmed in 5 patients (20%) by bronchoscopy and in 6 patients (24%) by CT-guided transthoracic needle biopsy while a definitive diagnosis was achieved by frozen section (FS) examination in 14 others (56%).

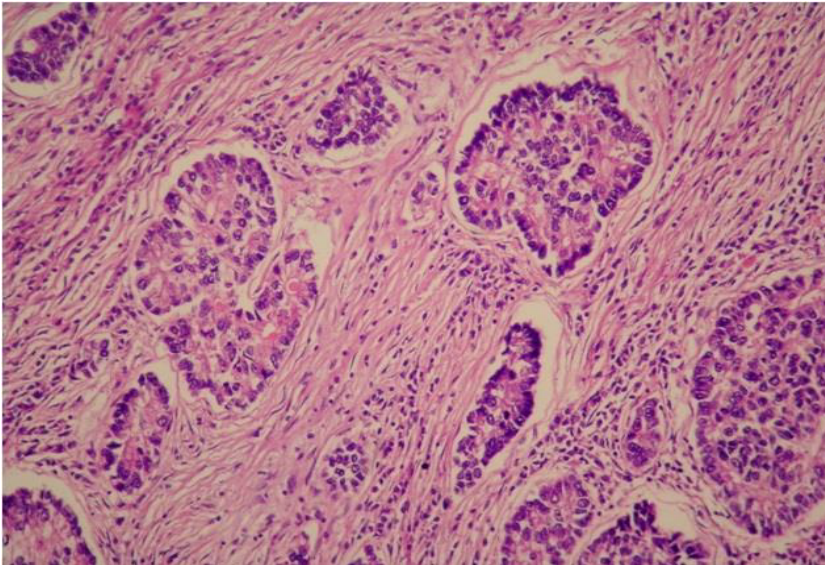
We performed various types of thoracotomies on these patients based on the localization of the tumor and we planned pulmonary resection under single-lung anesthesia. We also performed either an anatomic or nonanatomic complete resection while preserving most of the functioning lung tissue. During the operation, undiagnosed tumors were confirmed by FS examinations. For centrally located lesions, FS examination of the cut edges was performed routinely, with the hope of finding a

tumor-free margin of at least 5 mm. In addition, systematic mediastinal and hilar lymph node sampling was done, and mediastinal lymph node dissection was carried out if lymph node metastasis was confirmed by FS after sampling. The specimens were pathologically examined and classified as large-cell neuroendocrine carcinoma after the surgery (Figures 3 and 4).

The following parameters were investigated from the medical records: patient sex, age, smoking index, tumor size, tumor location, surgical procedure, pathologic TNM stage, adjuvant chemotherapy, time of recurrence, site of recurrence, response to treatment, and patient outcome. During the follow-up period, these data were prospectively



**Figure 3.** Rosettes and palisading patterns in large cell neuroendocrine carcinoma (HEX200).



**Figure 4.** Chromogranin positivity in large cell neuroendocrine carcinoma (ChromograninX400).

recorded in the database, and then all patients were contacted either in person or by telephone.

We performed routine follow-ups of patients with LCNEC 4 times per year, checking symptoms and chest roentgenography. We also performed chest CT at least one time per year. If abnormal findings were observed, we used CT to evaluate the hilar-mediastinal and extrathoracic lymph nodes, the lung field, and the abdomen, and we used magnetic resonance imaging or CT to evaluate brain lesions. Bone scintigraphy was used to evaluate

bone metastases. In some patients, we used positron emission tomography scans to detect postoperative distant metastases. If recurrent tumors were suspected, other sites were also examined.

### 3. Results

A summary of the 25 patients is presented in Table 1. Left posteriolateral thoracotomy was performed in 6 patients and right posteriolateral thoracotomy in 19 patients. Lobectomy, bilobectomy inferior, pneumonectomy,

**Table 1.** A summary of the 25 patients.

Patient	Age & sex	Localization & size	Microscopy	Follow-up
1	56-M	On the periphery of the right upper lobe, adjacent to 2nd, 3rd ribs, 3 × 3 × 3 cm in size	Chromogranin A+, NCAM+	Postop 41st month
2	56-M	On the periphery of the right upper lobe, 5 × 3 × 2 cm in size	Synaptophysin+, NCAM+	Postop 36th month
3	57-M	On the periphery of the right lower lobe, 4 × 3.5 × 3 cm in size	Synaptophysin+, NCAM+	Postop 33rd month
4	50-M	On the periphery of the right lower lobe, 4 × 3 × 3 cm in size	NCAM+	Postop 27th month
5	69-M	On the periphery of the right upper lobe, 1 × 1 × 1 cm in size	Chromogranin A+, NCAM+	Postop 26th month
6	63-M	In the center of the right upper lobe, 2 × 2 × 2 cm in size	NCAM+	Postop 16th month
7	61-M	On the periphery of the right lower lobe, adjacent to 7th rib, 5 × 5 × 5.5 cm in size	Synaptophysin+, NCAM+	Postop 15th month
8	61-M	In the center of the right middle& lower lobe, 4 × 4.5 × 4 cm in size	Chromogranin A+, NCAM+	Postop 8th month exitus
9	63-M	In the center of the right upper lobe, 7 × 10 × 11 cm in size	Chromogranin A+, NCAM+	Postop 3rd month exitus
10	61-M	On the periphery of the left upper lobe, 2.5 × 1.5 × 1.6 cm in size	NCAM+	Postop 21st month exitus
11	59-M	On the periphery of the right upper lobe, 2.8 × 2 × 3 cm in size	NCAM+	Postop 3rd month exitus
12	48-M	In the center of the left lung, 2 × 3 × 3.5 cm in size	Chromogranin A+, NCAM+	Postop 41st month
13	71-F	On the periphery of the left lower lobe, adjacent to 5th rib, 3 × 3.3 × 4.3 cm in size	Synaptophysin+, NCAM+	Postop 33rd month
14	64-M	On the periphery of the right upper lobe, 9.5 × 8 × 5 cm in size	Synaptophysin+, NCAM+	Postop 29th month
15	62-F	On the periphery of the right lower lobe, 2 × 2 × 1.5 cm in size	Chromogranin A+, NCAM+	Drop-out
16	77-M	In the center of the right upper lobe, 8 × 5 × 5 cm in size	NCAM+	Drop-out
17	55-F	On the periphery of the right upper lobe, 3 × 3 × 3 cm in size	Chromogranin A+, NCAM+	Drop-out
18	58-M	On the periphery of the right upper lobe, 4 × 5 × 3 cm in size	Synaptophysin+, NCAM+	Postop 79th month
19	62-M	On the periphery of the right upper lobe, 10 × 11 × 12 cm in size	Chromogranin A+, NCAM+	Postop 37th month
20	57-M	On the periphery of the left upper lobe, 2 × 1.5 × 1.2 cm in size	Synaptophysin+	Postop 32nd month exitus
21	62-M	On the periphery of the left lower lobe, 1 × 1.3 × 1 cm in size	NCAM+	Postop 45th month exitus
22	59-M	In the center of the right upper lobe, 2.5 × 2 × 2 cm in size	Chromogranin A+, synaptophysin+	Postop 14th month
23	66-M	On the periphery of the left lower lobe, adjacent to 5th, 8th, 9th ribs, 10 × 13 × 17 cm in size	Synaptophysin+, NCAM+	Postop 11th month exitus
24	57-M	In the center of the right lung, 7 × 4 × 4 cm in size	Chromogranin A+, synaptophysin+, NCAM+	Postop 83rd month exitus
25	65-M	On the periphery of the right upper lobe, 4 × 3 × 3 cm in size	Chromogranin A+, synaptophysin+	Postop 3rd month

lobectomy with chest wall resection, and wedge resection were performed in 14 (56%), 1 (4%), 3 (12%), four (16%), and 3 patients (12%), respectively.

In one patient, a mass in the opposite lung was observed at the same time. Therefore, left upper lobectomy and right upper lobectomy with posterolateral thoracotomy were performed. Postoperative pathology revealed epidermoid carcinoma (stage IIA). The other

side's postoperative pathology was reported as stage IB LCNEC. Another patient with left upper lobe epidermoid carcinoma underwent left posterolateral thoracotomy and sleeve upper lobectomy; postoperative stage was IB and 3 months after surgery because of a right lower lobe nodule right posterolateral thoracotomy and lower lobectomy were performed. Postoperative pathology was reported as stage IB LCNEC, but the patient died from cardiac

causes 3 months after the second operation. One of our patients who had chest wall resection and right lower lobectomy with posterolateral thoracotomy for LCNEC had had radiotherapy (RT) because of carcinoma of the hypopharynx 6 years before. Furthermore, 15 of the 25 patients with an advanced stage of LCNEC underwent oncological therapy, with 12 receiving only chemotherapy and three chemoradiotherapy. These 25 patients are presented in Table 2 according to whether they received postoperative chemotherapy.

At the time of writing, the longest patient follow-up period was 83 months, and the newest patient had been followed up for 3 months. Three of the patients dropped out during the follow-up period. There was a recurrence of one patient's tumor and a rethoracotomy was suggested, but the patient refused the operation, received adjuvant chemotherapy and RT, and was still being followed up. In another patient, with stage IIA LCNEC who received adjuvant chemoradiotherapy, liver metastases and widespread bone metastases were observed in the follow-up period and the patient died 8 months after

surgery. However, the other patients had no distant organ metastases or local recurrences.

Among the 25 patients with LCNEC, 21 were diagnosed before 2013, followed up for 1 year; however, four patients did not complete the follow-up (Table 1). The 1-year survival rate of these cases was 80.95% (17/21). Seventeen patients were diagnosed before 2012 and 12 before 2011. The 2-year survival rate was 76.47% (13/17) and the 3-year survival rate was 50% (6/12).

#### 4. Discussion

The true incidence of LCNEC is low in all probability, although it has not been well defined. The incidence of LCNEC surgically resected lung cancers appears to be between 2.1% and 3.5% based on the available literature. The incidence of LCNEC in lung cancers not treated surgically is unknown but is likely to be higher, given the aggressive nature of these tumors (5–9). At our institution from January 2004 through December 2014, there were 25 cases of LCNEC out of 926 surgically resected primary lung cancers (2.6%).

**Table 2.** Characteristics of 25 informative patients with large-cell neuroendocrine carcinoma between group with adjuvant chemotherapy and group without.

Factor	Category	Adjuvant chemotherapy	
		+	-
Number		15	10
Sex	Male	13	9
	Female	2	1
Pathologic stage			
	1a	0	3
	1b	9	2
	2a	2	1
	2b	3	2
	3a	1	2
Surgery			
	Pneumonectomy	2	1
	Bilobectomy	1	-
	Lobectomy	7	7
	Lobectomy with chest wall resection	2	2
	Wedge resection	1	2
Second cancer	+	3	-
	-	12	7
	Unknown	-	3
Postoperative recurrence	+	2	1
	-	13	6
	Unknown	-	3

LCNEC of the lung is a relatively uncommon and aggressive subset of pulmonary neuroendocrine tumors, which include typical and atypical carcinoid, and SCLC (1–3). Men most commonly make up 80% to 90% of patients with LCNEC (7,10,11). More than 85% of patients have a history of smoking (10,12). Therefore, smoking appears to be the primary cause in LCNEC development. The median age of patients ranged between 62 and 68 years (9,11–14). Iyoda et al. found a male to female ratio of 11:1 in their study (15). In our study, the male to female ratio was 22:3; 88% of our patients were male. Twenty-one patients (84%) had a history of smoking and none of the female patients were smokers. As recognition and reporting of LCNEC increases, the epidemiology of this neoplasm will be better defined, including possible associated environmental and genetic risk factors.

Regarding the tumor location, LCNECs mostly present as large primary lung masses in the peripheral lung fields. They are more frequently identified on chest radiographs (3,9), as opposed to the central carcinoids and SCLC site, and therefore clinical symptoms are less commonly detected. A computed tomography appearance generally shows a well-defined and lobulated/mass that resembles other expansively growing tumors, such as peripheral SCLC, poorly differentiated adenocarcinomas, and squamous cell carcinomas (16–19). Because of their peripheral location, diagnosis is most often made by transthoracic biopsy due to its ease of accessibility. Regarding 2-[18F]-fluoro-2-deoxy-D-glucose positron-emission tomography findings, Kaira et al. reported that the standardized uptake value peak was significantly higher in LCNEC as well as in SCLC than in carcinoid, with a mean value of 13.7 (20). In our study, tumors in 7 cases (28%) were centrally located, while 18 cases (72%) had peripheral lesions.

LCNEC is rarely diagnosed preoperatively because the accurate differentiation of LCNEC from other lung tumors requires a careful review of the pathologic specimen. Diagnosis of LCNEC is often a difficult task that requires histological analysis, cytological evaluation, and immunohistochemistry (21–23). In addition, due to the small specimen, tissue extrusion, and deformation, immunohistochemistry is difficult. Therefore, LCNEC has been usually diagnosed in surgical specimens postoperatively. In our study, the pathology of the FOB biopsy was reported as LCNEC in 1 patient, neuroendocrine carcinoma in 2, and NSCLC in 2. Transthoracic biopsy pathology in 4 patients was NSCLC, while it was neuroendocrine carcinoma in 1 patient. FS examination of the remaining 14 patients during the operation revealed malignant tumors. Only one case (4%) was confirmed or considered to be LCNEC by FOB biopsy. The other 24 patients were diagnosed by postoperative surgical specimen.

Before the diagnosis of LCNEC, neuroendocrine differentiation must be confirmed by light microscopy and subsequently distinguished from typical carcinoma, atypical carcinoma, and SCLC by size, presence or absence of necrosis, and mitotic rate. LCNEC shows histological features such as organoid nesting, trabecular growth, rosettes, and perilobular palisading patterns, suggesting neuroendocrine differentiation. The tumor cells are generally large, with moderate to abundant cytoplasm. Nucleoli are frequent and prominent and their presence facilitates separation from small cell carcinoma. Mitotic counts are typically 11 or more (average 75) per 2 mm<sup>2</sup> of viable tumor. Confirmation of neuroendocrine differentiation is required using immunohistochemical markers such as chromogranin, synaptophysin, and neural cell adhesion molecule (NCAM). One positive marker is sufficient if the staining is clear cut. Rossi et al. were the first to report the percentage of chromogranin A (65%), synaptophysin (53%), and NCAM (93%) in LCNEC (24). In our study, NCAM 92%, synaptophysin 40%, chromogranin A 44%, and 3 marker positivity only in 1 patient (4%) were observed. Postoperative pathologic staging was evaluated as stage IA in 3 patients, while 11 patients had stage IB, 3 patients had stage IIA, 5 patients had IIB, and the remaining 3 patients had stage IIIA.

The optimal treatment for LCNEC has not been determined. Zacharias et al. reported that patients with LCNECs, which are aggressive tumors, had a good prognosis if they underwent complete tumor resection with systematic nodal dissection (25). Iyoda et al. revealed that adjuvant chemotherapy was effective for treating patients with LCNEC (26). Rossi et al. and Iyoda et al. showed that patients receiving adjuvant chemotherapy had a good prognosis after complete surgical resection and that adjuvant chemotherapy was promising for patients with LCNEC (24,27). We performed complete R0 resection of the tumor with systematic nodal dissection in our 22 patients because of LCNEC for 10 years. In 3 patients operated on previously, wedge resection was performed due to the limited respiratory reserve. Pneumonectomy, bilobectomy inferior, lobectomy, and lobectomy with resection of the chest wall were performed in patients with complete tumor resection. Furthermore, 15 of the 25 patients with an advanced stage of LCNEC underwent oncological therapy; 15 received chemotherapy (Table 2) and four chemoradiotherapy. Three patients had palliative radiotherapy. Although it has been reported that LCNEC patients have frequent recurrent tumors and very poor prognoses, Iyoda et al. determined that platinum-based adjuvant chemotherapy after surgery significantly prevents recurrence and that recurrent tumors might also be responsive to platinum-based chemotherapy, radiation therapy, or the combination of the two (15). The role of

adjuvant therapy for LCNEC should be examined in large-center prospective, randomized trials.

The 1-, 2-, and 3-year survival rates in our study were 80.95%, 76.47%, and 50%, respectively. There were four patients in 1-year follow-up, four in 2-year follow-up, and six in 3-year follow-up who did not complete the follow-up time. Compared to our study results, Varlotto et al. found 1-, 2-, and 4-year survival rates of, respectively, 76%, 56%, and 41% (28). In a retrospective study by Liang et al., the 1-year survival rate of their patients was 57.8% (48/83) (29).

LCNEC of the lung is an uncommon but aggressive neoplasm with a poor prognosis. No studies have established the optimal treatment for patients with

LCNEC. These tumors should be classified separately from grade III neuroendocrine carcinoma large-cell type, part of the neuroendocrine spectrum of lung cancer. The optimal approach to LCNEC is surgical complete resection of the tumor, and the diameter, stage, and lymph node involvement of the tumor are among the factors that determine the prognosis. Chemotherapy after radical surgical treatment improves survival. Our study showed that adjuvant chemotherapy after surgery yielded better results. Despite the aggressive behavior of this type of tumor being associated with a poor prognosis, patients will survive for many years if complete surgical resection and adjuvant chemotherapy are possible.

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