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REVIEW

Treatment of lung large cell neuroendocrine carcinoma

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Abstract Lung large cell neuroendocrine carcinoma (L-LCNEC) is a rare, aggressive, and difficult-to-treat tumor. It is classified as a neuroendocrine subtype of large cell lung carcinoma (LCLC) belonging to the non-small cell lung cancer (NSCLC) group, but it is also included in the neuroendocrine tumor (NET) group. Most of the available data related to its treatment derive from retrospective analyses or small case series. For patients with L-LCNEC, prognosis is generally very poor. In early stages (I–II–III), surgery is recommended but does not seem to be sufficient. Platinum-based adjuvant chemotherapy may be useful while the role of neoadjuvant chemotherapy is still not well defined. In patients with advanced L-LCNEC, the chemotherapy regimens used in SCLC still remain the standard of treatment, but results are not satisfactory. Due to their peculiar clinical and biological features and the lack of literature data, there is an emerging need for a consensus on the best treatment strategy for L-LCNEC and for the identification of new therapeutic options. In this review, we will discuss the key aspects of L-LCNEC management with the aim to clarify the most controversial issues.

Keywords Large cell neuroendocrine carcinoma · Lung neuroendocrine tumor · Chemotherapy · Treatment options

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Introduction

Lung large cell neuroendocrine carcinoma (L-LCNEC) is a rare but highly aggressive tumor type accounting approximately for 2–3 % of all lung cancers. This neoplasm occurs more frequently in heavy smokers males while it is not common in non-smoking females [1–3].

Specifically, L-LCNEC arises from lung cells belonging to the neuroendocrine system. It is generally included in the non-small cell lung carcinoma (NSCLC) group since it is currently classified as a neuroendocrine subtype of large cell lung carcinoma (LCLC) [4–7]. However, it is also a member of the lung neuroendocrine tumor (NET) group [8, 9]. Lung NETs account for approximately 20–30 % of all NETs and represent about 25 % of lung cancers [10]. These tumors include a wide range of diseases, and they have been classified by the 2004 World Health Organization (WHO) into four different subtypes characterized by increasing biological aggressiveness: typical carcinoid (TC), atypical carcinoid (AC), L-LCNEC, and small-cell lung cancer (SCLC) [11]. The 2015 WHO classification of lung NETs substantially maintained the same terminology, but enucleated L-LCNECs from the group of LCLC and included all lung NETs in a single entity, abandoning the previous division into separate subgroups of tumors [12]. In fact, although L-LCNEC is traditionally classified as a type of NSCLC, its biological, clinical, and prognostic characteristics in advanced stages are similar to those of SCLC [13].

Today, due to the lack of literature data related to these neoplasms and because of their peculiar features, there is an emerging need for an agreement on the best treatment strategy for managing L-LCNEC. In this review, the key aspects of L-LCNEC management will be discussed with the aim to clarify the most controversial issues.

Methods

We performed a literature review on L-LCNECs. We investigated histological features and treatment strategies used in the management of L-LCNEC. We searched digital databases including PubMed, EMBASE, and the Cochrane Library. The search was done using the following keywords: "lung large cell neuroendocrine carcinoma," "lung neuroendocrine tumor" associated with "prognosis," "treatment," "diagnosis," "epidemiology," "histology," "surgery," "chemotherapy," and "target therapy." We restricted the search to English language publications. The majority of the studies were excluded based on title and content of abstract. We focused on number of reported L-LCNEC and used treatment regimens. We favored the most recent scientific works and the journals with the highest impact factor. We analyzed the full text of all relevant literature (abstracts were considered when the extended version of the paper was not available), and we evaluated the relevant information for the management of L-LCNEC. The reference list of articles were examined and used as document source. Examining 1015 papers, 928, considered irrelevant or of minor importance, were excluded, while the remaining 87 studies were included in our review. In the "introduction," we referred to 13 studies; 9 and 20 papers were used for the sections "diagnosis and staging " and "histological and genomic features," respectively; in the sections "management of resectable of potentially resectable disease (ADC/SQC-like group)," "management of advanced/metastatic disease (SCLC-like group)," and "new approaches, " we considered 23, 8, and 11 studies respectively; finally, in the "conclusion," we referred to 8 scientific works. Twenty-eight papers, excluding reviews, meta-analysis, and guidelines, were selected for qualitative synthesis (Tables 1, 2, and 3) (Fig. 1).

Diagnosis and staging

L-LCNEC presents the same clinical and radiological features of the other lung cancers; therefore, it is difficult to be distinguished on the solely basis of its presentation. In most cases, L-LCNEC develops peripherally, and only in a minority of cases it is located in the central part of lung causing concomitant atelectasis. It often appears as a necrotic and invasive lesion with evident infiltration of the bronchial wall and possible extension to the adjacent mediastinal structures [14]. The margins are usually well defined, but spiculated nodules and lobulations with cavitations, air bronchogram, or central necrosis can be present too [15, 16]. The histological diagnosis of the rare cases of L-LCNEC characterized by endobronchial lesions involving central airways can be achieved through endobronchial biopsies (standard bronchoscopy) [17]. On the contrary, central peribronchial lesions, without intraluminal component, can be diagnosed using preferably ultrasound-guided needle transbronchial aspiration [18, 19]. Total body computed tomography (CT) is indicated to stage each case [14]. Fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful in selected cases, according with the higher typical FDG uptake of L-LCNEC (differential diagnosis with TC and AC) [20–22].

Histological and genomic features

The histological characterization of L-LCNEC is very complex and requires an expert pathologist [23, 24]. Preoperative biopsies are usually insufficient for a correct diagnosis. Frequently, diagnosis is obtained postoperatively on surgical specimens. The diagnosis of NSCLC with L-LCNEC characteristics results from the recognizing of the neuroendocrine cellular morphology and, if possible, from the immunohistochemistry confirmation of neuroendocrine differentiation [25, 26].

Approximately 10–20 % of surgically resected cases are combined L-LCNECs, more frequently with adenocarcinoma (ADC) [27]. Morphological and biochemical characteristics of L-LCNEC are different from those of LCLC. L-LCNEC tumors are composed of large cells with neuroendocrine differentiation, low nuclear-to-cytoplasmic ratio, frequent nucleoli, and abundant necrosis. Palisade cells, rosettes, and necrosis are more frequent in L-LCNEC as well as higher Ki-67 labeling index and expression rates of BCL2 [28, 29]. The mitotic rate is high (>10 mitoses per 10 high-power fields) [8]. If typical cell morphology of neuroendocrine carcinomas (organoid nesting, palisading, rosettes, trabeculae) is absent, it is not recommended to perform immunohistochemical staining for neuroendocrine markers such as chromogranin A, synaptophysin, and neural cell adhesion molecule. In not clearly defined cases, the assessment of Ki-67 helps avoid the over-diagnosis of lung carcinoids. If the morphology is unclear, particularly when diagnostic material (biopsy or cytology) is limited, the differentiation between SCLC and L-LCNEC should be skipped. In these cases, the diagnosis of poorly differentiated neuroendocrine carcinoma is made, and the evaluation of Ki-67 labeling index is frequently sufficient for the correct therapeutic management of these tumors [11, 25, 30, 31].

While often L-LCNEC and SCLC show similar characteristics on histological specimens, sometimes they differ as regard genic, chromosomal, and biomolecular aspects [32]. The telomerase activity and the loss of heterozygosity in microsatellite markers resemble those of SCLC [33, 34], but there are many differences in the chromosomal alterations reported in 2q, 3p, 3q, 4q, 6p, 10q, 16q, and 17p regions [35, 36]. Moreover, the expression of b-catenin, CK7, CK18, and E-cadherin is more typical of L-LCNEC than of SCLC [37].

Compared with ADC or squamous cell carcinoma (SQC), L-LCNEC and SCLC have similar expression profiles for the major receptor tyrosine kinases [38]. Fernandez-Cuesta et al. conducted a genomic characterization of 69 L-LCNECs, and they distinguished two major groups of LCNEC: an ADC/SQC-like group with alterations in TTF1, KEAP1-NFE2L2,

Table 1 Role of chemotherapy in resectable and potentially resectable L-LCNEC (ADC/SQC-like group)

Authors	Study	Patients (PTS)	Treatment	Results
Iyoda A et al., 2001 [47]	Single-center retrospective	73 pts with large cell carcinoma with neuroendocrine features	16 pts underwent NA-CT or A-CT based on cisplatin, carboplatin, or cyclophosphamide vs 57 pts underwent only surgery	In stage I, OS was significantly higher in the group treated with A-CT ($p < 0.05$). No differences reported in other stages
Iyoda A et al., 2006 [50]	Single-center prospective	47 resected L-LCNEC pts	15 L-LCNEC pts treated with A-CT cisplatinum/etoposide vs 32 L-LCNEC pts underwent only surgery	2-year survival rate: 88 vs 65 % in pts treated with A-CT vs only surgery pts 5-year survival rate: 88 vs 47 % in pts treated with A-CT vs only surgery pts
Iyoda A et al., 2009 [51]	Single-center retrospective	79 resected L-LCNEC pts	30 pts received platinum-based A-CT vs 42 pts non platinum-based A-CT or no A-CT	Tumor recurrence rate: significantly lower in pts treated with platinum-based A-CT vs pts treated with non-platinum-based A-CT or no A-CT ($p = .0168$) DFS: higher rate in pts treated with platinum-based A-CT vs pts treated with non-platinum-based A-CT or no A-CT (59 vs 33 %; $p < 0.0444$)
Rossi G. et al., 2005 [52]	Multicenter retrospective	83 L-LCNEC pts	28 pts received A-CT: 13 SCLC-based A-CT vs 15 NSCLC-based A-CT	Median survival: 42 vs 11 months in SCLC-based A-CT pts vs NSCLC-based A-CT pts, respectively ($p = 0.0001$). Stage I LCNEC pts treated with SCLC-based A-CT had the best prognosis ($p = 0.0001$)
Veronesi G et al., 2006 [7]	Multicenter retrospective	144 resected L-LCNEC pts	21 pts received NA-CT; 24 pts received A-CT	5-year survival: 42.5 % in all pts, 52 % for stage I, 59 % for stage II, and 20 % for stage III ($p = 0.001$). RR to NA-CT: 80 % 3-year survival in stage I pts: 100 % in pts treated with NA-CT or A-CT vs 58 % in only resected pts ($p = 0.077$)
Saji H et al., 2010 [53]	Single-center retrospective	45 resected L-LCNEC or mixed L-LCNEC pts	23 pts received CT: 7 pts received NA-CT and 16 pts A-CT.	Survival: significantly higher in NA-CT or A-CT pts vs surgery alone pts ($p = 0.04$) 5-year survival rate: 87.5 vs 58.5 % in NA-CT or A-CT pts vs surgery alone pts respectively Perioperative A-CT favored survival even in stage I, compared with surgery alone.
Sarkaria et al., 2011 [54]	Single-center retrospective	100 resected L-LCNEC pts	22 pts received NA-CT platinum-based; 20 pts received A-CT platinum-based	RR to NA-CT platinum based: 68 % Median survival in completely resected (R0) stage IB-IIIA pts receiving platinum-based NA-CT and (or) A-CT: 7.4 vs 2 years ($p = 0.052$)
Abedallaa et al., 2012 [55]	Single-center retrospective	74 resected limited disease SCLC and LCNEC	45 received perioperative chemotherapy	Median survival: 2.3 and 6.1 years in the surgery ($n = 20$) and surgery plus CT ($n = 39$) groups, respectively, HR for death 0.48 ($p = 0.04$)
Tanaka et al., 2013 [56]	Single-center retrospective	63 resected L-LCNEC pts	23 pts received perioperative chemotherapy (3 pts NA-CT and 20 pts A-CT)	5-year survival rate: better with perioperative CT than surgery alone (74.4 vs 32.3 %, respectively; $p = 0.042$) 5-year survival rate: among neurendocrine marker-negative pts, significantly greater in pts underwent perioperative CT vs pts underwent surgery alone (100 and 34.5 %, respectively; $p = 0.0081$)
Fournel et al., 2012 [46]	Single-center retrospective	63 resected L-LCNEC pts	16 pts received NA-CT, 44 pts received A-CT	Overall 5- and 8-year survival rates: 49.2 and 42 %, respectively
Kenmotsu et al., 2014 [57]	Multicenter single-arm phase II		Pts received irinotecan/cisplatin A-CT	3-year OS rate:81 %

Table 1 (continued)

Authors	Study	Patients (PTS)	Treatment	Results
		40 resected stage I–IIIA HGNEC (LCNEC 57 % and SCLC 43 %)		3-year RFS rate:74 % 3-year OS and RFS rates: 86 and 74 % among 23 LCNEC pts, and 74 and 76 % among 17 SCLC pts, respectively
Eba J et al., ongoing [58]	Multicenter randomized phase III	220 stage I–IIIA resected HGNEC pts will be accrued	HGNEC pts will receive irinotecan/cisplatin vs etoposide/cisplatin as A-CT	Ongoing
Rieber et al., 2015 [60]	Single-centre retrospective	70 resected L-LCNEC pts	34 pts treated only with surgery (early stages); 30 pts (≥IIIA) received surgery followed by A-CT, RT, or CRT (SCLC or NSCLC protocols)	OS an local PFS similar between the two groups, respectively ($p = 0.298$) and ($p = 0.412$)
Ricciuti et al., 2015 [61]	Single-center retrospective	16 L-LCNEC pts and 33 LD-SCLC pts	All pts received platinum-etoposide CT with or without thoracic RT or PCI	Significantly less L-LCNEC pts received thoracic RT (8/16 vs. 27/33, respectively, $p = 0.04$) and PCI [2/16 (12 vs 18/33, $p = 0.005$] compared with SCLC pts Median OS = 10.4 vs 16.3 months in L-LCNEC and SCLC pts, respectively, $p = 0.05$)

pts patients, *NA-CT* neoadjuvant chemotherapy, *A-CT* adjuvant chemotherapy, *OS* overall survival, *L-LCNEC* lung large cell neuroendocrine carcinoma, *DFS* disease-free survival, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *RR* response rate, *HR* hazard ratio, *PFS* progression-free survival, *RT* radiotherapy, *CRT* chemoradiotherapy, *HGNEC* high-grade neuro-endocrine carcinoma, *RFS* recurrence-free survival, *LD* limited disease, *PCI* prophylactic cranial irradiation.

STK11, and CDKN2A and an SCLC-like group with TP53, ISR2, RB1, and MYCL1 aberrations. The authors concluded that L-LCNEC could be a distinct entity from which both SCLC or ADC/SQC can develop [39]. The clinical analysis by Derks et al. seem to be in agreement with this hypothesis. The authors compared data of SCLC ($n = 11\,844$), SQC ($n = 19\,633$), and ADC ($n = 24\,253$) with data of L-LCNEC ($n = 952$) registered in the Netherlands Cancer Registry from 2003 to 2012. Several clinical features (treatments performed, metastasis at diagnosis, site of metastases, and median OS) were analyzed for stage I–II, III, and IV. Also, for these authors two groups of L-LCNEC should be defined: SCLC-like group that corresponds to the metastatic stage L-LCNEC and is similar to SCLC for median OS, metastatic pattern, and therapies; and ADC/SQC-like group that corresponds to the early stage L-LCNEC and shows outcome comparable to NSCLC requiring the same therapeutic management [40].

Management of resectable or potentially resectable disease (ADC/SQC-like group)

Available literature regarding the management of limited disease in patients with L-LCNEC is scant. Most L-LCNECs are diagnosed postoperatively by surgical specimens, and most information derives from retrospective analyses or small case series [5, 41, 42].

For radically resected limited L-LCNEC, prognosis is always poor, even in pathological stage I patients, with a 5-year survival rate of 27–67 % [5, 41–45]. Differently from SCLC in which surgery is indicated only in stage I, in patients with L-LCNEC surgery is useful also in stage II/III. Nevertheless, surgery alone does not seem to be sufficient to effectively treat this disease. Adjuvant or neo-adjuvant chemotherapy may play a major role in L-LCNECs (Table 1) [7, 46–50].

A Japanese study prospectively compared the survival of 15 resected L-LCNECs treated with two cycles of cisplatin + etoposide as adjuvant chemotherapy with 32 L-LCNECs treated with surgery alone. The group receiving adjuvant chemotherapy after surgery had an equivalent 2- and 5-year survival (88 %), while the group treated with surgery alone showed a 65 and 47 % survival at 2 and 5 years, respectively. This is the only prospective study on adjuvant treatment for L-LCNEC [50]. A subsequent expansion of this series with a retrospective data analysis on a total of 72 patients confirmed the usefulness of adjuvant treatment previous data. Five-year disease-free survival (DFS) was 59 % for patients treated with adjuvant therapy versus 33 % for patients who underwent surgery alone ($p < 0.0444$) [51].

Rossi et al., in a retrospective study, reported that adjuvant chemotherapy based on cisplatin plus etoposide was effective for patients with L-LCNEC. At univariate and multivariate analyses, platinum plus etoposide chemotherapy was the most important variable correlating with survival both in adjuvant and metastatic setting ($p < 0.0001$) [52].

Table 2 Role of chemotherapy in advanced/metastatic L-LCNEC (SCLC-like group)

Authors	Study	Patients (Pts)	Treatment	Results
Sun et al., 2012 [62]	Single-center retrospective	45 advanced L-LCNEC pts	11 pts received SCLC-based regimens; 34 pts received NSCLC standard CT	First-line SCLC and NSCLC regimens reported respectively RR: 73 vs 50 % ($p = 0.19$) Median PFS: 6.1 vs 4.9 months ($p = 0.41$) Median OS: 16.5 vs. 9.2 months ($p = 0.10$) High OR with SCLC drugs (taxanes, irinotecan, or platinum retreatment) and no OR with standard NSCLC drugs (pemetrexed, gefitinib, or erlotinib)
Le Treut et al., 2013 [63]	Multicenter prospective phase II	42 advanced L-LCNEC pts	Pts received cisplatin/etoposide-based CT	Median PFS: 5.2 months Median OS: 7.7 months
Igawa et al., 2010 [64]	Single-center retrospective	14 unresectable HNSCNEC pts and 77 advanced SCLC pts	14 unresectable HNSCNEC pts received platinum-based combination or vinorelbine or docetaxel or irinotecan; 77 advanced SCLC pts received platinum-based CT	RR: 50 % (7/14) vs 53 % (41/77) 1-year survival rate: 34 vs 48 % Median OS: 10 vs 12.3 months in HNSCNEC and SCLC, respectively
Yamazaki et al., 2005 [65]	Single-center retrospective	20 L-LCNEC pts (14 chemo-naive pts and 6 underwent CT)	9 pts received cisplatin/etoposide; 6 cisplatin/vindesine/mitomycin; 4 cisplatin/vindesine; and 1 cisplatin alone	RR 50 % (1 CR and 9 PR) RR in chemo-naive pts: 64 % RR in treated pts: 17 %
Shimada et al., 2012 [66]	Single-center retrospective	25 HGNEC-probable LCNEC pts s 180 SCLC pts	18 HGNEC-probable LCNEC pts received CT; 7 pts received CT + RT 101 SCLC pts received CT; 79 pts received CT + RT	In stage IV HGNEC-probable L-LCNEC: RR of CT pts: 61 % RR of CT + RT pts: 86 % RR of II line CT pts: 17 % 1-year survival: 34 % In SCLC: RR of CT pts: 63 % RR of CT + RT pts: 98 % RR of II line CT pts: 45 % 1-year survival: 49 %
Tokito et al., 2012 [67]	Single-center retrospective	34 pts, 10 L-LCNEC pts 24 possible L-LCNEC pts	Pts received platinum-based CT: SCLC-based CT (60 % LCNEC pts (6/10) and 67 % possible LCNEC pts received platinum/irinotecan or platinum/etoposide)	The LCNEC and possible LCNEC groups, respectively, showed: RR: 70 vs 54 % ($p = 0.39$) Median PFS: 2.9 vs 4.4 months ($p = 0.20$) Median OS: 12.8 vs 9.1 months ($p = 0.50$)
Fujiwara et al., 2007 [68]	Single-center retrospective	22 L-LCNEC pts	Pts received cisplatin/irinotecan ($n = 9$), platinum/paclitaxel ($n = 6$), paclitaxel alone ($n = 1$), cisplatin/vinorelbine ($n = 1$), cisplatin/docetaxel ($n = 1$), and platin/etoposide ($n = 4$) CT	RR: 59.1 % OR: 5 pts receiving irinotecan and 5 receiving paclitaxel PFS: 4.1 months Median OS: 10.3 months 1-year survival rate: 43.0 % In pts treated with irinotecan or paclitaxel: Median OS: 10.3 months 1-year survival rate: 47.6 %
Niho et al., 2013 [70]	Multicenter prospective phase II	41 pts: 30 advanced L-LCNEC, 10 SCLC pts, 1 NSCLC pts	Pts received irinotecan/cisplatin CT	L-LCNEC group and SCLC group showed respectively: RR: 40 vs 80 % ($p = 0.0823$) Median OS: 12.6 vs 17.3 months ($p = 0.047$)

pts patients, *L-LCNEC* lung large cell neuroendocrine carcinoma, *SCLC* small cell lung cancer, *NSCLC* non-small cell lung cancer, *CT* chemotherapy, *RR* response rate, *PFS* progression free survival, *OS* overall survival, *OR* objective response, *HNSCNEC* unresectable high-grade non-small cell neuroendocrine carcinoma, *CR* complete response, *PR* partial response, *HGNEC* high-grade neuro-endocrine carcinoma, *RT* radiotherapy

Table 3 New approaches in the treatment of L-LCNEC

Authors	Study	Patients (pts)	Treatment	Results
Filosso et al., 2005 [71]	Single-center retrospective	18 resected L-LCNEC pts	In 10 L-LCNEC pts (with positive preoperative octreoscan) octreotide alone or in combination with RT was administered as adjuvant treatment. Adjuvant RT was performed when stage was higher than Ib	9/10 treated pts are alive and free of disease at the study publication The other 8 pts had liver and brain metastases 21 months after surgery. ($p = 0.0007$)
Yoshida et al., 2011 [72]	Single-center retrospective	18 advanced previously treated L-LCNEC pts	Amrubicin monochemotherapy	RR: 27.7 % Median PFS: 3.1 months Median OS: 5.1 months
Kenmotsu et al., 2012 [73]	Single-center retrospective	14 L-LCNEC pts treated (9 advanced disease)	Nedaplatin at 50 mg/mq and irinotecan at 50 mg/mq on days 1 and 8 every 4 weeks for 4 cycles	In 9 pts with advanced disease median OS was 12.3 months with 4 PR and 2 CR.
De Pas et al., 2011 [75]	Case report	1 advanced L-LCNEC with activating EGFR mutation (exon 19 , p.L747_A755 > AT)	Gefitinib 250 mg day^{-1}	CR brain CR lung TTP > 6 months
Wang et al., 2015 [77]	Case report	1 advanced L-LCNEC with activating EGFR mutation (exon 19 deletion)	Icotinib 125 mg 3 times a day	PR after 1 month, PFS 8 months
Yokouchi et al., 2012 [78]	Case report	1 advanced L-LCNEC	Intravitreal bevacizumab	PR

pts patients, *L-LCNEC* lung large cell neuroendocrine carcinoma, *RT* radiotherapy, *RR* response rate, *PFS* progression-free survival, *OS* overall survival, *PR* partial response, *CR* complete response, *EGFR* epidermal growth factor receptor, *TTP* time to progression

Veronesi et al. retrospectively evaluated a series of 144 patients with diagnosis of L-LCNEC who underwent lung resection. Induction chemotherapy was given to 21 and postoperative chemotherapy to 24 patients. Five-year survival was 42.5 %: 52 % for stage I, 59 % for stage II, and 20 % for stage III ($p = 0.001$). The response rate (RR) to preoperative chemotherapy was 80 % with a complete response in one patient. In stage I disease, a trend to better outcome was associated with adjuvant or induction chemotherapy ($p = 0.077$) compared with no chemotherapy [7].

In the study by Saji et al., 45 patients with surgically resected L-LCNEC or mixed L-LCNEC, containing at least one portion of neuroendocrine morphology, were retrospectively enrolled. Twenty-three (41 %) out of 45 patients received chemotherapy (7 preoperative and 16 postoperative chemotherapy). Survival of patients who underwent systemic treatment was significantly higher than those who received surgery alone ($p = 0.04$). The five-year survival rate was 87.5 % for patients treated with perioperative adjuvant chemotherapy and 58.5 % for exclusively surgical patients. Even in patients with stage I disease, adjuvant chemotherapy favored survival compared with surgery alone. In the multivariate analysis, surgery with or without chemotherapy showed an independent prognostic influence on overall survival (OS) ($p = 0.0457$) [53].

Sarkaria et al. performed a retrospective review of a prospective database. One hundred patients with resected L-LCNEC were identified. Twenty-two patients received neoadjuvant platinum-based chemotherapy with a RR of 68 %. Seventy-one percent were stage I–II, and 20 of these 71 patients received platinum-based adjuvant chemotherapy. Considering the complete series of patients treated with adjuvant or neoadjuvant chemotherapy, median OS was 7.4 years compared with 2.0 years in patients treated with surgery alone ($p = 0.052$) [54]. This survival positive trend was more recently confirmed by Abedallaa et al. [55].

In the study by Tanaka et al., which evaluated 63 resected L-LCNECs, three neuroendocrine markers (chromogranin A, neural cell adhesion molecule, and synaptophysin) have been investigated on tumor tissue. Patients positive for all three markers were categorized as triple-positive and those who were negative for one or two markers as non-triple-positive. Perioperative chemotherapy resulted in better OS than surgery alone ($p = 0.042$). Moreover, in the non-triple-positive group, a significantly higher 5-year survival rate was observed for the patients who underwent chemotherapy than in those who underwent surgery alone ($p = 0.0081$). In contrast, no difference was found in the triple-positive group [56].

Fournel et al. retrospectively analyzed 63 L-LCNECs resected between 2000 and 2010. Neoadjuvant chemotherapy was administered in 25.4 % of cases, adjuvant treatment in 70 %. Overall, 5- and 8-year survival rates were 49.2 and 42 %, respectively [46].

In the pilot study by Kenmotsu et al., 23 L-LCNEC and 17 SCLC patients with completely resected stage I–IIIA received

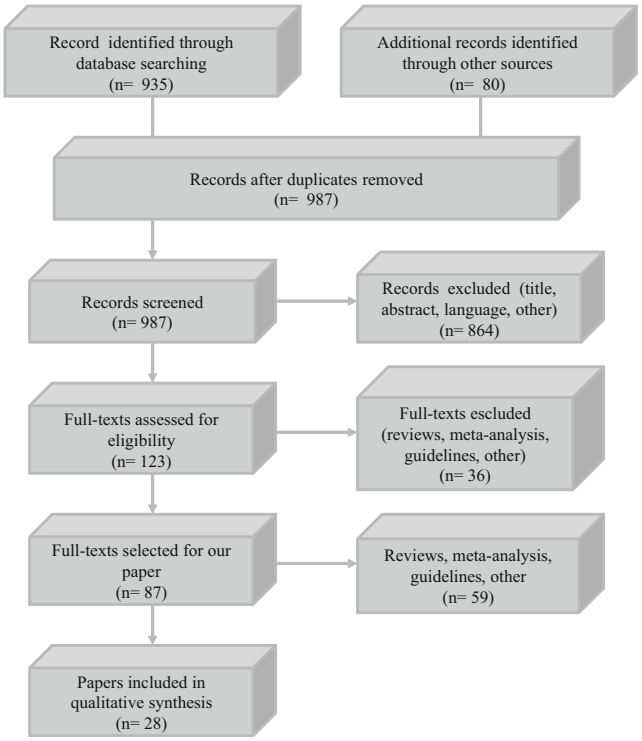

Fig. 1 Flow diagram: criteria for selection of articles

4 cycles of irinotecan (60 mg/mq, day 1, 8, 15) plus cisplatin (60 mg/mq, day 1). This regimen was repeated every 4 weeks. The rates of survival and recurrence-free survival at 3 years were respectively 86 and 74 % in the L-LCNEC group versus 74 and 76 % among SCLC patients. Regarding safety, 48 % of patients experienced grade 3 or 4 neutropenia, but only 13 % developed febrile neutropenia. Two patients (5 %) developed grade 3 diarrhea, and four patients (10 %) had grade 3 nausea. The authors concluded that in patients with resected high-grade neuroendocrine carcinoma (HGNEC), the irinotecan and cisplatin combination was feasible and active as postoperative adjuvant chemotherapy [57]. Based on these preliminary results, a randomized phase III trial is now ongoing in Japan to compare the irinotecan/cisplatin adjuvant regimen with the standard etoposide/cisplatin in patients with completely resected HGNEC [58].

The specific role of radiotherapy in the treatment of limited or locally advanced L-LCNEC is unclear as well as the role of prophylactic cranial irradiation [59, 60]. Rieber et al. retrospectively collected data of 70 patients with histologically confirmed L-LCNEC. The authors compared 34 patients who were treated only with surgery (early stages) to 30 patients who received surgery followed by adjuvant chemotherapy (NSCLC or SCLC schemes), radiotherapy, or radiochemotherapy because of their higher tumor stages (≥IIIA). The OS and local progression-free survival (PFS) were similar between the two groups [60]. More recently Ricciuti et al. reviewed the data of 31 L-LCNECs and 107 SCLCs all treated with platinum/etoposide. Sixteen L-LCNECs and 33 SCLCs showed limited disease at diagnosis. Significantly fewer limited disease L-LCNEC patients received thoracic radiotherapy or prophylactic cranial irradiation compared with SCLC patients. Moreover, the median OS was poorer in limited disease L-LCNECs (10.4 vs 16.3 months; $p=0.05$). In the authors' opinion, the observed different clinical outcome, especially in limited stage disease, could be explained with the lower use of thoracic radiotherapy and prophylactic cranial irradiation in the L-LCNEC group [61].

Management of advanced/metastatic disease (SCLC-like group)

To date, the gold standard chemotherapy for advanced or metastatic L-LCNEC is debated (Table 2) [62–70].

Sun et al., in their retrospective study, evaluated whether advanced L-LCNEC should be treated similarly to SCLC or NSCLC. Of 45 patients with advanced L-LCNEC, 11 were treated with regimens typically used for SCLC and 34 with NSCLC standard chemotherapy. Regarding the efficacy of first-line chemotherapy, the RR was 73 versus 50 % ($p=0.19$), the median PFS was 6.1 versus 4.9 months ($p=0.41$), and the median OS was 16.5 versus 9.2 months ($p=0.10$) in the SCLC and NSCLC regimen groups, respectively. As observed in the first-line setting, even for second-line treatment the most common drugs used in SCLC (taxanes, irinotecan, or platinum retreatment) have proved to be clearly superior to those used in NSCLC (pemetrexed, gefitinib, or erlotinib) [62].

Le Treut et al. conducted a multicenter prospective phase II trial on 42 good-condition advanced L-LCNEC patients (PS 0/1 and stage IIIB/IV) with the aim to evaluate the efficacy of cisplatin and etoposide regimen. The median PFS and median OS were 5.2 and 7.7 months, respectively. Moreover, in this study a centralized pathologist review reclassified 11 of 40 (27.5 %) cases: 9 as SCLCs, 1 as undifferentiated NSCLC, and 1 as ADC. The authors therefore concluded that advanced L-LCNECs treated with cisplatin/etoposide doublets show still poor outcomes, similar to those of patients with advanced SCLC. Furthermore, in future trials, according with the difficulty in the histological diagnosis, centralized pathologist review will be necessary [63].

The studies by Igawa et al. and Yamazaki et al. led to the same conclusions [64, 65]. The former evaluated the clinical response to chemotherapy and the survival of 14 unresectable high-grade non-small cell neuroendocrine carcinomas (HNSCNECs) and 77 advanced SCLCs. In the 77 patients with advanced SCLC, platinum-based combination regimens were used. Instead, platinum-based combination or vinorelbine or docetaxel or irinotecan alone were the chemotherapy regimens used in the 14 patients with unresectable HNSCNEC. In HNSCNEC and SCLC, the RR was 50 % (7/14) versus 53 % (41/77), the 1-year survival rate was 34 versus 48 %, and the median OS was 10 versus 12.3 months,

respectively [64]. In the study by Yamazaky et al., 20 L-LCNEC patients were enrolled. Fourteen were chemo-naive and six had received prior chemotherapy. Nine patients received a combination of cisplatin and etoposide; six cisplatin, vindesine, and mitomycin; four cisplatin and vindesine; and one cisplatin alone. The RR was 50 %, with one complete response and nine partial responses. The RR in chemo-naive patients reached 64 % and was significantly different from that in previously treated patients (17 %). The authors concluded that the RR to cisplatin-based chemotherapy in L-LCNEC was comparable to that in SCLC [65].

Shimada et al. retrospectively examined 25 patients who underwent chemotherapy or chemo-radiotherapy as first-line treatment after the diagnosis of HGNEC-probable L-LCNEC and compared their data with those of 180 patients with SCLC. The overall RR to initial chemotherapy or chemo-radiotherapy and the 1-year survival rate of stage IV HGNEC-probable L-LCNEC were comparable to those of SCLC (86 vs 98 and 34 vs 49 %, respectively). On the contrary, the effectiveness of second-line chemotherapy appeared significantly lower for HGNEC-probable L-LCNEC (RR of 17 % in HGNEC-probable L-LCNEC patients vs 45 % in SCLC patients) [66].

Tokito et al. retrospectively selected 34 patients (10 L-LCNECs diagnosed using surgical specimens and 24 possible L-LCNECs diagnosed using biopsy specimens). SCLC-based chemotherapy, such as platinum/etoposide or platinum/irinotecan, was used for treating 60 % L-LCNEC patients and 67 % possible L-LCNEC patients. In the L-LCNEC and possible L-LCNEC groups, the RR was 70 and 54 % ($p=0.39$), median PFS was 2.9 and 4.4 months ($p=0.20$), and median OS was 12.8 and 9.1 months ($p=0.50$), respectively [67].

Some activity of irinotecan and paclitaxel in patients with L-LCNEC has been observed by Fujiwara et al. In their experience (22 L-LCNEC patients enrolled), the median OS of patients treated with irinotecan or paclitaxel with or without platinum was 10.3 months and the 1-year survival rate was 47.6 % [68].

On the basis of the effectiveness of the irinotecan/cisplatin regimen as first-line treatment for patients with SCLC reported by a meta-analysis [69], Niho et al. conducted a phase II study to test the same irinotecan/cisplatin combination in patients with advanced L-LCNEC. Forty-four naive patients were initially enrolled, but a central pathological review of 41 specimens demonstrated that 30 were L-LCNECs but 10 were SCLCs and 1 was a NSCLC. The RR and median OS was 40 versus 80 % ($p=0.0823$) and 12.6 versus 17.3 months ($p=0.047$) for L-LCNEC group and SCLC group, respectively. The authors conclude that this regimen was active in L-LCNEC, but RR and OS seemed to be inferior to those of SCLC [70].

New approaches

Despite that the chemotherapy regimens used in SCLC can be considered useful also in L-LCNEC, especially for patients with advanced disease, the results are still not satisfactory. Therefore, some authors have tried to explore new different alternatives for the treatment of L-LCENC (Table 3).

The role of octreotide, alone or in combination with radiotherapy, in the adjuvant setting for L-LCNEC patients was investigated in the preliminary experience by Filosso et al. Between 1990 and 2001, 18 radically resected L-LCNEC patients were enrolled. Adjuvant radiotherapy was performed when stage was higher than Ib. Ten patients (55.5 %), with positive results of preoperative In^{111} pentetreotide scintigraphy (octreoscan), received octreotide after surgery, alone or in combination with radiotherapy as adjuvant treatment; nine of these (90 %) were alive and disease free ($p=0.0007$) at the time of publication [71].

Yoshida et al. evaluated the role of amrubicin monotherapy for patients with previously treated advanced L-LCNEC. Eighteen patients were enrolled, and all had already received at least one platinum-based chemotherapy (13 had received one prior chemotherapy, 5 two or more chemotherapies). Amrubicin has proved to be potentially active. The RR, median PFS, and OS were 27.7 %, 3.1 and 5.1 months, respectively. However, hematological toxicity was significant (febrile neutropenia G3 occurred in 33 % of the patients) [72].

In the retrospective study by Kenmotsu et al., 14 patients with L-LCNEC were treated with nadaplatin and irinotecan combination. In nine patients with advanced disease, median OS was 12.3 months with four partial responses and two complete responses. The authors concluded that this is an effective and safe regimen for patients with L-LCNEC [73].

Regarding target therapy, literature reports some cases of L-LCNEC patients with presence of EGFR mutations who have shown a good response after therapy with EGFR-TKI. However, these mutations are extremely rare in "pure" L-LCNEC while they occur more frequently in mixed forms (especially if the associated component is ADC) [48, 74–77]. Moreover, Yokouchi et al., in a case report on iris metastasis from L-LCNEC, showed response to intravitreal bevacizumab [78].

Anti-c-KIT, anti-VEGF, and anti-HER2 agents could be interesting new drugs for L-LCNEC treatment [79].

Last, another potential therapeutic target is the TrkB/BDNF signaling pathway, but the data on targeting this pathway are still very preliminary [80, 81].

Conclusions

L-LCNEC is a rare and aggressive tumor. Due to its rarity, the histological diagnosis of L-LCNEC is often controversial and requires the opinion of at least an expert pathologist [23, 24, 82, 83]. Moreover, literature regarding the management of L-LCNEC is scant and frequently derives from retrospective analyses or limited case series (Tables 1, 2, and 3). Often, the

therapeutic indications are simply extrapolated from clinical practice or extracted from the treatment of NSCLC and SCLC.

However, there is consensus on some issues. In L-LCNEC patients with stage I, II, and III (ADC/SQC-like group), surgery should be always considered if technically possible. Patients with radically resected locally advanced L-LCNEC should be treated with adjuvant chemotherapy containing cisplatin or carboplatin/etoposide. The role of irinotecan/cisplatin regimen in these patients is still under investigation in an ongoing phase III Japanese trial [58]. Literature data regarding the role of neoadjuvant chemotherapy in patients with potentially resectable L-LCNEC are not well defined and therefore, in our opinion, this therapeutic approach cannot be recommended in clinical practice.

Although not all authors agree [84, 85], patients with advanced L-LCNEC (SCLC-like group) and good clinical conditions should be treated, both in first- and second-line setting, with chemotherapy regimens used for the treatment of SCLC (cisplatin or carboplatin plus etoposide or irinotecan). The recent guidelines of the American Society of Clinical Oncology for treatment of stage IV NSCLC conclude that L-LCNEC patients may receive both the same therapy as other NSCLCs and etoposide/platinum combinations. Nevertheless, the evidence quality is low and the strength of recommendation is weak. So, due to the clinical similarity of L-LCNEC to SCLC, the committee believes that etoposide/platinum combinations may provide optimal efficacy in these patients [86].

Further studies are needed to identify the best therapeutic approach for these rare tumors and to better clarify their biomolecular characteristics and the potential role of new target therapies. The inclusion of L-LCNEC patients in clinical trials is recommended.

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Compliance with ethical standards

Conflict of interest None

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