Current Problems in Cancer 43 (2019) 54–65

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Treatment outcomes and incidence of brain metastases in pulmonary large cell neuroendocrine carcinoma

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ARTICLE INFO

Keywords:
Large cell neuroendocrine carcinoma
Brain metastasis
Pattern of recurrence
Prophylactic cranial irradiation

ABSTRACT

Introduction: Large cell neuroendocrine carcinoma (LCNEC) is a rare type of high-grade pulmonary neuroendocrine tumor. The study objective is to investigate its survival outcomes, incidence of brain metastases, and patterns of recurrence.
Methods: This is a single center study of patients with pathologic diagnosis of pulmonary LCNEC. Patient data were collected retrospectively and analyzed, including survival, incidence of brain metastases, and patterns of recurrence.
Results: Of 87 patients (stages I: 24, II: 14, III: 23, IV: 26), 52 were managed curatively and 35 palliatively. The median follow-up time was 17.3 months (range 0.6-89.5) for those treated with curative intent and 7.0 months (range 0.1-28.6) for those treated palliatively. The 2- and 5-year overall survival (OS) rates are 48.4% and 25.5% for the curative group, with a median OS of 13.5 months. In the palliative group, the OS are 30.8% at 1 year and 6.8% at 2 years, with a median OS of 7.0 months. Thirty-eight of 52 (73%) patients

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https://doi.org/10.1016/j.currproblcancer.2018.05.006

treated with curative intent had disease relapse, with the common sites being regional lymph nodes (20), brain (18), bones (11), and liver (9). The incidence of brain recurrence among those managed curatively are 21.4% and 41.3%, respectively at 1 and 2 years. Of 18 patients experiencing brain metastases, 14 developed them as part of a first relapse.

Conclusions: LCNEC's survival outcomes are poor. The incidence of brain metastases is higher than what is observed for other types of nonsmall cell lung cancers. Prophylactic cranial irradiation should be investigated as a means of improving outcomes.

Introduction

Large cell neuroendocrine carcinoma (LCNEC) accounts for 2.1%-3.5% of surgically resected lung cancers.[1] Travis et al[2] identified it in 1991 as a distinct type of pulmonary neuroendocrine tumors, separate from small cell lung cancer (SCLC) and typical and atypical carcinoid tumors. In 1999 and 2004, the World Health Organization (WHO) classified it as a variant of large cell carcinoma (LCC), in the group of nonsmall cell lung cancer (NSCLC).[1,3] In 2015, the WHO reclassified it under the grouping of neuroendocrine tumors, separate from LCC.[4]

Based on genomic analysis of commonly altered genes (TP53, RB1, STK11, KEAP1, and KRAS), LCNEC is a biologically heterogeneous group of tumors, expressing genetic signatures of SCLC, NSCLC, and rarely of highly proliferative carcinoids.[5] LCNEC shares notable pathologic and clinical similarities with SCLC. Both are proliferative neuroendocrine neoplasms with large zones of necrosis.[6] Analysis of TP53, Ki-67, KRAS-2, C-RAF-1,[7] and telomerase activity suggests that LCNEC is genetically more similar to SCLC than NSCLC.[8]

Previous retrospective series reported a wide range of 5-year overall survival (OS) rates for pulmonary LCNEC, varying from 13% to 57%.[9-15] On one hand, Varlotto et al[16] demonstrated that the survival outcomes of LCNEC are more comparable to LCC than SCLC. On the other hand, a population-based study by Derks et al[17] and a series by Asamura et al[18] showed that LCNEC's prognosis is worse than NSCLC and similar to SCLC.

LCNEC has not been prospectively studied in randomized trials, and the optimal treatment algorithm remains unknown. Management has incorporated elements of both NSCLC and SCLC management. Like NSCLC, primary surgery is indicated for all patients with resectable disease.[1,19-23] As for adjuvant chemotherapy, NSCLC platinum-based regimens, and SCLC regimens including etoposide are generally recommended.[12,24-31] A retrospective analysis by Derks et al[30] detected superior OS outcomes in the metastatic setting with the use of NSCLC platinum-based regimens over SCLC regimens incorporating etoposide. However, the choice of chemotherapy in the adjuvant setting remains controversial and is evolving. Although not yet incorporated in routine practice, prospective phase II studies also examined the role of targeted therapy, such as the combination of everolimus with carboplatin and paclitaxel,[32] and of other chemotherapy regimens, such as irinotecan and cisplatin,[31] and have detected positive response rates. There is no firm recommendation for the management of unresectable and metastatic disease.

The role of prophylactic cranial irradiation (PCI) for LCNEC is a subject of debate. PCI has not been demonstrated to improve outcomes in NSCLC.[33,34] On the other hand, PCI has been demonstrated to improve survival for both limited and extensive stage SCLC.[35,36] As for LCNEC, a small retrospective series by Arsela et al[37] demonstrated an improvement in survival outcomes with the addition of PCI in patient with stage III and IV disease. However, Rieber et al[38] demonstrated a low rate of brain metastases, which would argue against the use of PCI. To date, only few case series examined pulmonary LCNEC's treatment outcomes and patterns of recurrence, including the rate of brain metastases.

The present study reports the analysis of a retrospective series of patients with LCNEC. The primary objectives are to further investigate the survival outcomes, the incidence of brain metastases and the patterns of relapse of patients who underwent treatment for pulmonary LCNEC. The secondary objective is to identify significant factors impacting on prognosis.

Material and methods

This is a single center study of patients who underwent treatment at the Queen Elizabeth II Health Sciences Centre in Halifax, Nova Scotia, Canada. Full research ethics board approval was obtained. All patients who received a pathologic diagnosis of a primary LCNEC of the lung (biopsy sample or surgical specimen) between September 1998 and February 2014 were included. The cases with an uncertain diagnosis were reviewed by an expert lung pathologist and were excluded unless they met the required WHO criteria (neuroendocrine morphology, neuroendocrine differentiation with expression of chromogranin, synaptophysin or CD56, mitotic rate higher than 10/10 high power field, large cell morphology).[6] Those who received a diagnosis postmortem were excluded from the study.

Review of the medical records was performed to retrospectively collect data regarding patient demographics, disease variables, treatment methods, and outcomes (age, gender, treatment intent, clinical and pathologic stage, type of surgery, type of systemic therapy, chest radiotherapy dose fractionation, response to treatment, time and site of relapse, and time of last follow-up). The treatment intent (curative or palliative) was determined on review of clinical consultation notes. The timing of brain metastasis was recorded, including whether it was present at diagnosis, the isolated first site of relapse, part of the first but multifocal relapse (another site of metastasis identified within a 30 days period) or a later relapse. The date of death, if applicable, was obtained from multiple sources, including patient charts and the provincial vital statistics (though the Nova Scotia Cancer Registry). The disease staging was reviewed using the American Joint Committee on Cancer (AJCC) seventh edition classification for lung cancer.

Statistical analysis

OS was calculated from the date of diagnosis to the date of last follow-up or death. Disease-free survival (DFS) was calculated from the date of diagnosis to the date of documented disease recurrence, based on repeat imaging. Considering that not all patients suffered an event during the time of follow-up, the data analysis was censored. The Kaplan-Meier method was used to calculate the OS, DFS, and time to brain metastasis. Survival between groups was compared using the log-rank test. Cox proportional hazards regression analyses were performed to determine potential associations between patient variables for the survival outcomes. All the conducted tests are 2-tailed. The above analyses were performed with the Statistical Package for the Social Sciences version 23 (IBM Analytics, Armonk, New York).

Results

Patient characteristics and treatment received

Eighty-seven patients with a pathologically confirmed diagnosis of pulmonary LCNEC were included in this study. At the time of data analysis, 66 (75.8%) were deceased, with 57 (86.4%) of them passing away from lung cancer. Information on patient demographics, staging, and initial therapies is listed in Table 1. The intent of the initial therapy was curative in 52 (59.8%) patients and palliative in 35 (40.2%). One patient treated palliatively received PCI as part of the initial

Table 1
Characteristics of patients with a diagnosis of pulmonary large cell neuroendocrine carcinoma.

Factors	*n*
Sex	
Male	47 (54.0%)
Female	40 (46.0%)
Age at diagnosis	
Median	68
Range	44-85
Stage (American Joint Committee on	
Cancer seventh edition)	24 (27.5%)
I	14 (16.1%)
II	23 (26.4%)
III	26 (29.9%)
IV	
Intent of initial treatment	
Curative	52 (59.8%)
Stage I	24
Stage II	14
Stage III	14
Palliative	35 (40.2%)
Stage III	9
Stage IV	26
Initial therapy of patients treated with	
curative intent ($n = 52$)	34 (65.4%)
Surgery alone	9
Wedge resection	22
Lobectomy	2
Segmentectomy	1
Pneumonectomy	5 (9.6%)
Surgery and adjuvant chemotherapy	1
Wedge resection	3
Lobectomy	1
Pneumonectomy	5 (9.6%)
Surgery and adjuvant	1
chemoradiotherapy	4
Wedge resection	6 (11.5%)
Lobectomy	1 (1.9%)
Concurrent chemoradiotherapy	1 (1.9%)
Sequential chemoradiotherapy	0 (0%)
Radiotherapy alone	
Treatment including PCI	
Therapy of patients treated with	
palliative intent ($n = 35$)	5 (14.3%)
Palliative chemotherapy alone	12 (34.3%)
Palliative chest radiotherapy alone	8 (22.9%)
Palliative chemotherapy and chest	10 (28.6)
radiotherapy	1 (2.9)
Best supportive care	
Treatment including PCI	

AJCC, American Joint Committee on Cancer; PCI, prophylactic cranial irradiation.

treatment. The median follow-up time for all the patients was 12.7 months (range 0.1-89.5), 17.3 months (range 0.6-89.5) for those treated with curative intent and 7.0 months (range 0.1-28.6) for those treated with palliative intent. Platinum-based combination regimens were used first-line for nearly all patients receiving chemotherapy in this series, except for 2 who received single agent etoposide in the palliative setting (Table 2). For those treated with curative intent who received chest radiotherapy (13), the dose regimens included 40 Gy in 15 fractions (7), 45 Gy in 30 fractions delivered twice daily (2), 60 Gy in 30 fractions (3), and 52.5 Gy in 15 fractions

Table 2
First line chemotherapy regimens used in the curative and palliative settings for patients with pulmonary large cell neuroendocrine carcinoma.

Chemotherapy regimens	Patients treated curatively[a]	Patients treated palliatively[b]
Cisplatin and Vinblastine	1 (3.3%)	0 (0%)
Carboplatin and Paclitaxel	1 (3.3%)	0 (0%)
Cisplatin and Etoposide	9 (30%)	6 (20%)
Carboplatin and Etoposide	4 (13.3%)	4 (13.3%)
Etoposide	0 (0%)	2 (6.7%)
Unknown	2 (6.7%)	1 (3.3%)

[a] Total of 17 patients.
[b] Total of 13 patients.

Table 3
Univariate analysis for all-cause mortality in patients with pulmonary large cell neuroendocrine carcinoma.

Variables	Hazard ratio (95% confidence interval)	*P* value
Female vs male	0.62 (0.37-1.01)	0.056
Stages I vs IV	0.20 (0.10-0.39)	<0.0001
Stages II vs IV	0.24 (0.11-0.54)	0.0006
Stages III vs IV	0.51 (0.28-0.94)	0.0304

Table 4
Multivariate analysis for all-cause mortality in patients with pulmonary large cell neuroendocrine carcinoma.

Variables	Hazard ratio (95% confidence interval)	*P* value
Female vs male	0.57 (0.34-0.94)	0.0271
Stages I vs IV	0.18 (0.09-0.37)	<0.0001
Stages II vs IV	0.24 (0.11-0.55)	0.0006
Stages III vs IV	0.50 (0.27-0.92)	0.0265

(1). For those managed with palliative radiotherapy, the most common fractionations were 20 Gy in 5 fractions and 30 Gy in 10 fractions.

Survival outcomes

For the entire cohort, the OS rates are 31.9% at 2 years and 15.2% at 5 years, with a median OS of 13.9 months. Analyzing for each stage, the 2- and 5-year OS are respectively 65.4% and 29.5% for stage I; 34.8% and 23.2% for stage II; 15.2% and 15.2% for stage III; and 3.8% and 0% for stage IV ($P < 0.0001$, log-rank test) (Fig 1).

For the patients initially managed with curative intent, the OS was 48.4% at 2 years and 25.5% at 5 years. The median OS was 22.6 months. The DFS were 26.8% and 10.0% at 2 and 5 years, respectively, with a median of 13.5 months.

For the patients initially managed with palliative intent, the OS was 30.8% at 1 year and 6.8% at 2 years, with no patients alive at the 5-year mark. The median OS was 7.0 months in this group.

On univariate (Table 3) and multivariate (Table 4) analysis for the entire cohort, early disease stages were found to be independent prognostic factors for lower all-cause mortality. Female gender was identified as a favorable prognostic factor, statistically significant on multivariate analysis and approaching significance on univariate analysis. Age was analyzed as a continuous variable and was not found to be significant in Cox regression modeling ($P = 0.229$), when stage and gender were included in the model.

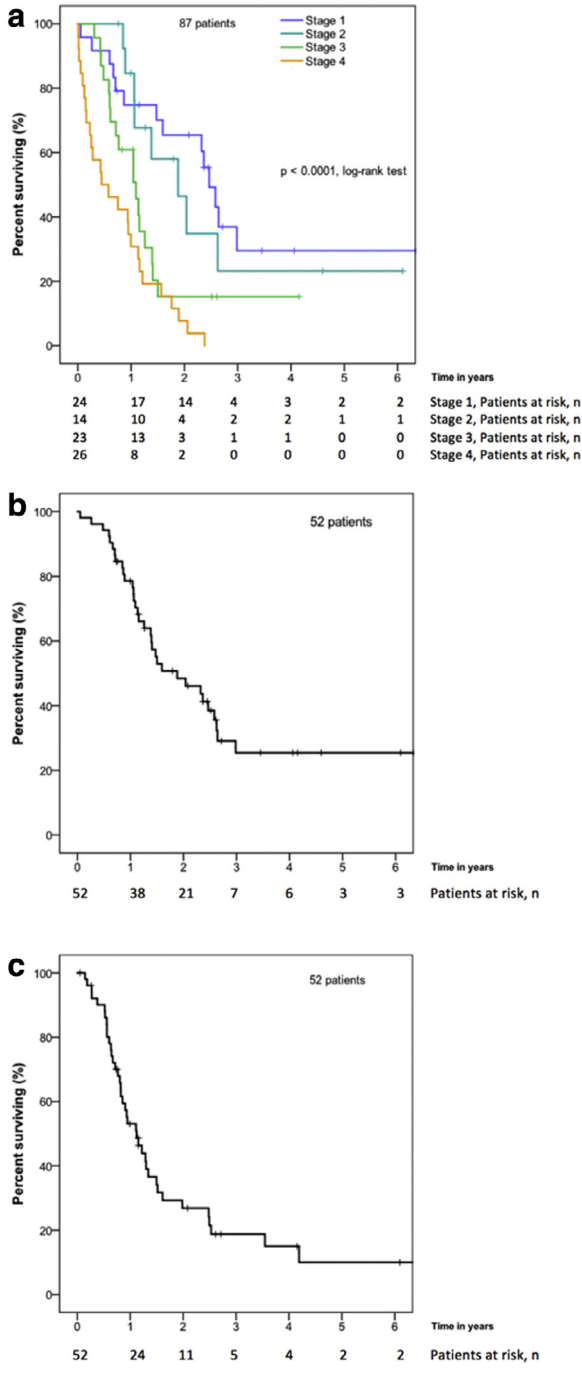

Fig. 1. Survival outcomes of patients with pulmonary large cell neuroendocrine carcinoma. (a) Overall survival of all patients per disease stage. (b) Overall survival of patients treated with curative intent. (c) Disease-free survival of patients treated with curative intent.

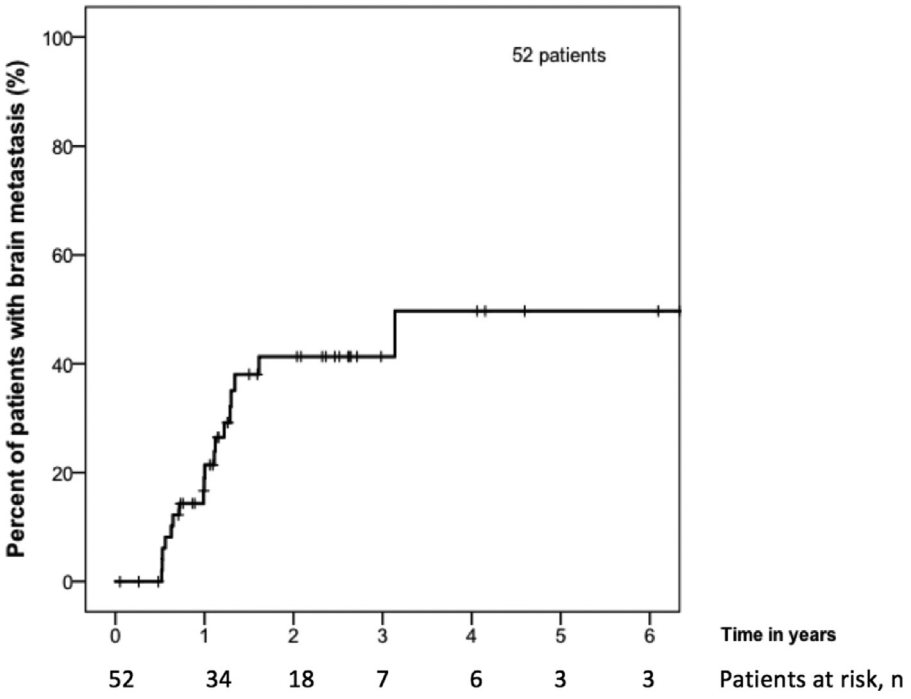

Fig. 2. Incidence of brain metastases in patients with pulmonary large cell neuroendocrine carcinoma treated with curative intent.

Incidence of brain metastases

In the entire cohort, 28 patients (32.2%) developed brain metastases at some point during the course of their illness. The rates of brain metastases were 25.0% at 1 year and 48.4% at 2 years. The patients' median OS was 2.4 months after the development of brain metastases.

Among the patients treated with curative intent, 18 (34.6%) developed brain metastases, with incidence rates of 21.4% at 1 year and 41.3% at 2 years (Fig 2). Ten (55.5%) of the recurrences happened within 1 year and 17 (94.4%) within 2 years. Brain metastasis was noted to be an isolated first site of relapse in 6 (33.3%) patients. Eight (44.4%) patients developed brain metastasis as part of an initial multifocal disease relapse, and 4 (22.2%) developed brain relapse later in their disease course.

In the patients managed palliatively, 10 (28.6%) developed brain metastases during their disease course, with 4 cases presenting at the time of diagnosis. The incidence of brain metastases in this group was 17.0% at 6 months and 28.5% at 1 year. Seven (70.0%) cases of brain metastases occurred within the first year and all of them occurred within 2 years. The single patient who received PCI as part of initial therapy ultimately developed relapse in brain and at other sites.

Patterns of relapse following curative intent treatment

Among the 52 patients treated with curative intent, 38 (73%) had subsequent disease progression. Of those who relapsed, 16 (42.1%) had disease limited to 1 site, while 22 (57.9%) had metastases disseminated to at least 2 locations. The sites and frequencies of disease relapse are listed in Table 5. The most common sites are the regional lymph nodes (20), brain (18), bone (11), and the liver (9).

Table 5
Sites of disease relapse in patients treated curatively[a] for pulmonary large cell neuroendocrine carcinoma.

Sites	*n*[a]
Regional lymph nodes[b]	20 (38.5%)
Brain	18 (34.6%)
Bone	11 (21.2%)
Lung	10 (19.2%)
Liver	9 (17.3)
Adrenal gland	4 (7.7%)
Retroperitoneum	2 (3.8%)
Skin	2 (3.8%)
Axillary lymph node	2 (3.8%)
Kidney	1 (1.9%)

[a] Total of 52 patients.
[b] Hilar, mediastinal and/or supraclavicular region.

Discussion

This study reports the results of a retrospective analysis of a series of 87 patients with pulmonary LCNEC. The median age at diagnosis of 68 is comparable to previously published reports.[6,39] The current standards of treatment have been applied. All patients with early stage and potentially resectable disease underwent upfront surgery.[1,19-23] In the adjuvant and palliative settings, NSCLC platinum-based and SCLC chemotherapy regimens were employed.[12,24-29]

The 5-year OS rate of 15.2% we report is relatively low compared to prior publications showing a long-term survival rate of 13%-57%.[9-15] The existing series are mostly surgical, analyzing patients with early stage disease treated with curative intent. For the patients treated curatively in our cohort, the 5-year OS rate of 25.5% is comparable to those in the literature.[10,11,14]

The poor survival outcomes of pulmonary LCNEC patients with localized disease at presentation reflect the disease's aggressive biology and its high rate of early lymphovascular and hematologic disease spread. Looking specifically at the stage I patients in our series, they were all managed with surgery alone. Their low 5 year OS rate of 29.5% highlights the fact that surgery alone is insufficient and suggests that adjuvant therapy should strongly be considered for early stage LCNEC.

Advanced disease stages were found to be significant adverse prognostic factors with increased all-cause mortality in our study. This is corroborated by 2 series by Filosso et al.[40,41] Age was identified as a significant prognostic factor in 1 series by Filosso et al,[40] but was not found to be a statistically significant factor in our study. We identified female gender as a significant favorable factor for lower mortality, but it has not been confirmed by other series.

The occurrence of brain metastases for pulmonary LCNEC has been closely analyzed. In the entire cohort, 32.2% of patients developed brain metastases. When considering only those initially managed with curative intent, 34.6% subsequently developed brain relapse, with incidences of 21.4% and 41.3% among those who are respectively alive at 1 and 2 years. Our results suggest a rate of brain metastases in patients with LCNEC which is intermediate between NSCLC (for which about 25% of patients would develop brain metastases during their course of disease)[42,43] and SCLC (for which about 50% of patients treated curatively would develop intracranial disease recurrence without PCI at 2 years).[35,44]

PCI is well established in the management of SCLC. In limited stage disease, Auperin et al[35] demonstrated an absolute survival benefit of 5.4% at 3 years with the use of PCI. Benefits were similarly demonstrated for extensive stage disease by Slotman et al,[36] reducing the risk of brain metastases at 1 year from 40.4% to 14.6% and increasing the 1-year survival rate by 13.8%. In contrast, there is no evidence from randomized trials to demonstrate a survival benefit from PCI for NSCLC.[33,34] Regarding LCNEC, a study by Arsela et al[37] looked into patients with stage III and IV disease managed as per SCLC treatment algorithm and demonstrated a trend in improvement

of PFS (20.5 vs 6.4 months, $P = 0.09$) and of OS (33.4 vs 8.6 months, $P = 0.05$) with the addition of PCI. The study did have limitations, mainly being retrospective in nature with a small sample size. In our study, the observed rate of brain metastases was higher than that observed typically in NSCLC, and further raises the question of its potential role in LCNEC. The survival outcomes following the development of brain metastases were poor in our patient cohort, with a median OS of 2.4 months. Among those who developed recurrence after curative intent treatment, 15.8% (6/38) developed brain metastasis as the first isolated site of relapse and 21.1% (8/38) as part of a first but multifocal relapse. For these patients, the development of brain metastases could be an important driver of survival outcomes, and PCI could potentially provide benefit.

Previous studies examining the incidence of brain metastases in patients with LCNEC have yielded conflicting results. The rates of brain metastases in our series are similar to those of Sun et al[29] and Mazieres et al,[45] who respectively detected brain recurrences in 36.0% and 38.9% of patients. On the other hand, series by Rieber et al[38] and Rossi et al[46] reported lower rates of brain metastases, of 25.0% and 27.7%, respectively. A population-based retrospective study by Derks et al[17] reported a rate of 23.0% among patients with stage IV disease. In comparison to our study, the series by Rieber et al and Rossi et al both included a higher proportion of early stage patients, and this may explain the comparatively lower rates of brain metastases which were observed. While stages I and II disease accounted for 43.7% (38/87) of the patients in our series, it constituted 61.4% (43/70) of the study population for Rieber et al and 84.3% (70/83) for Rossi et al A correlation between advanced disease stage and the development of brain metastases was also reported by Rieber et al.[38]

While we have included patient with early-stage and advanced disease, it is possible that our analysis may under-represent patients with advanced stages of pulmonary LCNEC. The diagnosis of LCNEC is typically made postoperatively on surgical pathology.[28] Making a diagnosis of LCNEC on needle biopsy alone can be challenging,[25,47] and subsequently there may be a population of nonoperable patients who did not receive an appropriate diagnosis of LCNEC on this basis.

Noting the low incidence of pulmonary LCNEC, there is a lack of evidence from randomized studies to guide management. Most of the published literature consists of retrospective analysis of case series, mostly surgical. The current study is also retrospective and similar limitations apply, though has the benefit of having analyzed patients across a wide spectrum of disease stages and management. The limited number of patients in our series makes it difficult to determine which subgroup of patients should be considered for further investigation. Considering the poor survival outcomes and the high risk of recurrence following the current treatment algorithm, novel management approaches should be investigated. While upfront surgery is recommended for early stage LCNEC, the survival outcomes are still relatively poor, and this treatment approach has not been compared nor proven to be superior to others. Variations in disease outcomes using either NSCLC or SCLC chemotherapy regimens in patients with different tumor genomic profiles have been demonstrated and may be subject to further research.[48] The potential survival benefit of PCI for LCNEC patients achieving a partial or complete response after initial treatment should be further evaluated in a prospective manner. Taking into account the rarity of this malignancy, a multicenter cooperative effort would be required.

In conclusion, LCNEC is an uncommon but aggressive type of high grade pulmonary neuroendocrine tumor, with poor overall prognosis. The incidence of brain metastases is higher than that observed for NSCLC. The high frequency of brain relapse after treatment suggests that further investigation should be undertaken of the role of PCI in pulmonary LCNEC.

Clinical practice points

- Large cell neuroendocrine carcinoma of the lung is a rare subtype of nonsmall cell lung cancer, with clinical and pathologic similarities to small cell lung cancer.
- The rate of brain metastasis after therapy is high and approaches that observed in small cell lung cancer. PCI should be investigated, noting the benefit of this therapy in small cell lung cancer.

Acknowledgments

The authors would like to thank Ron Dewar and the Surveillance and Epidemiology Unit at Cancer Care Nova Scotia for assistance with patient identification and the provincial tumor registry.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, ornot-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.currproblcancer.2018.05.006.

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