



Prognostic markers in resected large cell neuroendocrine carcinoma: a multicentre retrospective analysis

Christian Roesel^{1#}, Stefan Welter^{2#}, Karl-Otto Kambartel³, Gerhard Weinreich⁴, Thomas Krbeke¹, Monika Serke⁵, Mohammed Ibrahim², Yazan Alnajdawi⁶, Till Plönes⁶, Clemens Aigner⁶

¹Department of Thoracic Surgery, Bethanien Hospital, Moers, Germany; ²Department of Thoracic Surgery, Lung Hospital, Hemer, Germany; ³Department of Pneumology and Allergology, Bethanien Hospital, Moers, Germany; ⁴Department of Pneumology, Ruhrlandklinik, University of Duisburg-Essen, Essen, Germany; ⁵Department of Pneumology, Lung Hospital, Hemer, Germany; ⁶Department of Thoracic Surgery and Thoracic Endoscopy, Ruhrlandklinik, University of Duisburg-Essen, Essen Germany

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[#]These authors contributed equally to this work.

Correspondence to: Christian Roesel, MD. Department of Thoracic Surgery, Bethanien Krankenhaus, Bethanienstraße 21, 47441 Moers, Germany. Email: Christian.Roesel@bethanienmoers.de.

Background: Large cell neuroendocrine carcinomas (LCNEC) are rare pulmonary malignancies. Reported survival rates are heterogeneous and the optimal therapeutic strategy is still debated. The prognosis of LCNEC is generally inferior compared to other non-small lung cancers. In early stages, surgery is recommended but might not be sufficient alone.

Methods: We retrospectively analyzed all consecutive LCNEC patients operated at three institutions with curative intent between May 2005 and January 2017. Data retrieved from individual clinical databases were analyzed with the aim to identify prognostic parameters.

Results: A total of 251 patients with LCNEC underwent curative intent surgery during the observation period. The median age was 64 years, 156 patients (62.2%) were male and 88.4% were smokers. The pathologic AJCC stage was I in 136 patients, II in 77, III in 33, and IV in 5 patients. Median follow-up was 26 months. Lymphatic vessel invasion ($P=0.031$) was identified as significant prognostic factor by multivariable analysis. There was a trend towards decreased survival in patients with blood vessel invasion ($P=0.067$). Even in earlier tumor stages, adjuvant chemotherapy had a positive effect on survival. The overall 1-, 3- and 5-year survival rates were 79.2%, 48.6% and 38.8% respectively.

Conclusions: Lymphatic invasion (L1) is an independent prognostic factor. Surgery in LCNEC is beneficial in early tumor stages and platinum-based adjuvant chemotherapy may help in achieving better long-term outcomes resulting in most obvious survival differences in stage Ib.

Keywords: Large cell neuroendocrine carcinomas; pulmonary malignancies; lymphatic invasion; curative resection; platinum-based adjuvant chemotherapy

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Introduction

Large cell neuroendocrine carcinomas (LCNEC) are a rare subset of lung cancers, accounting for 15% of neuroendocrine tumors and 2–3% of all lung cancers (1–2).

The incidence could be even higher since neuroendocrine markers can be missed or misinterpreted if the diagnosis relies on small biopsy specimens (3). About 85% LCNEC present as a peripheral tumor in contrast to typical and atypical

carcinoids and small cell lung cancer (SCLC) that are often located centrally (4). Unlike carcinoid tumors, LCNECs often are associated with male sex, older age, and smoking habit (5).

In general, the prognosis in LCNEC patients is poor. A previous study reported that stage IV disease was found in 40% at initial diagnosis and survival was inferior to other NSCLC tumor types (6). The median overall survival (OS) of stages I–II, III and IV was found to be 32.4, 12.6 and 4.0 months, respectively, in a population-based cancer registry of the Netherlands. Based on retrospective studies the 5-year survival rates for these patients were between 21% and 62% in earlier studies (7–9).

Adjuvant therapy, mainly chemotherapy demonstrated benefits on survival and recurrence (9,10). Although the result was not statistically significant, a retrospective analysis of 144 surgically removed pulmonary LCNEC revealed a better outcome in patients treated with preoperative or postoperative chemotherapy in stage-I, suggesting that the adjuvant therapy has a promising role even in early stage disease (9). Due to the rarity of presentation and persistent difficulty in differential diagnosis, the prognosis and best treatment for this group of malignancies remain uncertain. It is still unclear whether the patients diagnosed with LCNEC should be treated with NSCLC or SCLC-based regimes (11).

Firstly, this triple center retrospective study investigated outcome after surgical resection of LCNEC focusing on prognostic factors that are able to identify subgroups with a worse outcome. A more aggressive treatment strategy could be beneficial for these subgroups. Secondly, we analyzed the value of adjuvant treatment.

Methods

The data of all consecutive LCNEC patients undergoing curative intended surgery at three different institutions between May 2005 and January 2017 were retrieved from clinical databases and retrospectively analyzed to explore prognostic parameters. Ethical approval was obtained from the ethic committee of the Medical Faculty of the University Duisburg-Essen (13-5363-BO). Follow-up data was obtained from medical records, routine pathology reports and the cancer centers databases. Oncologic staging included computed tomography (CT) of the chest, abdomen, magnetic resonance imaging of the head and bone scintigraphy. Since 2010, standard 18-FDG positron emission tomography (PET) had been integrated into the staging procedure. Preoperative clinical staging and mediastinal staging was performed according to the current

guidelines of European Society for Medical Oncology (ESMO) and the European Society of Thoracic Surgeons (ESTS) (12). The treatment decision was guided by an interdisciplinary tumor board in all cases. Patients of the early and late study period were reclassified to the 7th revision of the TNM classification.

Anatomical resection was completed by systematic lymph node dissection or systematic sampling at the discretion of the surgeon. If mediastinal N2 disease was confirmed by mediastinoscopy or EBUS-TBNA, neoadjuvant chemotherapy or chemo-radiotherapy was administered and surgery was performed in those cases that responded to the induction therapy. All operative specimens were investigated by experienced lung pathologists. Neuroendocrine morphology [abundant mitoses (>10 mitosis/ 2 mm^2), neuroendocrine morphology such as rosettes, trabecular growth pattern or palisading of cells and the presence of necroses] and positive staining for CD56, chromogranin A or synaptophysin were applied as criteria for histologic confirmation of LCNEC as recommended by the World Health Organization (13). Lymphatic (L1) and vascular invasion (V1) was certified by the pathologist if direct tumor invasion of lymphatic or vascular structures were observed or if tumor cells were found in these structures.

Depending on co-morbidity, age and cardio-pulmonary function, adjuvant or additive platinum-based chemotherapy was administered in patients with stage I (tumor diameter >4 cm) or stage II and III disease. Adjuvant chemotherapy was administered to selected patients in early stage Ia as well if they were in good clinical condition but presented with L1 or V1.

Statistical analysis

Descriptive variables studied in this research were analyzed and presented in frequency, mean \pm standard deviation and range. Statistical analyses were performed by using Statistical Package for Social Science (SPSS) Version 22.0 (SPSS Inc., Chicago, USA). Survival was defined as the time interval between the date of surgical intervention and the date of death or the last follow-up information of the patients. The latest follow-up of patients was censored.

Kaplan–Meier analysis was performed to compute univariate comparisons between different subsets, including overall survival, T status, N status and local lymphatic spread. Differences between survival times of two samples were assessed using log-rank tests. Cox regression analysis was performed in multivariable models. Differences with

Table 1 Patients demographics and characteristics

Characteristics	Number of patients (%)
Total	251
Gender	
Female	95 (37.8)
Male	156 (62.2)
Age (years)	
>65 years	112 (44.6)
≤65 years	139 (55.4)
Mean (range)	65 (38–87)
Smoking habit	
Smoker, ex-smoker (>20 py)	222 (88.4)
Non-Smoker/not known	29 (11.6)
Tumor localization	
Right upper lobe	92 (36.7)
Middle lobe	7 (2.8)
Right lower lobe	38 (15.1)
Left upper lobe	73 (29.1)
Left lower lobe	37 (14.7)
Central, not exactly specifiable	4 (1.6)
Lymphangitic invasion	
L0	218 (86.9)
L1	33 (13.1)
Vascular invasion	
V0	188 (74.9)
V1	63 (25.1)
Completeness of resection	
Complete (R0)	243 (96.8)
Incomplete (R1)	8 (3.2)
Stage of disease	
IA/IB	136 (54.2)
IIA/IIB	76 (30.3)
IIIA/IIIB	33 (13.1)
IV	5 (2.0)

$P < 0.05$ were considered statistically significant. Parameters that probably influenced survival in the univariate analysis with $P = 0.1$ or less were included into a multivariate Cox

regression analysis.

Results

The demographic characteristics of the patients (*Table 1*) are similar to a previous study (7).

Operative results

All 251 patients had surgical resections of the primary tumor, which were then histologically categorized as pure (77%) or mixed (23%) LCNEC, demonstrating features of both LCNEC and NSCLC, mainly adenocarcinoma. Operative procedures performed included 192 (76.5%) lobectomies, 5 (2%) bilobectomies, 22 (8.8%) wedge resections, 7 (2.8%) pneumonectomies, 4 (1.6%) sleeve lobectomies and 21 (8.4%) anatomical segmentectomies. The number of removed lymph nodes was 12.7 ± 7.4 . Of the treated patients, 243 patients had a complete resection (97%) and 8 patients (3%) had a microscopic residual tumor at the margin (R1) after surgical resection, which was not diagnosed during intraoperative frozen section. There were no intraoperative deaths. One patient developed bronchial-stump insufficiency and one other patient developed a fulminant mesenteric ischemia. Both of them died in the further clinical course. Thus, the perioperative 30- and 60-day mortality rate was 0.8%.

Pathological findings

An accurate tissue diagnosis by bronchoscopy or CT-guided biopsy was established in 23 (9.2%) patients preoperatively and was confirmed later on in the resected specimens. All other patients were diagnosed intra- or postoperatively based on the resected specimens.

The pathological examination revealed a median tumor size of 3.5 cm (mean 3.7 ± 2.1 cm; 95% CI, 0.7–13.0 cm). The pathologic stage was I in 136 (54.2%), II in 77 (30.7%), III in 33 (13.1%) and IV in 5 (2%) patients. All stage IV patients presented with an oligometastatic situation. They additionally underwent complete resection of a skin [1], brain [3] or adrenal [1] metastasis. Immunohistochemical staining was positive for CD56 in 214 (85.3%) patients, Synaptophysin-A in 133 (53%) patients and Chromogranin-A in 94 (37.5%) patients. Simultaneous expression of two and three immunohistochemical markers were found in 104 (41.4%) and 45 (17.9%) patients respectively.

Table 2 Tumor recurrences

Patient's status	Value
Total recurrence, n [%]	118 [47]
Loco-regional recurrence (total), n [%]	33 [28]
Mediastinal	19 [58]
Pulmonary/pleural metastasis	14 [42]
Distant recurrence (total), n [%]	85 [72]
Brain	5
Abdomen	4
Bone	6
Multiple (more than two sides)	70
Median time to local recurrence	18 [1–114] months
Median time to distant recurrence	15 [1–105] months

Causes of death

As mentioned above, 2 (0.8%) patients died in the early postoperative period and one other patient (0.4%) died following toxicity of adjuvant chemotherapy and 17 expired of comorbidities during follow-up. 118 additional patients died from tumor relapse. In this subgroup, distant disease occurred in 85 and local recurrence occurred in 33 patients. Local recurrence affected the lung (30.3%), mediastinum (57.5%), pleura (6.1%) and the chest wall (6.1%). A total of 17 (51.5%) patients with local recurrence received chemotherapy, 8 (24.2%) were treated with radiotherapy and 5 (15.2%) were treated with combined radio-chemotherapy. Two patients were re-operated due to recurrence in the chest-wall. The median time to local recurrence was 18 months. Distant metastases were noted in 85 (72%) cases after a median of 15 months. Among them 70 (56.9%) patients had multiple metastases and were treated with palliative chemotherapy (Table 2).

Survival/prognostic factors

Survival rate was calculated from the date of lung tumor removal to the last follow-up or date of death. The median follow-up was 26 months (mean 35.5±31.7 months). Three patients were lost to follow-up and were excluded from further survival analysis. The 5-year overall survival for the entire patient cohort was 38.8%. The five-year survival in stages I, II and III was 60.9%, 31% and 22.7% (Figure 1A) respectively.

Sex was not associated with survival ($P=0.295$). Age >65 years was associated with prognosis in the multivariable analysis ($P=0.017$) but not significant in the univariate analysis ($P=0.591$). There was no survival difference between pure LCNEC and mixed (LCNEC + NSCLC) histology ($P=0.331$). The pathologic T-stage (pT) significantly influenced the prognosis. The 5-year survival of patients with pT1–2 tumors was 43.1% compared to 23.1% in patients with a pT3–4 tumors ($P=0.045$) (Figure 1B). The 5-year survival rate decreased from 48.2% to 26.3% when lymph node metastases were present ($P=0.012$) (Figure 1C). Patients with lymphatic or vascular invasion faced inferior ($P=0.007$ and $P<0.001$) survival because of higher rates of distant metastasis (Figure 2A,B). Regarding median survival we do not find statistical significance for L0 patients compared with L1 patients in tumor stages I (61 vs. 13 months), II (30 vs. 26 months) and III (21 vs. 14 months) (Table 3). Beside stage, lymphatic invasion remained an independent predictor of survival in the multivariable analysis ($P=0.031$). Locoregional tumor recurrence was not associated with the presence of L1 ($P=0.697$) or V1 ($P=0.974$).

As a consequence, when survival was analyzed by stage, a worse prognosis was observed in stage III and IV disease compared to stage I–II disease ($P=0.007$). Expression of a single neuroendocrine marker (CGA, CD56 or SYN) did not predict overall survival ($P>0.05$). There was a trend that the simultaneous expression of two or even three markers was associated with an inferior survival. The median survival was 70 (95% CI: 40–100) months, 28 (95% CI: 20–36) months and 26 (95% CI: 17–35) months in patients with 1, 2 and 3 positive neuroendocrine markers ($P=0.08$).

Perioperative chemotherapy

Primary resection was performed in 232 patients (92.4%), and 19 (7.6%) patients received neoadjuvant chemotherapy or radiochemotherapy. A clinical response to induction therapy was observed in 15 of the 19 patients (78.9%). A total of 101 (40.2%) surgically resected patients received adjuvant chemotherapy. Data on the chemotherapy regimen were available in 99 of the 120 (82.5%) patients with perioperative chemotherapy. All patients had doublets with cisplatin or carboplatin, one had oxaliplatin. Platin was combined with etoposide, paclitaxel, vinorelbine or pemetrexed in decreasing frequency.

The 5-years survival was 44.6% for patients with adjuvant chemotherapy and 37.8% without ($P=0.02$). The

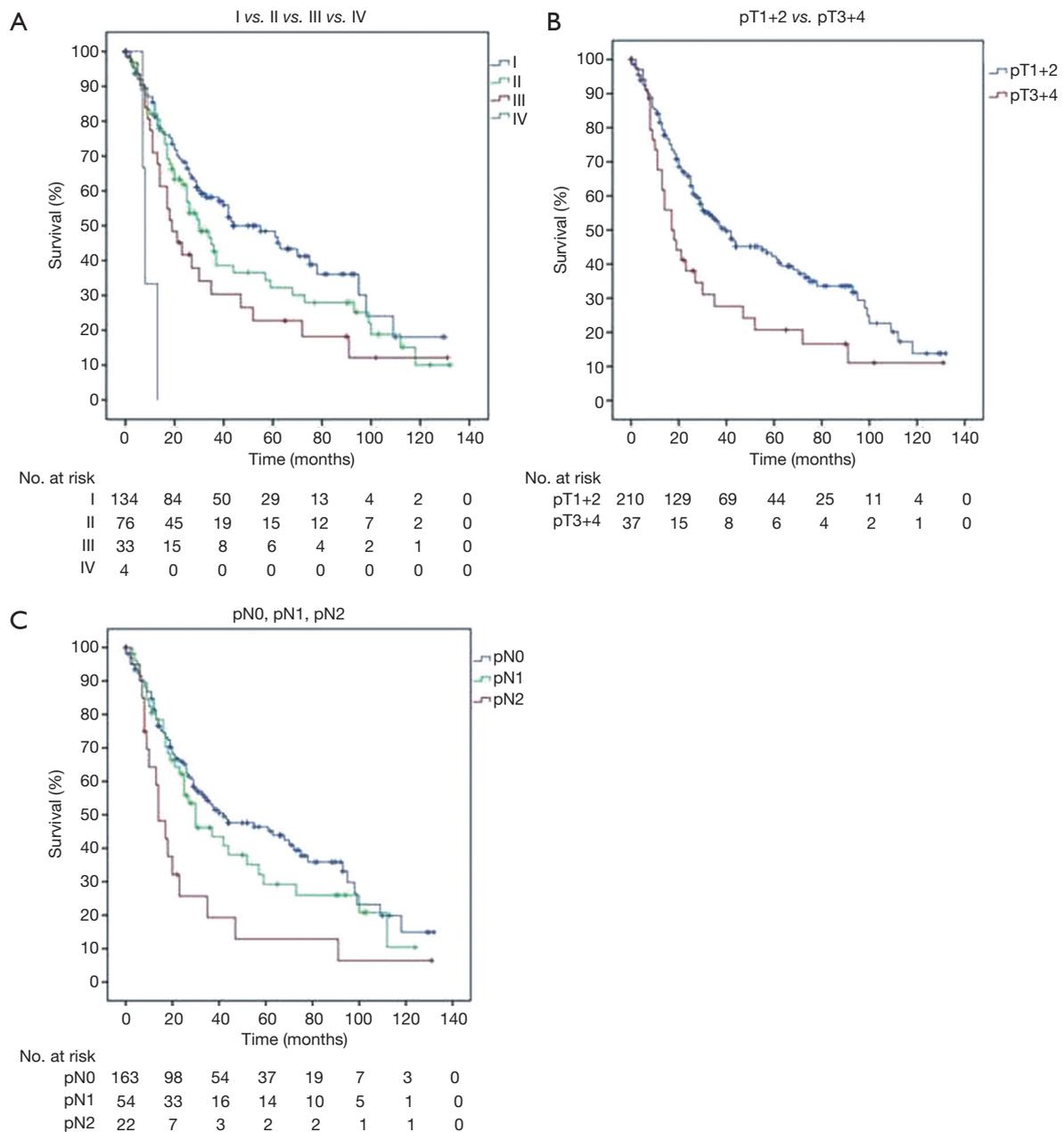


Figure 1 Kaplan-Meier estimates of survival. (A) Stage dependent survival according to Kaplan-Meier overall survival analysis. The number of patients at risk is 247. One case with follow-up data could not be classified by UICC stage. (B) Survival according to pT-stage. T-stage 1 and 2 were grouped together and compared with T-stage 3 and 4. One case with follow-up data could not be allocated to a T-stage. Survival of patients with T3/T4 tumors was significantly inferior to patients with T1/T2 tumors ($P=0.045$, univariate analysis). (C) Survival according to pN-stage. 8 cases were undefined concerning lymph node involvement (Nx) and one case with follow-up data had no information on n-stage. Therefore 239 patients could be included into survival analysis ($P=0.012$, univariate analysis).

administration of perioperative chemotherapy was found as an independent prognostic factor in multivariable analysis. A subgroup analysis of patients in stage I and stage II with

and without adjuvant therapy resulted in a positive effect of adjuvant chemotherapy on OS ($P=0.005$ and $P=0.0014$) (Table 3, Figure 3A,B). The effect of adjuvant chemotherapy

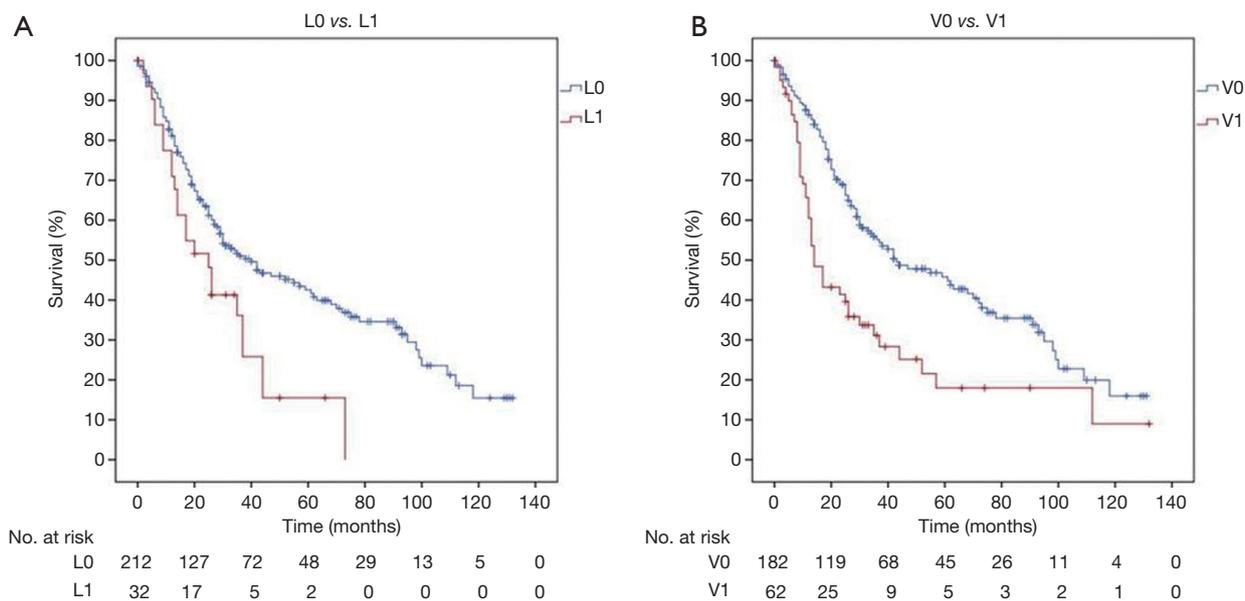


Figure 2 Kaplan-Meier estimates of survival. (A) Overall survival according to the presence or absence of lymphatic invasion ($P=0.007$, univariate analysis). Four of 248 cases did not have information about the L-status, therefore 244 cases could be included into survival analysis. (B) Overall survival according to the presence or absence of vascular invasion. 244 cases could be analyzed (A). V1 was associated with inferior prognosis in the univariate analysis ($P<0.001$).

was analyzed in the subgroups with different marker expression profiles. No difference was found for patients with CD56 or Synaptophysin, whereas patients positive for CgA had inferior median survival after adjuvant chemo compared to CgA negative patients (99 *vs.* 25 months, $P=0.003$). To define the effect of adjuvant chemo in early tumor stages IA and IB more precisely, we included age, sex, ECOG score and histology (LCNEC *vs.* mixed tumors) into a Cox regression model. Adjuvant chemo still had a significant positive effect on survival with a HR of 0.379 (95% CI: 0.168–0.852, $P=0.019$).

Discussion

In this study, we present the result of a large contemporary multi-institutional series of 251 resected patients with LCNECs of the lung, focusing on clinicopathologic factors, effects of perioperative chemotherapy and survival outcomes. The study aimed at determining prognostic factors, identifying patients with a poorer prognosis, who might benefit from a more aggressive therapy. In contrast to other neuroendocrine lung tumors, we found that most (85%) LCNEC had grown in the periphery of the lung. This might be one of the reasons why most of the

patients were asymptomatic and the tumor was diagnosed during routine imaging. In addition, this might also be an explanation why early tumor stages were over-represented in our retrospective data sets. Tumor stage and T-stage was associated with prognosis in our study as was described by others as well (14). Among others, lymphatic and vascular invasion was identified in univariable analysis, however lymphatic invasion remained an independent prognostic factor in multivariable analysis. Those cases are correlated with inferior prognosis after resection of LCNEC.

Previous studies reported that the presence of vascular invasion or lymphatic invasion was a significantly unfavorable prognostic factor in many malignant tumors (15). Lymphatic or vascular invasion (L1, V1) triggers an important process in the progression and local spread of cancer cells. Lymphatic vessels are regarded as an important route by which neoplastic cells reach local lymph nodes (16). When tumor cells penetrate a blood or lymphatic vessel, they can detach, disseminate and arrest in the microvasculature and migrate into the organs tissue. The presence of vascular invasion by neoplastic cells might indicate that the cancers are in a metastatic phase. In a meta-analysis, Saijo *et al.* reported that L1 is a prognostic factor for survival in patients with NSCLC (17). However,

Table 3 Prognostic factors and their association with survival

Factor	Univariable	Multivariable	
	P	Hazard ratio (95% CI)	P
Age			
<65 vs. ≥65 years	0.591	1.029 (1.005–1.053)	0.017
Sex			
Male vs. female	0.295		
T-stage			
pT1/2 vs. pT3/4	0.045	1.482 (0.842–2.609)	0.172
N-stage			
N0 vs. N1 vs. N2	0.012		
N0 vs. N+	0.041	1.961 (1.123–3.427)	0.018
L-stage			
L0 vs. L1	0.007	2.012 (1.064–3.805)	0.031
L-stage			
L0 vs. L1 stage I	0.110		
L0 vs. L1 stage II	0.184		
L0 vs. L1 stage III	0.332		
V-stage			
V0 vs. V1	0.001	1.612 (0.967–2.690)	0.067
Completeness of resection*			
R0 vs. R1/R2	0.002	*	*
Tumor size			
<5 vs. ≥5 cm	0.379		
Chemotherapy			
Chemo (induction or adjuvant) vs. no chemo	0.020		
Adjuvant chemo vs. no chemotherapy	0.011	2.081 (1.177–3.679)	0.012
Stage I	0.005		
Stage II	0.014		
Chromogranin A pos. vs. neg.	0.003		
CD56 pos. vs. neg.	0.983		
Synaptophysin pos. vs. neg.	0.743		
Presence of tumor locoregional relapse			
Relapse vs. no relapse	0.042	1.619 (0.928–2.825)	0.090
Immunohistochemical marker			
Chromogranin A	0.132		
Synaptophysin	0.406		
CD56	0.584		
1 vs. 2 vs. 3 marker	0.078		

*, resection status was not included into multivariable analysis as only 2 of 7 cases had complete data of all other parameters.

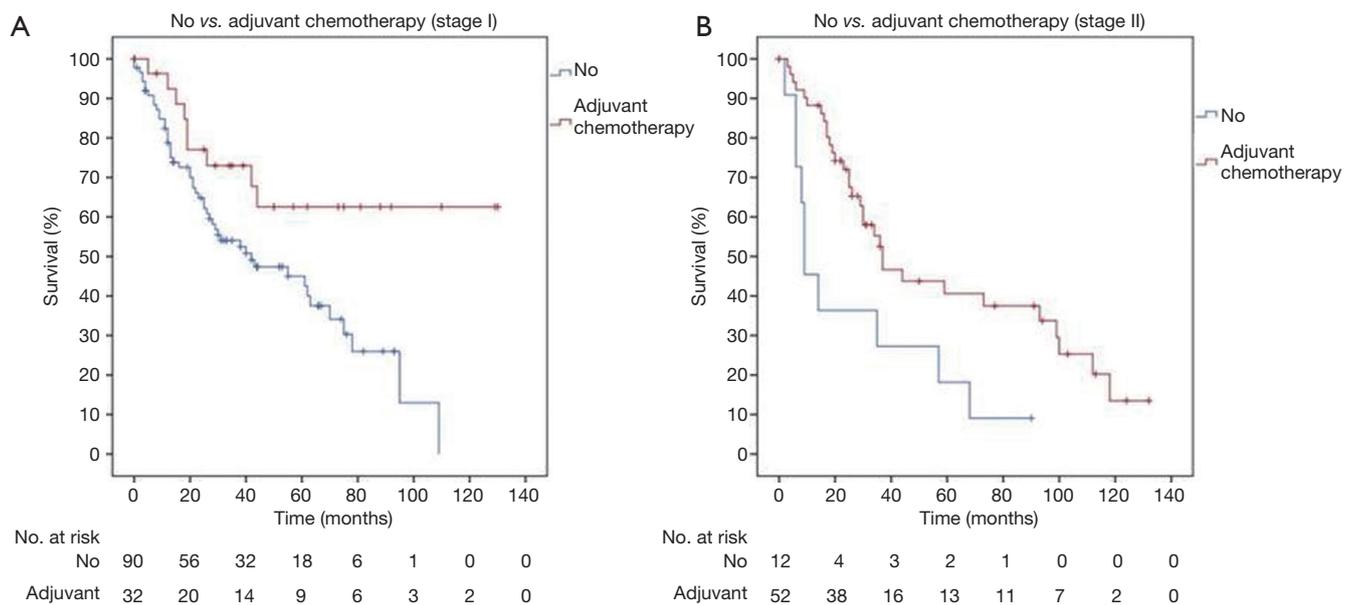


Figure 3 Kaplan-Meier estimates of survival. (A) Survival according to adjuvant chemotherapy in stage I patients ($P=0.005$). Of 125 patients in stage I, 2 were lost to follow-up and adjuvant treatment was unclear in 1 patient. Therefore 122 cases could be included into further survival analysis. (B) Survival according to adjuvant chemotherapy in stage II patients. Of 76 patients in stage II, 6 patients had been given neoadjuvant treatment and there was a lack of information about adjuvant treatment in another 6 cases. Therefore 64 cases could be included into further survival analysis. Univariate analysis demonstrating a positive effect of adjuvant chemotherapy in stage I and stage II ($P=0.005$ and 0.014).

L1 and V1 as prognostic factors for survival in NSCLC remain controversial and they are not considered in the current tumor staging system. The factor V1 has been reported as a strong predictor of recurrence or the cause of death among cancer patients by others, which was independent of lymph node metastasis (18).

The clinicopathologic features in this study were comparable with other studies. LCNECs affected males (62%) and almost exclusively smokers (>88%) and present the same clinical and radiological features like other lung cancers. Therefore, as of now, it is impossible to distinguish LCNEC from other NSCLC by clinical parameters. LCNECs are considered as a separate entity from other neuroendocrine tumors for clinical characteristics, prognosis, and survival. Varlotto *et al.* reported that the clinical, histopathological and biological characteristics of LCNEC were more similar to large-cell carcinoma than to small cell lung cancer (SCLC) (11). But histological differentiation between LCNEC and SCLC can be very challenging as both tumor entities often share many common features. Since 2004 the World Health Organization (WHO) categorizes LCNEC in the group of NSCLC.

Regarding immunohistochemistry analysis, pulmonary LCNECs express typical neuroendocrine markers such as chromogranin A, CD56 and synaptophysin, which are necessary to define the diagnosis. As reported in a previous study (4), we could establish preoperative LCNEC diagnosis only in 9.2%. The low rate might be explained by the fact that most nodules were localized in the periphery and intraoperative frozen section analysis was the standard procedure to establish histological diagnosis in our units. This rate was even higher than the previously published (4.8%) results (4). We now consider that this observed increment can be better explained by a growing awareness among pathologists, greater sample size and sample preparation during bronchoscopy and a more standardized and frequent immunohistochemical staining for neuroendocrine markers at routine pathological work-up. Neuroendocrine marker profiles may predict prognosis and therapy concepts. In our study we found a trend that the presence of more than one neuroendocrine marker was associated with inferior prognosis ($P=0.08$). In the study by Tanaka *et al.* perioperative chemotherapy resulted in better overall survival than surgery alone ($P=0.042$). Interestingly, in the non-triple-positive group,

a significantly higher 5-year survival rate was observed for the patients who underwent perioperative chemotherapy than in those who underwent surgery alone ($P=0.008$). No difference was found in the triple-positive group (19). We observed a reduced effect of adjuvant chemotherapy on OS when CgA was positive. The triple-positive group was too small to perform separate survival analysis. At least one can state, that CgA in the Tanakas (19) paper was positive in the triple-positive group and hence associated with inferior survival. This might be the key for future study conceptions.

Therapy

Primary surgery should be the first option in operable patients with stages I and II. This approach offers also a way to obtain an accurate diagnosis (8-10). Unfortunately, the majority (70%) of pulmonary LCNEC cases are not eligible for surgical resection due to the high prevalence of metastases at initial diagnosis. Even those patients with LCNEC at stage I have a poor prognosis, with 5-year survival rates ranging from 27% to 67% (10). Therefore, surgery alone may not be sufficient. As we did in our study, the retrospective analysis of 144 surgically removed pulmonary LCNECs by Veronesi revealed a better outcome, with preoperative or postoperative chemotherapy in stage I disease although not statistically significant. They stated that adjuvant therapy has a promising role in earliest diagnosed disease (9). Iyoda *et al.* found a significantly better 5-year OS in those patients treated with complete resection and adjuvant cisplatin–etoposide chemotherapy compared to those having no adjuvant treatment (20). Rossi *et al.* reported that adjuvant chemotherapy based on cisplatin plus etoposide was effective for patients with LCNEC (6). Saji *et al.* retrospectively enrolled 45 patients with surgically resected LCNEC in a study (21). Twenty-three patients received preoperative or postoperative chemotherapy and their 5-years survival was superior (87.5%) compared with the group without (58.5%) ($P=0.04$). In our study patients with stage I disease benefited from adjuvant chemotherapy. We had the impression, that even stage IA patients would benefit. Unfortunately, the survival advantage in stage IA with chemo was not significant ($P=0.472$). As the sample size of stage IA patients with adjuvant therapy was lower than in stage IB it cannot be excluded that a type II error may have occurred. The studies of Tanaka *et al.* (19) and Filosso *et al.* (10) also presented that perioperative chemotherapy might be beneficial for the survival of patients with pulmonary

LCNEC. These facts underline the importance of adjuvant treatment in LCNEC regarding over-all survival. New therapy options such as biological and molecular targeted therapies or immunotherapies have been used in individual cases with promising effects (22,23).

Survival

Pulmonary LCNEC behave aggressively. The 5-year survival in stages I, II and III was 60.9%, 31% and 22.7% respectively in our study. In this study we found that lymph vessel invasion and blood vessel invasion are important prognosticators. The prevalence of L1 was 13.1% and much lower than reported in a meta-analysis by Wang *et al.* (15). Blood vessel invasion was 25.1% in our series and comparable with other reported NSCLC series 29.8% (17). Both, L1 and V1 were associated with impaired survival in other NSCLC as well (20,21). Furthermore, L1 was associated with increased numbers of local recurrence after NSCLC resection (15). A significant number of local recurrences were found in patients with V1 in NSCLC stage I after resection (17). Increased local recurrences with L1 ($P=0.697$) or V1 ($P=0.974$) were not found in our study. In summary, we could demonstrate impaired survival in LCNEC tumors with L1 and V1. The prognostic impact of L1 was evaluated earlier for other NSCLC patients in a large meta-analysis as well (17). Due to the retrospective design of the study we did not perform a sample size calculation. Therefore, we cannot exclude that a type II error, including the prognostic importance of L1, may have occurred

Limitations

This study has some limitations due to the retrospective nature of the study and the long observation period including changes of patient management (e.g., PET-CT). Furthermore, the LCNECs are sometimes components of heterogenous tumors so that some cases might have been missed during normal pathologic work-up, especially in larger tumors. L1 was reported when obviously present at routine specimen work-up. A prospective focus on L1 might have identified further cases. On the other hand, the results of this large data set were very similar in all centers and comparable with published evidence. Because we did not differentiate between race and most patients but not all were Caucasians, our results should be interpreted with care in other populations.

Conclusions

This study analyzed a large pooled dataset and reported clinicopathologic factors and survival outcomes in patients with LCNEC. Besides stage, lymphatic invasion (L1) is an important prognostic factor for impaired survival after surgery. Although radical surgery is the mainstay of curative treatment and adjuvant chemotherapy is standard in stage IIIA, adjuvant therapy should be considered in stages IB–IIB, but may be ineffective when CgA is present in the tumor. A prospective randomized clinical trial is recommended to elucidate the effect of adjuvant therapy in early stages. Unfavourable prognostic factors like L1 might be also considered for inclusion in the future revision of the TNM staging system and for therapy decisions concerning adjuvant chemotherapy.

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Footnote

Conflicts of Interest: SW serves as the unpaid editorial board member of *Journal of Thoracic Disease* from May 2019 to Apr 2021. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Ethical approval was obtained from the ethic committee of the Medical Faculty of the University Duisburg-Essen (13-5363-BO).

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