Lung Cancer 137 (2019) 100–107

Contents lists available at ScienceDirect

Lung Cancer

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

First-line platinum-based chemotherapy and survival outcomes in locally advanced or metastatic pulmonary lymphoepithelioma-like carcinoma

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ARTICLE INFO

Keywords:
Lung cancer
Pulmonary lymphoepithelioma-like carcinoma
Chemotherapy
Radiotherapy
Nasopharyngeal carcinoma
Epstein-Barr virus

ABSTRACT

Objectives: Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subtype of primary lung cancer. Due to the lack of prospective studies, the optimal first-line chemotherapy regimens and survival outcomes remain unclear.

Materials and methods: This real-world, retrospective study enrolled consecutive patients with unresectable pulmonary LELC. The survival outcomes, prognosis, and comparative efficacy of different chemotherapy regimens were investigated.

Results: In total, 127 patients were included in the analyses. The first-line chemotherapy regimens included gemcitabine plus platinum (GP, n = 19 [15.0%]), taxanes plus platinum (TP, n = 70 [55.1%]) and pemetrexed plus platinum (AP, n = 38 [30.0%]). 25 (19.7%) patients underwent palliative thoracic radiotherapy. 60 (47.2%) patients had detectable baseline Epstein-Barr virus (EBV) DNA. For the entire cohort, objective response was obtained in 41 patients (32.3%). Median progression-free survival (PFS) and overall survival (OS) were 7.7 months (95% CI, 6.6–8.8) and 36.7 months (95% CI, 30.9–42.5), respectively. Among the three chemotherapy regimens, GP achieved the highest response rate (GP, 63.2% vs. TP, 30.0% vs. AP, 21.1%; $p = 0.005$). Median PFS in the GP group (8.8 months) was also significantly longer than that in the TP group (7.9 months) and AP group (6.4 months) ($p = 0.031$). In the multivariate model, cycles of first-line chemotherapy ($p < 0.001$), palliative thoracic radiotherapy ($p < 0.001$), and chemotherapy regimens ($p = 0.031$) remained independent prognostic factors for PFS; while cycles of first-line chemotherapy ($p = 0.002$), baseline EBV DNA ($p = 0.033$) and palliative thoracic radiotherapy ($p = 0.041$) were significantly associated with OS.

Conclusion: Gemcitabine-based chemotherapy and palliative thoracic radiotherapy are active in pulmonary LELC. These data provide added evidence for the similarity between pulmonary LELC and nasopharyngeal carcinoma in endemic area. Randomized controlled studies are needed to further define the standard-of-care for patients with advanced pulmonary LELC.

Abbreviations: LELE, lymphoepithelioma-like carcinoma; NPC, nasopharyngeal carcinoma; NSCLC, non-small cell lung cancer; EBV, Epstein-Barr virus; RECIST, Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; PR, partial response; CR, complete response; DCR, disease control rate; SD, stable disease; PFS, progression-free survival; PD, progressive disease; OS, overall survival; CIs, confidence intervals; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CNS, central nervous system; GP, gemcitabine plus platinum; TP, taxanes plus platinum; AP, pemetrexed plus platinum; NOS, not otherwise specific; CNASCA, China National Accreditation Service for Conformity Assessment; ISH, in situ hybridization

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https://doi.org/10.1016/j.lungcan.2019.09.007
Received 2 August 2019; Received in revised form 9 September 2019; Accepted 11 September 2019

1. Introduction

Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare and unique subtype of primary non-small cell lung cancer (NSCLC) that histologically resembles undifferentiated nasopharyngeal carcinoma (NPC) [1]. It is recognized to be etiologically associated with Epstein-Barr virus (EBV) infection in endemic areas [2]. Currently, pulmonary LELC is classified as "other and unclassified carcinomas" according to the 2015 World Health Organization Classification Lung Tumors [3]. Over the past decades, less than 600 cases have been reported in the literature. For patients with locally advanced or metastatic pulmonary LELC that are not suitable for radical treatment, palliative chemotherapy remains the principle option [4]. The reported chemotherapeutic agents include gemcitabine, taxanes, fluorouracil, vinorelbine, pemetrexed, and platinum [5–7]. However, most studies enrolled very limited number of patients. Whether there is survival difference among patients receiving different chemotherapy regimens is unclear. Furthermore, the survival outcomes and prognostic factors for advanced pulmonary LELC are undefined due to the rarity of this tumor type.

In this study, we report data from currently the largest cohort of patients with locally advanced or metastatic pulmonary LELC treated with first-line platinum-based chemotherapy. We comprehensively analyze the efficacy of different chemotherapeutic regimens and investigate the impact of palliative radiotherapy, baseline EBV DNA as well as other prognostic factors on survival.

2. Material and methods

2.1. Study design and patients

This was a retrospective, observational study carried out in Sun Yat-sen University Cancer Center evaluating patients with advanced pulmonary LELC who initiated first-line chemotherapy between January 2007 and September 2018. Patients were identified through the electronic medical records. Patients meeting the following criteria were included: (1) histologically diagnosed as pulmonary LELC. Pathological diagnoses were centrally established by the Department of Pathology in Sun Yat-sen University Cancer Center (which has obtained China National Accreditation Service for Conformity Assessment [CNASCA]). The diagnoses were further reviewed by another pathologist Dr. Sha Fu. EBV-encoded RNA (EBER) staining (EBV Probe In Situ Hybridization [ISH] Kit, Triplex International Biosciences, China) was used to help pathological diagnosis as previously described [2]; (2) exclusion of lung metastasis from nasopharyngeal carcinoma; (3) were at stage IIIB, IIIC or IV according to the 8th edition of American Joint Committee on Cancer staging manual; (4) had at least one measurable lesion; (5) had received first-line platinum-based chemotherapy for advanced disease; (6) had regular evaluation of response with computed tomography or magnetic resonance imaging scan; (7) aged ≥ 18 years. The study was carried out in accordance with the Declaration of Helsinki and was approved by the Sun Yat-sen University Cancer Center Institutional Review Board. All the patients have provided written informed consent for the treatment and the collection of blood samples necessary for laboratory tests.

2.2. Data collection

The following clinical and laboratory data was collected: age, gender, smoking history, Eastern Cooperative Oncology Group performance status (ECOG PS), metastatic sites, clinical stage, treatment modality, EBV DNA, EGFR mutation status, ALK rearrangement status. Patient follow-ups were obtained through medical records or by telephone interview. Efficacy was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

2.3. Statistical analyses

A prespecified sample size was not determined. Overall response rate (ORR) was defined as the proportion of patients with partial or complete response (PR/CR). Disease control rate (DCR) equals the proportion of PR/CR plus stable disease (SD). Progression-free survival (PFS) was defined as the time from the initiation of first-line chemotherapy to progressive disease (PD) or death from any causes, whichever occurred first. Patients who had not progressed were censored at the date of their last image scan. Overall survival (OS) was calculated from the initiation of first-line chemotherapy to death from any causes. Patients who did not die were censored at the date of last contact. Clinical characteristics were summarized by chemotherapy groups. Pearson chi square or Fisher's exact test and Wilcoxon tests were used to identify between-group differences for categorical variables and continuous variables, respectively. PFS and OS were estimated using the Kaplan-Meier methodology. The median and the 95% confidence intervals (CIs) and p-value from log rank tests are reported. Prognostic factors for PFS and OS were identified using Cox proportional hazard models. A 2-sided p value of less than 0.05 was deemed statistically significant. All the statistical analyses were done with the SPSS software, version 23.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

A total of 127 consecutive patients were included in the analyses (Fig. 1). As of data cutoff (March 12, 2019), 59 (46.5%) patients died, 25 (19.7%) patients lost to follow up and 43 (33.9%) remained alive. Median follow-up time was 22.7 months (range 1.5–81.4 months). Median time to first radiological assessment was 1.40 months (range, 0.70–3.63 months).

Baseline characteristics of the patients are summarized in Table 1.

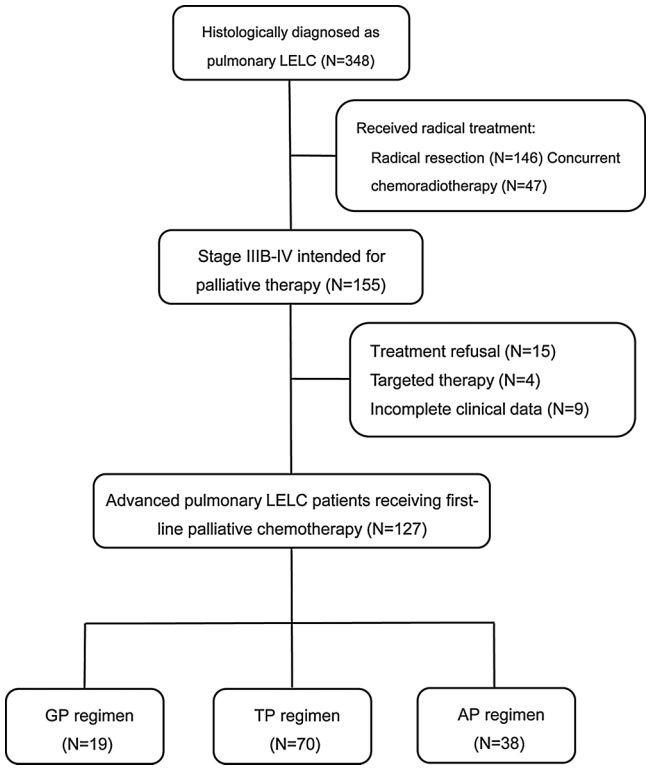

Fig. 1. Flow chart depicting patient deposition. LELC, Lymphoepithelioma-like carcinoma; GP, gemcitabine plus platinum; AP, pemetrexed plus platinum; TP, taxanes ([nab-]paclitaxel or docetaxel) plus platinum.

Table 1
Baseline characteristics of the included patients grouped by the first-line chemotherapy regimens.

	All (N = 127)		GP (N = 19)		TP (N = 70)		AP (N = 38)		P
	n	%	n	%	n	%	n	%	
Gender									0.392
Male	60	47.2	7	36.8	32	45.7	21	55.3	
Female	67	52.8	12	63.2	38	54.3	17	44.7	
Age, years									0.479
Median (range)	51 (29–73)		50.5 (37–70)		52.5 (36–70)		48 (29–73)		
Stage									0.606
IIIB-IIIC	15	11.8	2	10.5	10	14.3	3	7.9	
IV	112	88.2	17	89.5	60	85.7	35	92.1	
ECOG PS									0.402
0	116	91.3	17	89.5	66	94.3	33	86.8	
1	11	8.7	2	10.5	4	5.7	5	13.2	
Smoking history									0.381
Yes	37	29.1	3	15.8	22	31.4	12	31.6	
No	90	70.9	16	84.2	48	68.6	26	68.4	
Metastatic sites									–
Lung	38	29.9	5	26.3	23	32.9	10	26.3	0.726
Liver	36	28.3	9	47.4	19	27.1	8	21.1	0.109
Bone	44	34.6	6	31.6	25	35.7	13	34.2	0.943
Pleura	39	30.7	2	10.5	21	30.0	16	42.1	0.050
Adrenals	4	3.1	0	0.0	4	5.7	0	0.0	0.186
Lymph node	111	87.4	16	84.2	61	87.1	34	89.5	0.849
Others	16	12.6	4	21.1	4	5.7	8	21.1	0.086
EBV DNA									0.378
High	30	23.6	5	26.3	14	20	11	29.0	
Low	30	23.6	4	21.1	21	30	5	13.2	
Unknown	67	52.8	10	52.6	35	50	22	57.8	
EGFR mutation									0.178
Yes	0	0.0	0	0.0	0	0.0	0	0.0	
No	68	53.5	10	53.6	33	47.1	25	65.8	
Unknown	59	46.5	9	47.4	37	52.9	13	34.2	
ALK rearrangement									0.107
Yes	0	0.0	0	0.00	0	0.0	0	0.0	
No	46	36.2	6	31.6	21	30.0	19	50.0	
Unknown	81	63.8	13	68.4	49	70.0	19	50.0	
Cycles of platinum-based chemotherapy									0.324
< 4	36	28.3	3	15.8	23	32.9	10	26.3	
≥ 4	91	71.7	16	84.2	47	67.1	28	73.7	
Palliaitive Thoracic Radiotherapy									0.609
Yes	25	19.7	3	15.8	16	22.9	6	15.8	
No	102	80.3	16	84.2	54	77.1	32	84.2	

Abbreviations: GP, gemcitabine plus platinum; TP, taxanes plus platinum; AP, pemetrexed plus platinum; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Among the 127 patients, median age was 51 years (range, 29–73), 67 (52.8%) were female, 116 (91.3%) had an ECOG PS of 0, and 90 (70.9%) were non-smokers. No patients had central nervous system (CNS) metastases. 68 (53.5%) and 46 (36.2%) patients had genetic tests for *EGFR* mutation and *ALK* fusion, respectively. But none of them harbour these genetic alterations. 91 (71.7%) patients completed at least 4 cycles of first-line chemotherapy. Patients were further categorized according the chemotherapy regimens they received into gemcitabine plus platinum group (GP, n = 19 [15.0%]), taxanes plus platinum group (TP, n = 70 [55.1%]) and pemetrexed plus platinum group (AP, n = 38 [30.0%]). Baseline characteristics were similar among the three chemotherapy groups.

3.2. Treatment outcomes of patients with advanced pulmonary LELC

41 (32.3% [95% CI, 24.3–41.2%]) of 127 patients achieved an objective response and disease control was achieved in 115 (91.3% [95% CI, 85.2-95.1%]) patients. The short-term treatment efficacy is presented in Table 2. The proportion of patients who achieved an objective response was statistically different across the three treatment groups (GP, 63.2% [95% CI, 38.4–83.7%] vs. TP, 30.0% [19.6–42.1%] vs. AP, 21.1% [9.6–37.3%]; $p = 0.005$). DCR was not statistically different across the three arms (GP, 100.0% [95% CI, 83.2–100.0%] vs. TP, 92.9% [84.4–96.9%] vs. AP, 84.2% [69.6–92.6%]; $p = 0.108$).

Median PFS was 7.7 months (95% CI, 6.6–8.8) for the entire cohort (Fig. 2A). Among the three treatment arms, GP (median PFS, 8.8 months; 95% CI, 6.9–10.7) achieved longer PFS compared to AP (median PFS, 6.7 months; 95% CI, 5.3–8.1) and TP (median PFS, 7.9 months; 95% CI, 6.2–9.6), with difference reaching statistical significance ($p = 0.031$; Fig. 2B).

By the end of last follow-up, median OS for the 127 patients was 36.7 months (95% CI, 30.9–42.5; Fig. 3A). Median OS for patients treated with GP, TP and AP regimens was 25.6 months (95% CI, 17.7–33.5), 38.6 months (95% CI, 31.4–45.7) and 31.7 months (95% CI, 27.5–35.9), respectively. There was no significant difference in OS among the three treatment groups ($p = 0.116$; Fig. 3B).

3.3. Impact of palliative thoracic radiotherapy on survival

We next investigated the impact of palliative thoracic radiotherapy on survival of patients with advanced pulmonary LELC. Among the 127 patients included, 25 (19.7%) received thoracic radiotherapy after first-line treatment, while the remaining 102 patients did not. PFS was significantly longer in the radiotherapy group (median 14.7 months; 95% CI, 6.6–22.8) than in the non-radiotherapy group (median 6.5 months; 95% CI, 5.6–7.5), with an unadjusted hazard ratio (HR) of 0.19

Table 2
Tumor response according to three chemotherapy regimens.

Arms	Best tumor response					
	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	ORR* (95% CI)	DCR& (95% CI)
Total, n = 127	1 (0.8)	40 (31.5)	75 (59.0)	11 (8.7)	32.3% (24.3–41.2%)	91.3% (85.2–95.1%)
GP, n = 19	0 (0.0)	12 (63.2)	7 (36.8)	0 (0.0)	63.2% (38.4–83.7%)	100.0% (83.2–100.0%)
TP, n = 70	1 (1.4)	20 (28.6)	44 (62.9)	5 (7.1)	30.0% (19.6–42.1%)	92.9% (84.4–96.9%)
AP, n = 38	0 (0.0)	8 (21.1)	24 (63.2)	6 (15.8)	21.1% (9.6–37.3%)	84.2% (69.6–92.6%)

Abbreviations: GP, gemcitabine plus platinum; TP, taxanes plus platinum; AP, pemetrexed plus platinum; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, objective response; DCR, disease control rate.
* ORR was statistically different among GP, TP and AP by chi-square test ($p = 0.005$).
& DCR was not significantly different among these three treatment arms ($p = 0.108$).

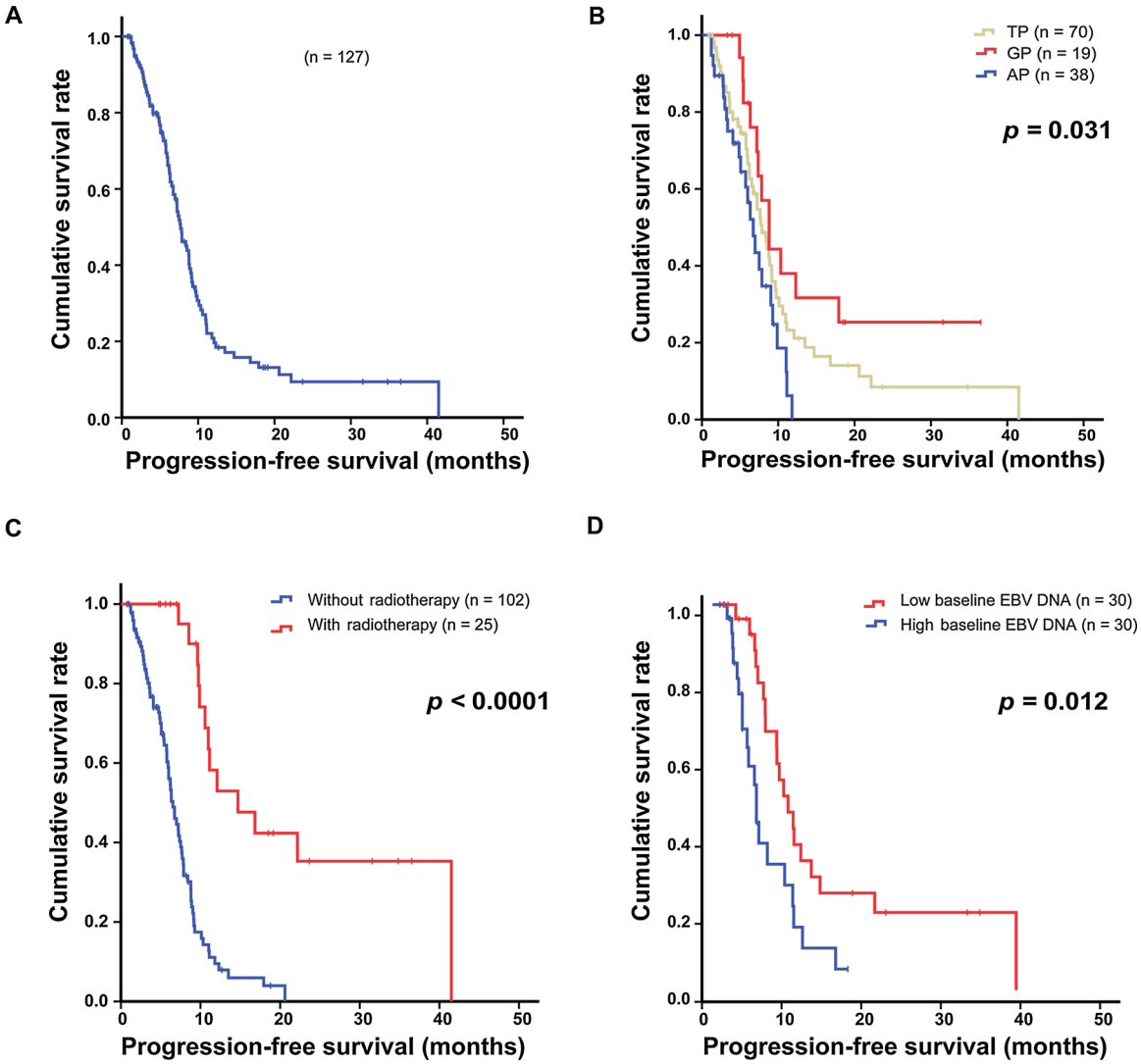

Fig. 2. Kaplan-Meier curves of PFS. (A) PFS for the entire cohort (n = 127); (B) PFS by the first-line chemotherapy regimens; (C) PFS according to whether or not palliative thoracic radiotherapy was done; (D) PFS by the level of baseline EBV DNA as stratified by median value. PFS, progression-free survival; GP, gemcitabine plus platinum; AP, pemetrexed plus platinum; TP, taxanes ([nab-]paclitaxel or docetaxel) plus platinum; EBV, Epstein-Barr virus.

(95% CI, 0.10-0.37; $p < 0{\cdot}0001$; Fig. 2C). Median OS was not reached in the radiotherapy group, which was significantly longer than that in the non-radiotherapy group (32.4 months; 95% CI, 26.4–38.4), with an unadjusted HR of 0.38 (95% CI, 0.17–0.85; $p = 0.018$; Fig. 3C). Patients at stage III were more likely to receive radiotherapy than those at stage IV (8 out of 15 [53.3%] vs. 17 out of 112 [15.2%]; $p = 0.002$). However, when stratified by clinical stage, similar protective effect of thoracic radiotherapy regarding PFS and OS were observed except that

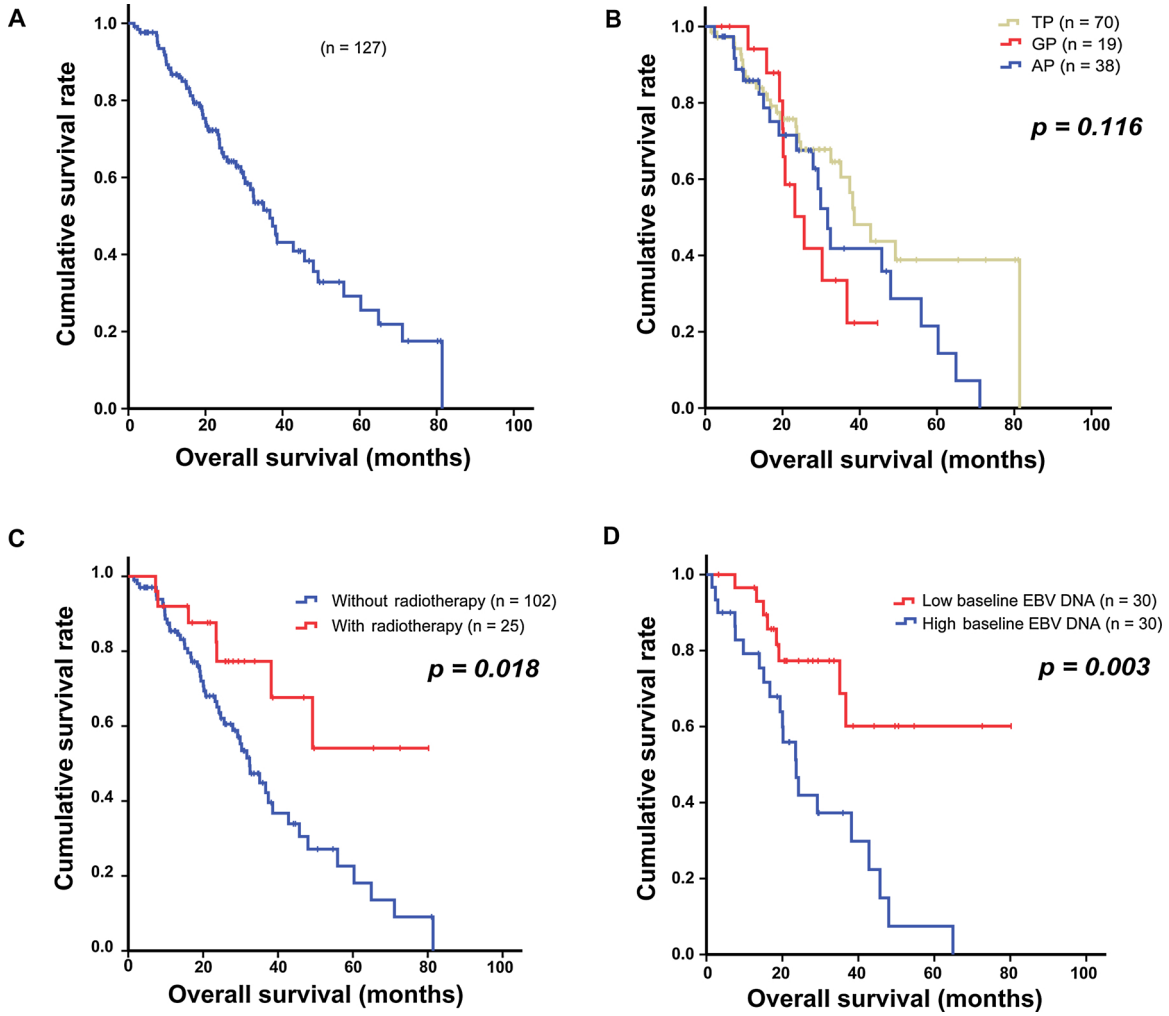

Fig. 3. Kaplan-Meier curves of OS. (A) OS for the entire cohort (n = 127); (B) OS by the first-line chemotherapy regimens; (C) OS according to whether or not palliative thoracic radiotherapy was done; (D) OS by the level of baseline EBV DNA as stratified by median value. OS, overall survival; GP, gemcitabine plus platinum; AP, pemetrexed plus platinum; TP, taxanes ([nab-]paclitaxel or docetaxel) plus platinum; EBV, Epstein-Barr virus.

radiotherapy has no significant effect on OS in patients with stage III (Supplementary Fig. 1).

3.4. EBV DNA as a risk factor for survival

Given pulmonary LELC is etiologically related to EBV infection, we sought to investigate the prognostic value of EBV DNA load. For the 60 (47.2%) patients who had available baseline EBV DNA, the median titre was 50600 copies/ml (range 0–7850000). Using median value as cut-off, 30 patients were deemed to have high EBV DNA (> 50600 copies/ml) and 30 patients have low EBV DNA (≤ 50600 copies/ml) at baseline. Patients with high baseline EBV DNA had significantly inferior PFS (median, 6.0 months [95% CI, 4.4–7.5] vs. 10.3 months [95% CI, 7.7–13.0]; HR 2.27 [95% CI, 1.20–4.32]; $p = 0.012$) and OS (23.6 months [95% CI, 17.9–29.3] vs. not reached; HR 3.78 [95% CI, 1.67–8.58]; $p = 0.003$) than those with low baseline EBV DNA (Figs. 2D, 3 D).

3.5. Prognostic factors for PFS and OS

Next, we comprehensively evaluated the prognostic values of the main clinical, pathological and biological factors for PFS and OS. In order not to miss out potentially important prognostic factors, a p value of ≤ 0.15 was used as the cut-off value for variable selection from the univariate model.

Significant prognostic factors for PFS identified in the univariate model included ECOG PS ($p = 0.009$; Supplementary Fig. 1A), baseline EBV DNA level ($p = 0.023$), cycles of first-line chemotherapy ($p = 0.033$; Supplementary Fig. 1B), palliative thoracic radiotherapy ($p < 0.001$), and first-line chemotherapy regimens ($p = 0.035$). In the multivariate model, cycles of first-line chemotherapy ($p < 0.001$), palliative thoracic radiotherapy ($p < 0.001$), and first-line chemotherapy regimens ($p = 0.031$) remained independent prognostic factors for PFS (Table 3).

For OS, we identified the following prognostic factors in the univariate analysis: ECOG PS ($p = 0.011$; Supplementary Fig. 1C), cycles of first-line chemotherapy ($p < 0.001$; Supplementary Fig. 1D), baseline EBV DNA level ($p = 0.003$), palliative thoracic radiotherapy ($p = 0.018$). Multivariate Cox regression analysis revealed that less than 4 cycles of chemotherapy ($p = 0.002$), without palliative thoracic radiotherapy ($p = 0.041$), and high baseline EBV DNA ($p = 0.033$) remained significantly associated with inferior OS (Table 3).

4. Discussion

In this report, we assessed a large series of patients with advanced pulmonary LELC treated with first-line chemotherapy. Our results indicate that gemcitabine plus platinum achieved the highest response rate and the longest progression-free survival compared with taxanes plus platinum and pemetrexed plus platinum, though these short-term

Table 3
Prognostic factors for Progression-free survival and overall survival.

	PFS				OS			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Covariate	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)
Gender	0.494				0.404			
Male		1				1		
Female		1.17 (0.75–1.81)				1.25 (0.74–2.10)		
Age	0.541	1.01 (0.99–1.03)			0.592	1.01 (0.98–1.03)		
Stage	0.113		0.808		0.168			
IV		1		1		1		
IIIB-IIIC		0.53 (0.24–1.16)		0.89 (0.35–2.29)		0.55 (0.24–1.29)		
ECOG PS	0.009		0.133		0.011		0.280	
1		1		1		1		1
0		0.64 (0.46–0.89)		0.56 (0.26–1.19)		0.37 (0.17–0.79)		0.64 (0.28–1.45)
Smoking history	0.295				0.837			
Yes		1				1		
No		0.88 (0.68–1.12)				0.94 (0.53–1.66)		
EBV DNA	0.023		0.159		0.003		0.033	
Low		1		1		1		1
Unknown	0.016	1.97 (1.14–3.42)	0.175	1.51 (0.83–2.75)	0.126	1.85 (0.84–4.04)	0.866	1.08 (0.46–2.52)
High	0.012	2.27 (1.20–4.32)	0.057	1.97 (0.98–3.97)	0.001	3.78 (1.67–8.58)	0.070	2.26 (0.94–5.44)
Cycles of chemotherapy	0.033		< 0.001		< 0.001		0.002	
≥ 4		1		1		1		1
< 4		1.73 (1.05–2.87)		2.89 (1.65–5.08)		2.68 (1.59–4.51)		2.48 (1.41–4.37)
Palliative Thoracic radiotherapy	< 0.001		< 0.001		0.018		0.041	
Yes		1		1		1		1
No		2.30 (1.65–3.19)		6.01 (2.78–12.99)		2.62 (1.18–5.78)		2.40 (1.04–5.55)
Chemotherapy regimens	0.035		0.031		0.123		0.137	
AP		1		1		1		1
TP	0.860	0.65 (0.39–1.06)	0.789	0.93 (0.53–1.62)	0.097	0.62 (0.35–1.09)	0.869	0.95 (0.52–1.74)
GP	0.011	0.40 (0.20–0.81)	0.017	0.41 (0.19–0.85)	0.701	1.16 (0.54–2.50)	0.095	2.02 (0.88–4.60)

Abbreviations: PFS, progression-free survival; OS, overall survival; ECOG, Eastern Cooperative Oncology Group; PS, Performance Status; EBV, Epstein-Barr virus; GP, gemcitabine plus platinum; TP, taxanes plus platinum; AP, pemetrexed plus platinum.

advantages did not translate into overall survival benefit, which is probably due to post-progression cross-over treatment. We also revealed several key prognostic factors including baseline EBV DNA level, numbers of chemotherapy cycles and palliative thoracic radiotherapy. Our results provide clinically relevant information for the selection of first-line chemotherapy and estimating the prognosis of patients with advanced pulmonary LELC. More importantly, our data further lend support for the similarity between pulmonary LELC and NPC from the aspect of treatment efficacy and prognostication.

First reported in 1987, pulmonary LELC has been recognized as a unique lung cancer that is closely related to EBV infection in endemic areas [8–11]. Compared with other types of lung cancer, pulmonary LELC has distinct clinicopathological features. It preferentially affects non-smokers of younger age in Asian population [12,13]. Driver mutations such as *EGFR* mutation and *ALK* rearrangement are rarely detected in pulmonary LELC [1,2,14,15]. These features, in line with the current study, indicate that the key carcinogenic factors for pulmonary LELC might be those other than tobacco exposure and somatic driver mutations. The involvement of EBV infection in the pathogenesis of pulmonary LELC has been implicated in our previous whole-exome sequencing study [13]; however, the underlying mechanisms warrant further investigation. Cell-free EBV DNA can be found in the plasma of patients with pulmonary LELC [16]. Furthermore, several studies have demonstrated a potential association between circulating EBV DNA and survival of pulmonary LELC [11,17]. However, most of them enrolled either small sample size or early stage disease. The role of EBV DNA in the risk stratification of patients with advanced pulmonary LELC remains not fully understood. Herein, we reported a significant association between increased values of baseline EBV DNA level and inferior PFS and OS, with an unadjusted HR of 2.27 and 3.78, respectively. These results imply that cell-free circulating EBV DNA might be a surrogate tumor marker in patients with pulmonary LELC and serve as a poor prognostic factor for survival. The reasonable explanation would be that the level of EBV DNA provides a reflection of the tumor load of pulmonary LELC.

Currently, due to the lack of clinical trials, the optimal chemotherapy regimens for pulmonary LELC have not been established. The selection of first-line chemotherapy is mainly empirical and is typically based on the histological classification of NSCLC (e.g. as non-squamous or not otherwise specific [NOS]). As previously reported, the most commonly used regimens included paclitaxel/ docetaxel plus platinum, pemetrexed plus platinum, and gemcitabine plus platinum. In a phase III clinical trial, we demonstrated that gemcitabine plus cisplatin has better efficacy than fluorouracil plus cisplatin did in metastatic or recurrent NPC (ORR, 64% vs. 42%; median PFS, 7.0 vs. 5.6 months; median OS, 29.1 vs. 21.9 months) [18]. By contrast, the antitumor activity of pemetrexed in NPC was very limited (ORR, 2.9%; DCR, 42.9%; median PFS, 1.5 months) [19]. In this study, we showed that gemcitabine plus platinum achieved the highest response rate compared with taxanes plus platinum and pemetrexed plus platinum did. Progression-free survival and overall survival also favor the gemcitabine group. These results imply that, similar to NPC, pulmonary LELC is more sensitive to gemcitabine-based chemotherapy. Worthy of note, in a retrospective study enrolling 33 advanced pulmonary LELC patients, the authors also demonstrated longer PFS with GP regimen than with AP regimen (median 10 vs. 5 months; $p = 0.001$) [6]. However, the sample size is too small to draw robust conclusion and the overall survival data was not available. Nevertheless, these data collectively support the hypothesis that pulmonary LELC is clinically and chemotherapeutically similar to NPC.

For patients with metastatic NPC, it has been reported that palliative radiotherapy to the primary tumor could improve the quality of life and prolong survival [20–22]. The rationale for this approach is that NPC is moderately sensitive to chemotherapy and highly sensitive to

radiotherapy [23,24]. Palliative radiotherapy to the primary foci could reduce tumor bulk and those chemo-resistant cell clones. This approach might retard the development of disease progression. Furthermore, radiotherapy might potentiate anti-tumor immunity by promoting neoantigen release [25]. For pulmonary LELC, it was also reported to be sensitive to chemotherapy and radiotherapy [4,5]. However, the value of adding palliative thoracic radiotherapy to first-line chemotherapy is unknown. In the current study, 25 of 127 patients received thoracic radiotherapy after the initiation of first-line chemotherapy, whose PFS and OS was significantly longer than those without radiotherapy. Worthy of note, patients at stage III were more likely to receive thoracic radiotherapy than those at stage IV, implying that the benefit of radiotherapy may be at least partially attributable to the stage. However, the protective effect of radiotherapy was similar when stratified by stage. Moreover, multivariate analysis that controlling confounding factors including stage demonstrated that thoracic radiotherapy independently predicted better survival. Collectively, these data imply that palliative thoracic radiotherapy contributes to survival prolongation in patients with advanced pulmonary LELC. It is also reasonable to assume that chemoradiotherapy combination might have potential survival benefits for selected patients. Further randomized studies are needed to evaluate the added value of thoracic radiotherapy in locally advanced or metastatic pulmonary LELC.

Finally, we comprehensively explored the prognostic factors for advanced pulmonary LELC. We found that patients who had completed $\geq$ 4 cycles of first-line chemotherapy, received palliative thoracic radiotherapy, or treated with GP regimen had lower risk of disease progression; whereas cycles of first-line treatment of at least 4, lower baseline EBV DNA, and thoracic radiotherapy were significantly associated with favorable OS. These results could aid the estimation of patient's survival and be used as stratification factors in clinical trials. Interestingly, these prognostic factors could also predict survival of advanced NPC patients.

Our study has several limitations. Firstly, this is a retrospective, single-center study. The results need further validation by external cohorts. Nevertheless, this is currently the largest cohort study of advanced LELC. Considering that prospective clinical trials for pulmonary LELC will be impractical due to the rarity of this tumor type, the findings from our real-world study could be deemed clinically relevant. Secondly, the findings that gemcitabine-based chemotherapy and palliative thoracic radiotherapy lead to improved survival was not evaluated in a randomized clinical trial. The conclusion should be regarded as hypothesis-generating. Future clinical studies with larger sample sizes could help address this question. Finally, though EBV has been recognized to be etiologically associated with pulmonary LELC, only about half of the included patients have available baseline EBV DNA. Given its clear prognostic value in advanced pulmonary LELC, we advise incorporating baseline and on-treatment EBV DNA levels into routine clinical practice.

Albeit the limitations above, our study comprehensively evaluated the survival outcomes of patients with unresectable pulmonary LELC who received first-line platinum-based chemotherapy. Gemcitabine-based chemotherapy and palliative thoracic radiotherapy are active in pulmonary LELC, which warrant further investigation in prospective studies. The results of this study further support the similarity between pulmonary LELC and NPC, in terms of treatment response and prognostication.

Authors' contributions

Zuan Lin collected and analyzed clinical data and wrote the article. Xuanye Zhang reviewed the radiological findings and wrote the article. Yixin Zhou gathered detailed clinical information for the study. Sha Fu reviewed the pathological findings and wrote the article. Shaodong Hong and Li Zhang conceived the study and wrote the manuscript. All authors were involved in the drafting, review, and approval of the report and the decision to submit for publication.

Financial support

This study was funded by the National Key R&D Program of China (grant number: 2016YFC0905500 and 2016YFC0905503); National Natural Science Funds of China (grant number: 81972898, 81602005, 81702283, 81872499, and 81602011); the Outstanding Young Talents Program of Sun Yat-sen University Cancer Center (grant number: 16zxyc04); the Central Basic Scientific Research Fund for Colleges-Young Teacher Training Program of Sun Yat-sen University (grant number: 17ykpy81); the Science and Technology Program of Guangdong Province (grant number: 2017B020227001). Shaodong Hong also receive support from the Sun Yat-sen University Cancer Center Promotion Program for Talent Youth of National Natural Science Funds of China. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of Competing Interest

The authors declare no conflicts of interest that pertain to this work.

Acknowledgment

We appreciate Yidu Cloud Technology Ltd. (Beijing, China) for data management.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.09.007.

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