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ORIGINAL SCIENTIFIC REPORT

Large Cell Neuroendocrine Tumor Size >3 cm Negatively Impacts Long-Term Outcomes After R0 Resection

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Abstract

Background Minimal knowledge exists regarding the outcome, prognosis and optimal treatment strategy for patients with pulmonary large cell neuroendocrine carcinomas (LCNEC) due to their rarity. We aimed to identify factors affecting survival and recurrence after resection to inform current treatment strategies.

Methods We retrospectively reviewed 72 patients who had undergone a curative resection for LCNEC in 8 centers between 2000 and 2015. Univariable and multivariable analyses were performed to identify the factors influencing recurrence, disease-specific survival and overall survival. These included age, gender, previous malignancy, ECOG performance status, symptoms at diagnosis, extent of resection, extent of lymphadenectomy, additional chemo- and/or radiotherapy, tumor location, tumor size, pT, pleural invasion, pN and pStage.

Results Median follow-up was 47 (95%CI 41–79) months; 5-year disease-specific and overall survival rates were 57.6% (95%CI 41.3–70.9) and 47.4% (95%CI 32.3–61.1). There were 22 systemic recurrences and 12 loco-regional recurrences. Tumor size was an independent prognostic factor for systemic recurrence [HR: 1.20 (95%CI 1.01–1.41); $p = 0.03$] with a threshold value of 3 cm (AUC = 0.71). For tumors ≤3 cm and >3 cm, 5-year freedom from systemic recurrence was 79.2% (95%CI 43.6–93.6) and 38.2% (95%CI 20.6–55.6) ($p < 0.001$) and 5-year disease-specific survival was 60.7% (95%CI 35.1–78.8) and 54.2% (95%CI 32.6–71.6) ($p = 0.31$), respectively.

Conclusions A large proportion of patients with surgically resected LCNEC will develop systemic recurrence after resection. Patients with tumors >3 cm have a significantly higher rate of systemic recurrence suggesting that adjuvant chemotherapy should be considered after complete resection of LCNEC >3 cm, even in the absence of nodal involvement.

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Introduction

Large cell neuroendocrine carcinoma (LCNEC) represents approximately 3% of all lung cancers [1]. Due to its aggressive behavior, characterized by a high rate of lymph node and distant metastasis at presentation (60–80% and 40%, respectively) and poor survival (5-year survival rate: 27–67%), it is categorized as a high-grade neuroendocrine carcinoma [1]. Owing to its rarity, limited series are reported in the literature and a minimal knowledge exists regarding outcome, prognosis or optimal treatment strategy of patients with LCNEC.

The objective of this study is to determine patient outcomes after lung resection for early-stage LCNEC with the goals of (1) identifying factors affecting survival and recurrence and (2) evaluating the efficacy of the current treatment strategy.

Materials and methods

We retrospectively reviewed a multi-institutional series of consecutive patients who underwent lung resection for primary LCNEC between 2000 and 2015. Participating institutions included Swedish Cancer Institute, Seattle, WA; UC Davis Health, Sacramento, CA; Catholic University 'Sacred Heart', Rome, Italy; San Giovanni Battista Hospital, Turin, Italy; University of Insubria, Ospedale di Circolo, Varese, Italy; University of Washington Medical Center, Seattle, WA; Providence Regional Medical Center, Everett, WA; and Virginia Mason Hospital and Medical Center, Seattle, WA. Patients with stage IV disease, no surgical lymph node staging (pNX), incomplete resection (R1–R2) and follow-up <4 months were excluded from the study. The institutional review board at each center approved this study, and de-identified data were transmitted between centers. Individual patient consent was waived due to the retrospective nature of the study.

For each patient we collected the following data: age, gender, smoking habit, Eastern Cooperative Oncology Group (ECOG) performance status, previous malignancy, preoperative investigations, tumor location, clinical 7th edition TNM stage, surgical reports, pathological findings and induction/adjuvant therapy. Standardized definitions for each data point were decided a priori based on previous literature and distributed to each center for use. Tumor location was classified as 'central' if tumor was visualized at bronchoscopy or associated with distal atelectasis or obstructive pneumonia and 'peripheral' if it did not meet these criteria [2].

Recurrence rates and patterns and both disease-specific and overall survival were analyzed. Univariable and multivariable analyses were performed, stratified by center to identify factors influencing recurrence, disease-specific and overall survival. Variables analyzed included age, gender, previous malignancy, ECOG performance status, symptoms at diagnosis, extent of resection, extent of lymphadenectomy, additional therapy, tumor location, tumor size, pT, pleural invasion, pN and pathologic stage. pT, pN and pStage were defined according to the 7th edition TNM staging system.

Continuous data were reported as median with interquartile range (IQR). Categorical and count data were presented as frequencies and percentages and compared using Chi-square test. We defined recurrence as local when disease recurred along surgical margins or in the same lobe after sublobar resection; regional when tumor recurred in the ipsilateral lung or in any thoracic lymph node station; and systemic when disease recurred in any other districts. Overall survival was defined as time interval in months from date of surgery until last follow-up. Disease-free interval was defined as time interval in months from date of surgery until date of tumor recurrence. Overall and disease-free survivals were analyzed using Kaplan–Meier method. Univariable and multivariable analyses were performed using Cox regression modeling. Multivariable analysis included variables statistically significant in univariable analyses or known possible factors influencing the outcomes. If two factors correlated to each other (i.e., tumor size and pT) were significant at univariable analyses, they were tested separately with other significant or relevant factors at multivariable analyses. Receiver operating characteristic (ROC) analysis was used to assess tumor size threshold associated with recurrence and survival. P value < 0.05 was considered statistically significant. Statistical analyses were undertaken using SPSS 24.0 software (IBM Corp, Armonk, NY).

Results

Between 2000 and 2015, 116 patients underwent lung resection for primary LCNEC. A total of 44 patients were excluded from the study, leaving 72 patients for the statistical analysis (5 stage IV disease, 3 pNX disease, 10 R1–R2 resection and 26 follow-up <4 months). Patients' characteristics are reported in Table 1.

Induction therapy was used in 6 (8%) patients (4 chemotherapy only and 2 chemo-radiotherapy). In 4 cases the tumor was reduced in size, and in 2 cases there was no response. Additionally, lymph node metastases completely resolved in 3 and partially in 1. All 6 patients underwent resection given that there was no progression of disease. In

follow-up, 3 patients died of disease, 2 were alive and disease-free, and 1 was alive with disease.

Pneumonectomy was performed in 6 (8%) patients, bilobectomy in 1 (1%), lobectomy in 56 (78%) and sublobar resection in 9 (3 segmentectomies and 6 wedge resections) (13%). Lymph node sampling was performed in 37 (52%) cases and complete lymphadenectomy in 33 (46%). No data were available on the extent of lymphadenectomy or sampling in 2 patients. Pathological findings are reported in Table 1.

Adjuvant therapy was delivered in 22 (31%) patients: 17 chemotherapy only, 2 radiotherapy only and 3 chemo-radiotherapy. Adjuvant therapy details were not reported in 1 patient. The decision to proceed with adjuvant therapy was the presence of lymph node metastasis (14) and tumor size ≥4 cm (6). In 2 patients the decision of adding adjuvant therapy was not specified. 2/22 patients had both induction and adjuvant therapy.

Patients' characteristics and outcomes based on treatment (surgery alone, induction therapy before surgery and adjuvant therapy after surgery) received are summarized in Table 2. Patients offered surgery had lower clinical stage, whereas those receiving induction therapy were more clinically advanced. Comparatively, adjuvant therapy was given with more advanced pathologic stages.

Median follow-up was 47 months (95%CI 40–79). Disease recurred in 34 (47%) patients, and the proportion of patients free of disease at 5 years post-operation was 42.0% (95%CI 28.4–55.0%). Recurrence was local in 4 (6%) patients, regional in 8 (11%) and systemic in 22 (31%). Systemic recurrences were cerebral ($n = 7$), hepatic ($n = 4$), skeletal ($n = 4$), adrenal ($n = 3$), in the contralateral lung ($n = 2$) and not specified in 2 patients.

When tumor recurred after surgical resection only, 5 patients underwent chemotherapy, 2 radiotherapy, 3 chemo-radiotherapy, 1 thermo-ablation, 6 palliative support, and in 1 case data were not available. Patients who received induction therapy followed by surgery had recurrence treated with chemotherapy in 2 patients and radiotherapy in 1, and in 1 case, data were not available. Finally, 2 patients who underwent surgery followed by adjuvant treatment and had recurrence underwent additional chemotherapy, 7 radiotherapy, 1 chemo-radiotherapy, 1 palliative support, and in 3 cases, data were not available.

Univariable analysis failed to identify factors influencing recurrence when both local–regional and systemic recurrences were considered as one event (data not shown). When considered as a unique event, systemic recurrence was influenced by tumor size, pT and pStage on univariable analysis (Table 3). Multivariable models were not pursued because of the correlation between these prognostic factors.

Table 1 Patients' clinical and pathological data

Patients' characteristics and histological reports	
Age, median (IQR) years	65 (58–71)
Male, *n* (%)	43 (60)
Current/former smoker, *n* (%)[a]	68 (96)
Previous cancer, *n* (%)	16 (22)
ECOG performance status, *n* (%)	
0	40 (56)
1	24 (33)
≥2	8 (11)
FEV_1, median (IQR) %[b]	83 (71–94)
No symptoms, *n* (%)[a]	37 (51)
Peripheral tumor location, *n* (%)	62 (86)
Tumor size, median (IQR) cm	3.2 (1.6–5.0)
pT, *n* (%)	
pT1	26 (36)
pT2	28 (39)
pT3	16 (22)
pT4	2 (3)
pN, *n* (%)	
pN0	44 (61)
pN1	20 (28)
pN2	8 (11)
pStage, *n* (%)	
I	32 (45)
II	24 (33)
IIIA	16 (22)

IQR interquartile range, FEV_1 forced expiratory volume in 1 s

[a]Data not available in 1 patient

[b]Data not available in 4 patients

Loco-regional recurrences were influenced only by tumor size.

For systemic recurrences, the influence of tumor size was further evaluated using logistic regression to conduct a ROC analysis. A cutoff value of 3 cm was identified by the ROC curve at the point of convergence of the highest values along both the sensitivity and 1-specificity axes (AUC = 0.71) (Fig. 1).

We then compared the outcomes of patients with tumor size ≤3 cm to those with tumor size >3 cm. There were 3 systemic recurrences among patients with tumor size ≤3 cm and 19 among those with tumor size >3 cm, leading to estimated recurrence rates of 0.03 (95%CI 0.01–0.09) and 0.17 (95%CI 0.11–0.27) per person year of follow-up, respectively, and 5-year freedom from recurrence of 79.2% (95%CI 43.6–93.6) and 38.2% (20.7–55.6), respectively ($p < 0.001$) (Fig. 2). Five-year disease-specific survival was 60.7% (95%CI 35.1–78.8) and 54.2% (95%CI 32.6–71.6) ($p = 0.31$), respectively, among

Table 2 Characteristics and outcomes of patients according to the treatment they received (surgery alone, induction therapy before surgery and adjuvant therapy after surgery)

Characteristics and outcomes	Surgery alone (n = 45)	Induction therapy (n = 6)[a]	Adjuvant therapy (n = 22)[a]
cStage, n (%)			
I/II/III	29/4/4 (64/9/9)[b]	1/1/4 (17/17/66)	9/7/5 (41/32/23)[c]
pStage, n (%)			
I/II/III	26/16/3 (58/35/7)	1/4/1 (17/66/17)	5/6/11 (23/27/50)
Recurrence, n (%)			
Local	1 (2)	0	3 (14)
Regional	7 (16)	0	1 (5)
Systemic	10 (22)	4 (66)	10 (45)
Total	18 (40)	4 (66)	14 (64)
Death, n (%)			
Death of lung cancer	12 (26)	3 (50)	9 (41)
Death of other causes	7 (16)	0	1 (4)
Total	19 (42)	3 (50)	10 (45)

1 Patient had no data about adjuvant treatment and was excluded from this table

[a]2 Patients had both induction and adjuvant treatment

[b]Data not available in 8 patients

[c]Data not available in 1 patient

patients with tumor size ≤3 cm and those with tumor size >3 cm (Fig. 2).

During follow-up 30/72 (42%) patients died. The cause of death was lung cancer in 22 cases and other causes in 8 (1 heart disease, 1 respiratory failure in chronic obstructive pulmonary disease, 1 ictus cerebri and 5 were not specified). Five-year disease-specific and overall survival rates were 57.6% (95%CI 41.3–70.9) and 47.4% (95%CI 32.3–61.1), respectively. There were no variables significantly associated with disease-specific or overall survival (Table 4).

Discussion

The primary finding in this study is that the resection of early-stage pulmonary LCNEC leads to a 5-year survival rate of 47.4% (95%CI 32.3–61.1) and that nearly half of patients developed recurrent disease with a predominately systemic pattern. Increasing tumor size, and in particular size >3 cm, was associated with a significant increase in systemic recurrence. Our findings are consistent with the literature, which has reported high rates of recurrence ranging from 35 to 73% and a predominantly systemic pattern of recurrence occurring in 20–55% of cases (Table 5). Moreover, these studies reported similar rates of overall survival (21–54%), indicating that surgery achieves satisfactory results in terms of survival in LCNEC treatment, but that many patients may potentially benefit from additional therapy (Table 5) [3–11].

In most modern LCNEC series, treatment regimens used are widely variable and the current series is no exception. Surgical resection alone appeared to be chosen in patients with predominantly clinical stage I tumors. Comparatively, induction or adjuvant therapy was offered to more advanced clinical stages (II and III) with the expected dismal results. The utilization of adjuvant therapy was predominantly offered to patients with pathologic stage II and III disease. The commonality remains surgical resection in all groups but is generally undertaken first followed by adjuvant therapy in the majority of cases.

Several additional key observations can be made from our data and that of others. First, surgery alone for LCNEC may not be sufficient and a combined modality approach could potentially lead to improved disease-free and overall survival since most patients die from recurrence [3–11]. Indications for and types of additional therapy in LCNEC treatment are still debated, and the aggressive behavior of these tumors has led some authors to consider chemotherapy and/or radiotherapy even for those with early-stage disease [3, 12–15]. Second, the threshold of 3 cm appears to be an important prognostic factor below which survival is high but above which recurrence is frequent and survival drops significantly [6, 13, 16].

According to the National Comprehensive Cancer Network (NCCN) guidelines, LCNEC stage-specific

Table 3 Univariable analysis of factors influencing systemic and loco-regional recurrence: Cox regression analysis

Factors	Systemic recurrence		Loco-regional recurrence	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (continuous)	0.97 (0.92–1.03)	0.29	1.01 (0.95–1.08)	0.74
Gender (female vs male)	1.61 (0.57–4.54)	0.36	0.39 (0.09–1.68)	0.21
ECOG performance status (reference 0)				
1	0.63 (0.19–2.01)	0.43	1.78 (0.47–6.64)	0.39
≥2	0.92 (0.24–3.61)	0.91	1.09 (0.12–9.79)	0.94
Previous malignancy (no vs yes)	0.68 (0.21–2.13)	0.50	1.58 (0.35–7.19)	0.55
Presence of symptoms (no vs yes)	2.00 (0.79–5.03)	0.14	0.18 (0.03–0.94)	0.04
Extent of resection (greater vs sublobar resections)[a]	–		5.04 (1.09–23.31)	0.04
Lymphadenectomy (complete dissection vs sampling)[b]	1.19 (0.13–10.72)	0.88	–	
Additional chemo-/radiotherapy (no vs yes)	2.12 (0.80–5.59)	0.13	1.14 (0.28–4.56)	0.85
Tumor location (central vs peripheral)[b]	1.04 (0.35–3.13)	0.94	–	
Tumor size (continuous)	1.20 (1.01–1.41)	0.03	0.66 (0.43–1.00)	0.05
pT (reference pT1)				
pT2	5.31 (1.13–25.05)	0.03	0.16 (0.03–0.81)	0.03
pT3/4	9.41 (1.85–47.75)	<0.01	0.29 (0.06–1.45)	0.13
Pleural invasion (yes vs no)	0.81 (0.30–2.18)	0.68	0.54 (0.11–2.59)	0.44
pN (reference pN0)				
pN1	1.80 (0.68–4.71)	0.23	0.95 (0.21–4.23)	0.94
pN2	2.29 (0.44–11.75)	0.32	2.46 (0.44–13.69)	0.31
pStage (reference I)				
II	2.89 (0.95–8.76)	0.06	0.69 (0.19–2.57)	0.58
III	3.49 (1.05–11.56)	0.04	0.68 (0.12–3.71)	0.65

HR hazard ratio, *CI* confidence interval

[a]Hazard ratio cannot be estimated for systemic recurrence

[b]Hazard ratio cannot be estimated for loco-regional recurrence

management should follow the non-small cell lung cancer (NSCLC) algorithm which recommends adjuvant chemotherapy or chemo-radiotherapy after resection in the presence of nodal metastases, positive resection margins, poorly differentiated tumor histology, tumor size >4 cm and the presence of pleural invasion [17]. Our results suggest that for N0 resected LCNEC the cutoff could be 3 cm to consider adjuvant chemotherapy after complete resection given the high risk of systemic recurrence. Alternatively, one could also justify adjuvant therapy based on the fact that LCNEC is a poorly differentiated tumor histology. These findings are supported by Rossi et al. [13] who identified that tumor size >3 cm is an independent prognostic factor for survival in a series of patients undergoing surgery ± adjuvant chemotherapy for LCNEC. When taken with the results from Sarkaria et al. [6] showing stage IB LCNEC portended a worse prognosis compared to stage IA, the evidence suggests that the consideration for adjuvant chemotherapy should exist with resected disease as early as pStage IB. We suggest that all patients with a tumor size >3 cm, pT2a and possibly pStage IB disease or greater be considered to undergo adjuvant systemic therapy to hopefully reduce the risk of distant metastasis and potentially improve survival.

Adjuvant chemotherapy has been suggested to improve survival after LCNEC resection in some studies including patients with early-stage disease, but the number of patients is limited in these series [3, 12, 13, 18]. As well, a recent study by Kujtan et al. [16] reported a significant improvement in overall survival when chemotherapy was added to surgery in a retrospective series of 1232 stage I LCNEC patients in the National Cancer Database (5-year survival rate after surgery plus chemotherapy and after surgery alone: 64.5% and 48.4% respectively; $p < 0.001$). In this study, this improvement remained significant when patients were stratified by stage (IA and IB). However, chemotherapy benefit seemed to have a greater impact on patients with stage IB than on those with stage IA LCNEC, increasing 5-year survival rate, respectively, from 44.7 to 68.7% and from 50.4 to 59.4% [16]. Similarly, a European

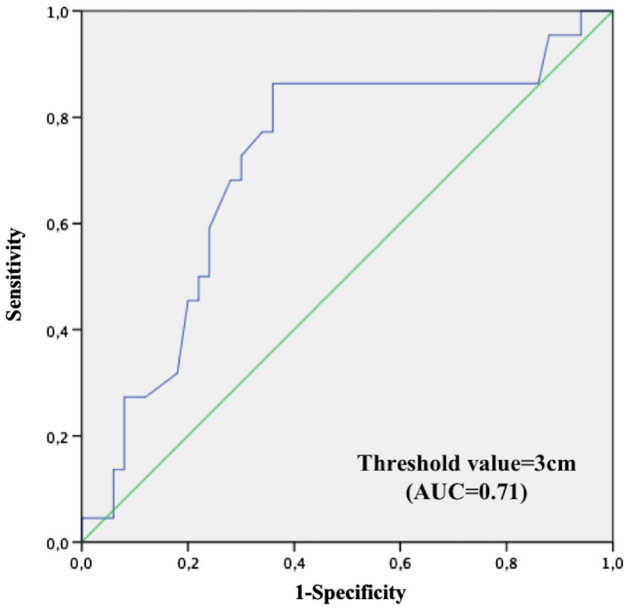

Fig. 1 ROC curve: tumor size and systemic recurrence

multicentered study has concluded that adjuvant chemotherapy has some benefits above surgery alone. In this study it was used predominantly for stage II or greater though nearly 25% of group receiving adjuvant chemotherapy was stage I [18].

When adjuvant chemotherapy is recommended, the choices of agents remain controversial. Given its histological similarity to small cell lung cancer, the obvious choice is the doublet of cisplatin and etoposide, but because LCNEC resides within the NCCN NSCLC guidelines oncologists may be apt to choose a cisplatin doublet with gemcitabine, docetaxel or vinorelbine. Some data suggest that survival was significantly improved when patients were treated with cisplatin and etoposide compared to other NSCLC cisplatin doublets [12, 13, 19, 20]. In advanced-stage non-surgical LCNEC, the combination of cisplatin and etoposide has been favored over other NSCLC doublets with superior survival [12, 13, 19, 20].

Finally, in the treatment of resected LCNEC radiotherapy is still unclear and debated. Postoperative radiotherapy is recommended for the same scenarios as for more common other NSCLC: in the presence of incomplete resection (R1 or R2 resection) or mediastinal lymph nodes metastases (pN2 or pN3 disease). Given that surgical resection provides excellent local control, its role in the induction setting seems limited as well particularly when combined with the fact that systemic recurrences are most common. Like other NSCLCs, there is a potential role for radiotherapy in recurrent disease and in patients with isolated oligometastatic disease. It seems highly effective for limited brain metastases and while prophylactic cranial radiation, which is part of the early-stage small cell neuroendocrine carcinoma treatments, is not recommended

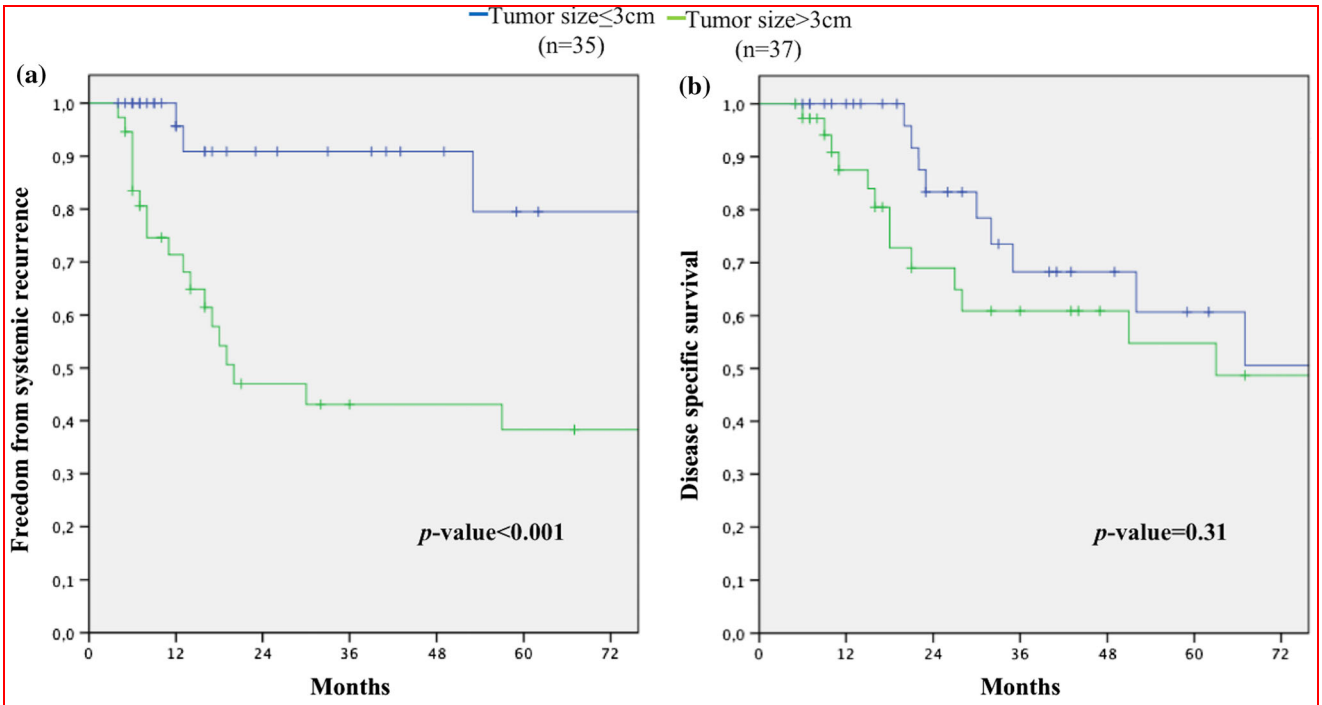

Fig. 2 Freedom from systemic recurrence (**a**) and disease-specific survival (**b**): comparison between patients with tumor size ≤3 cm and patients with tumor size >3 cm (Kaplan–Meier method)

Table 4 Factors influencing disease-specific and overall survival: Cox regression analysis

Factors	Disease-specific survival		Overall survival	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (continuous)	0.99 (0.94–1.04)	0.74	0.99 (0.95–1.04)	0.72
Gender (female vs male)	1.12 (0.42–2.98)	0.82	1.00 (0.42–2.35)	0.99
ECOG performance status (reference 0)				
1	0.91 (0.31–2.66)	0.87	0.99 (0.39–2.48)	0.98
≥2	0.34 (0.04–2.92)	0.33	0.26 (0.03–2.07)	0.20
Previous malignancy (no vs yes)	0.85 (0.26–2.79)	0.79	0.78 (0.28–2.20)	0.64
Presence of symptoms (no vs yes)	0.84 (0.33–2.14)	0.72	0.99 (0.78–1.26)	0.94
Extent of resection (greater vs sublobar resections)	0.51 (0.11–2.41)	0.40	0.62 (0.17–2.23)	0.47
Lymphadenectomy (complete dissection vs sampling)	2.57 (0.36–18.41)	0.35	3.76 (0.62–22.71)	0.15
Additional chemo-/radiotherapy (no vs yes)	1.61 (0.62–4.15)	0.33	1.13 (0.50–2.60)	0.76
Tumor location (central vs peripheral)	0.46 (0.10–2.04)	0.31	0.87 (0.32–2.35)	0.78
Tumor size (continuous)	1.00 (0.84–1.19)	0.99	1.01 (0.86–1.18)	0.91
pT (reference pT1)				
pT2	1.72 (0.61–4.82)	0.30	1.14 (0.46–2.81)	0.77
pT3/4	1.22 (0.36–4.13)	0.75	1.22 (0.43–3.43)	0.71
Pleural invasion (yes vs no)	1.00 (0.37–2.76)	0.99	1.14 (0.47–2.76)	0.77
pN (reference pN0)				
pN1	1.10 (0.37–3.27)	0.86	0.79 (0.29–2.14)	0.65
pN2	3.49 (0.61–19.90)	0.16	2.84 (0.69–11.64)	0.15
pStage (reference I)				
II	1.84 (0.66–5.11)	0.24	1.31 (0.55–3.13)	0.54
III	1.09 (0.25–4.72)	0.91	0.92 (0.27–3.19)	0.89

HR hazard ratio, *CI* confidence interval

Table 5 Recurrence and survival after lung resection for large cell neuroendocrine carcinoma reported in the literature

Study	Year	No of patients	Overall *R n* (%)	Loco-regional *R n* (%)	Systemic *R n* (%)	Five-year OS rate (%)
Roesel et al. [4]	2016	127	86 (69)	38 (31)	48 (38)	54
Filosso et al. [5]	2015	135	60 (73)	15 (18)	45 (55)	28
Sarkaria et al. [6]	2011	100	38[a]	9 (9)	23	41
Saji et al. [23]	2010	45	n/a	n/a	n/a	69
Veronesi et al. [3]	2006	144	58 (40)[b]	7 (5)	31 (22)	43
Asamura et al. [7]	2006	141	68 (48)[c]	17 (12)	34 (24)	40
Battafarano et al. [24]	2005	56	n/a	n/a	n/a	30
Paci et al. [8]	2004	48	34 (71)	0	34 (71)	21
Zacharias et al. [25]	2003	21	7 (35)	3 (15)	4 (20)	47
Takei et al. [9]	2002	87	35 (40)[d]	12 (14)	20 (23)	57
García-Yuste et al. [26]	2000	22	13 (59)	n/a	n/a	20

R recurrence, *OS* overall survival, *n/a* not available data

[a]2 Patients had both loco-regional and systemic recurrence

[b]Site of recurrence was not available in 20 patients

[c]16 Patients had both loco-regional and systemic recurrence and 1 patient had no data about recurrence site

[d]3 Patients had both loco-regional and systemic recurrence

in the treatment of resected LCNEC at this stage. Although, there is at least one small series suggestion that it might have some benefits [1, 15, 17, 21, 22].

This study has several limitations. First, a centralized review process for pathology was not available. However, all results were reviewed in each center, which provides more granular data than an administrative data study. Second, there was no pre-specified treatment regimen. The majority of patients, however, underwent surgical resection followed by adjuvant therapy as determined by local practices and tumor board discussions. Third, there were only a limited number of patients who received chemotherapy after surgery which did not allow for an in-depth analysis of the impact of adjuvant chemotherapy on recurrence and survival. Lastly, even though the number of cases is consistent with that of other studies, the number of patients remains small and as such can influence the statistical results.

Patients undergoing surgery for LCNEC have a 5-year survival rate of 51.6%. Systemic recurrences dominate as the first site of failure. We have identified that tumor size >3 cm is associated with a significantly higher rate of systemic recurrence and a slightly lower survival: Adjuvant chemotherapy may be indicated for patients with completely resected N0 LCNEC >3 cm.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Fasano M, Della Corte CM, Papaccio F et al (2015) Pulmonary large-cell neuroendocrine carcinoma: from epidemiology to therapy. J Thorac Oncol 10:1133–1141
2. Detterbeck FC (2010) Management of carcinoid tumors. Ann Thorac Surg 89:998–1005
3. Veronesi G, Morandi U, Alloisio M et al (2006) Large cell neuroendocrine carcinoma of the lung: a retrospective analysis of 144 surgical cases. Lung Cancer 53:111–115
4. Roesel C, Terjung S, Weinreich G et al (2016) A single-institution analysis of the surgical management of pulmonary large cell neuroendocrine carcinomas. Ann Thorac Surg 101:1909–1914
5. Filosso PL, Rena O, Guerrera F et al (2015) Clinical management of atypical carcinoid and large-cell neuroendocrine carcinoma: a multicentre study on behalf of the European Association of Thoracic Surgeons (ESTS) Neuroendocrine Tumours of the Lung Working Group. Eur J Cardiothorac Surg 48:55–64
6. Sarkaria IS, Iyoda A, Roh MS et al (2011) Neoadjuvant and adjuvant chemotherapy in resected pulmonary large cell neuroendocrine carcinomas: a single institution experience. Ann Thorac Surg 92:1180–1186
7. Asamura H, Kameya T, Matsuno Y et al (2006) Neuroendocrine neoplasms of the lung: a prognostic spectrum. J Clin Oncol 24:70–76
8. Paci M, Cavazza A, Annessi V et al (2004) Large cell neuroendocrine carcinoma of the lung: a 10-year clinicopathologic retrospective study. Ann Thorac Surg 77:1163–1167
9. Takei H, Asamura H, Maeshima A et al (2002) Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. J Thorac Cardiovasc Surg 124:285–292
10. Eichhorn F, Dienemann H, Muley T et al (2015) Predictors of survival after operation among patients with large cell neuroendocrine carcinoma of the lung. Ann Thorac Surg 99:983–989
11. Fournel L, Falcoz PE, Alifano M et al (2013) Surgical management of pulmonary large cell neuroendocrine carcinomas: a 10-year experience. Eur J Cardiothorac Surg 43:111–114
12. Iyoda A, Hiroshima K, Toyozaki T et al (2001) Adjuvant chemotherapy for large cell carcinoma with neuroendocrine features. Cancer 92:1108–1112
13. Rossi G, Cavazza A, Marchioni A et al (2005) Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRalpha, PDGFRbeta, and Met in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol 23:8774–8785
14. Dresler CM, Ritter JH, Patterson GA et al (1997) Clinicalpathologic analysis of 40 patients with large cell neuroendocrine carcinoma of the lung. Ann Thorac Surg 63:180–185
15. RieberJ SJ, Warth A et al (2015) Outcome and prognostic factors of multimodal therapy for pulmonary large-cell neuroendocrine carcinomas. Eur J Med Res 20:64–71
16. Kujtan L, Muthukumar V, Kennedy KF et al (2018) The role of systemic therapy in the management of stage i large cell neuroendocrine carcinoma of the lung. J Thorac Oncol 13:707–714
17. NCCN Clinical Practice Guidelines in Oncology. Small cell lung cancer. Version 1.2016. https://www.NCCN.org
18. Filosso PL, Guerrera F, Evangelista A et al (2017) Adjuvant chemotherapy for large-cell neuroendocrine lung carcinoma: results from the European Society for Thoracic Surgeons Lung Neuroendocrine Tumours retrospective Database. Eur J Cardiothorac Surg 52:339–345
19. Kozuky T, Fujimoto N, Ueoka H et al (2005) Complexity in the treatment of pulmonary large cell neuroendocrine carcinoma. J Cancer Res Clin Oncol 131:147–151
20. Yamazaki S, Sekine I, Matsuno Y et al (2005) Clinical responses of large cell neuroendocrine carcinoma of the lung to cisplatin-based chemotherapy. Lung Cancer 49:217–223
21. Ramirez RA, Chauhan A, Gimenez J et al (2017) Management of pulmonary neuroendocrine tumors. Rev Endocr Metab Disord 18:433–442
22. Mazières J, Daste G, Molinier L et al (2002) Large cell neuroendocrine carcinoma of the lung: pathological study and clinical outcome of 18 resected cases. Lung Cancer 37:287–292
23. Saji H, Tsuboi M, Matsubayashi J et al (2010) Clinical response of large cell neuroendocrine carcinoma of the lung to perioperative adjuvant chemotherapy. Anticancer Drugs 21:89–93
24. Battafarano RJ, Fernandez FG, Ritter J et al (2005) Large cell neuroendocrine carcinoma: an aggressive form of non-small cell lung cancer. J Thorac Cardiovasc Surg 130:166–172
25. Zacharias J, Nicholson AG, Ladas GP et al (2003) Large cell neuroendocrine carcinoma and large cell carcinomas with neuroendocrine morphology of the lung: prognosis after complete resection and systematic nodal dissection. Ann Thorac Surg 75:348–352

26. García-Yuste M, Matilla JM, Alvarez-Gago T et al (2000) Prognostic factors in neuroendocrine lung tumors: a Spanish Multicenter Study. Spanish Multicenter Study of Neuroendocrine Tumors of the Lung of the Spanish Society of Pneumonology and Thoracic Surgery (EMETNE-SEPAR). Ann Thorac Surg 70:258–263