Lung Cancer 138 (2019) 116–123

Contents lists available at ScienceDirect

Lung Cancer

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

Thorough survey and analysis of pulmonary lymphoepithelioma-like carcinoma in Macau and multimodality treatment for advanced disease

Na Zhou[a], Yi Lin[b], Xianghong Peng[b], Yingyi Wang[a,*], Yuzhou Wang[b,*]

[a] Department of medical oncology, Peking Union Medical College Hospital, No. 1, Shuaifuyuan, Wangfujing, Dongcheng district, Beijing, China
[b] Department of oncology, Centro Hospitalar Conde de Sao Januario, Estrada do Visconde de S. Januario, Macau, China

ARTICLE INFO

Keywords:
Lung cancer
Lymphoepithelioma-like carcinoma
Multimodal treatment
Thorough survey
Chemotherapy
Radiotherapy

ABSTRACT

Objective: Pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare type of non-small cell lung cancer. The clinical course and prognosis of advanced LELC are largely unknown. Few reports have discussed multimodality treatment for LELC.

Materials and methods: This retrospective study identified records from 2007 to 2018 of pulmonary LELCs and other lung cancer subtypes from hospital information systems and collected demographic, treatment, and survival data.

Results: In this cohort of 69 LELCs (median age: 55.4), more female, non-smokers, and fewer right upper lobe tumors (4.3%) were observed in the LELC subgroup compared with others. The median overall survival (OS) of LELCs was 40 months, superior to other subtypes ($p < 0.05$), except adenocarcinoma ($p = 0.062$). Patients with early stage disease and primary tumor resection tended to have better OS in univariate analysis, but surgery was the independent predictor in multivariate analysis (0.042). The median OS of 52 advanced LELCs was 22.7 months. Platinum-based chemotherapy and radiotherapy with curative purpose were independent predictors for OS of advanced LELCs ($p = 0.004$ and 0.003, respectively). For patients who received multimodality treatment in advanced setting, the median line of treatments was two. The overall response and disease-control rates were 61.8% and 80.6%, respectively. There were no differences in response or survival between patients receiving taxane-combined and non-taxane-combined chemotherapy. However, patients treated with radiotherapy in upfront settings had significantly favorable response and progression-free survival compared with those without. One case with PD-L1 positivity had pembrolizumab in the 4th line and achieved tumor shrinkage and stable disease for 12 months.

Conclusion: Patients who underwent radical resection of primary tumors had better prognoses. Patients with advanced LELC could achieve satisfactory survival by receiving multimodality treatment, including platinum-based chemotherapy and/or radiotherapy. Immune checkpoint inhibitors may be part of future therapies. A well-organized clinical trial should be performed to determine the optimal treatment regimen.

1. Introduction

Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare type of non-small cell lung cancer (NSCLC) that was first separated out as a unique Epstein-Barr virus (EBV)-associated and histologically nasopharyngeal-like malignancy in 1987 [1]. Apart from the classic morphology of a poorly differentiated tumor with highlighted lymphocytic invasion, the latest study also discovered a subtype of non-classic LELCs with little lymphocytic infiltration, which makes them difficult to distinguish from nonkeratinizing squamous cell carcinomas, suggesting Epstein-Barr encoding region (EBER) in-situ hybridization is a necessary diagnostic tool for this disease [2]. Hundreds of LELC cases have been reported, mostly from Southeast Asia including Guangdong, Hong Kong, Taiwan, and Singapore [3–11]. A review of these

Abbreviations: LELC, lymphoepithelioma-like carcinoma; NSCLC, non-small cell lung cancer; EBV, epstein-barr virus; EBER, epstein-barr encoding region; NPC, nasopharyngeal carcinoma; EGFR, epidermal growth factor receptor; ALK, naplastic lymphoma kinase; PD-L1, programmed death ligand-1; RT, radiotherapy; 5-FU, 5-fluorouracil; CHCSJ, Centro Hospitalar Conde de São Januário; AC, adenocarcinomas; SCC, squamous cell carcinomas; NET, neuroendocrine tumors; MRI, magnetic resonance imaging; CT, computed tomography; PET, positron emission tomography; RECIST, evaluation criteria in solid tumors; PFS, progression-free survival; OS, overall survival; CI, confidence interval; DCR, disease-control rate

* Corresponding authors.
E-mail addresses: wangyingyi7363@163.com (Y. Wang), Yuzhouw@yahoo.com (Y. Wang).

https://doi.org/10.1016/j.lungcan.2019.10.004
Received 10 July 2019; Received in revised form 2 September 2019; Accepted 7 October 2019

retrospective studies will help sketch an outline of demographic and clinicopathological characteristics of the disease. The endemic area of pulmonary LELCs overlaps with that of nasopharyngeal carcinoma (NPC), where EBV infection prevails. It affects a younger, non-smoking population, with no obvious predisposition between men and women. Most of the common driver mutations found in NSCLC, such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), are seldom found in LELCs [12,13]. Recent studies have consistently detected a high rate of programmed death ligand-1 (PD-L1)-positivity in this virus-related cancer [14]. The majority of early stage LELCs have been treated with radical resection of primary tumors, while LELCs at advanced stages may need intricate multimodality treatment that involves chemotherapy and radiotherapy (RT).

Due to its rarity, demographics differ greatly across studies. Although there have been direct comparisons between LELCs and other types of NSCLCs, their conclusions might be impaired by relatively small control groups and primarily recruiting early stage LELCs [8,15]. Furthermore, treatments and outcomes for LELCs has rarely been systemically analyzed by previous studies, especially the multimodality treatments for advanced or metastatic LELCs, including the various systemic chemotherapy regimens. The lack of such clinical data makes the natural course of LELCs far from understood and the establishment of standard management impossible. It also compromises efforts to screen prognostic factors for LELCs. A few studies have found responses of advanced pulmonary LELCs to platinum-based chemotherapy by combining with other anti-neoplastic agents, such as 5-fluorouracil (5-FU) and taxanes with or without radiotherapy [5,16,17]. But the long-term prognosis of advanced pulmonary LELCs is uncertain given the limited number of cases. For example, which agent is the best chaperon for doublet platinum chemotherapy is still unknown.

This study collected and investigated a cohort of 69 Macau cases of primary pulmonary LELCs, approximately 75% of which were diagnosed at advanced stage or as a later recurrence of prior early-stage LELC. Most cases were recorded with detailed treatment modalities and long-term outcomes. We also built a database that included other types of lung cancers as the control group to compare with LELCs. We aimed to fill the gaps here by disclosing the demographics of LELCs at Macau and analyzing the efficacy of multimodality treatment, especially chemotherapy and its impact on survival in advanced pulmonary LELCs. This is the largest study that concentrates on multimodality treatment for LELCs.

2. Methods

2.1. Study design and subjects

In this retrospective study, medical records of patients who were diagnosed with primary pulmonary LELC, adenocarcinoma, squamous cell carcinoma, and neuroendocrine tumors between July 2007 and June 2018 at Centro Hospitalar Conde de São Januário (CHCSJ), Macau were reviewed. Rare histologic subtypes, cases with uncertain or unspecified histology, and large cell carcinoma were excluded because of the modification to the WHO standard. Histologic subtypes were classified according to the 2015 WHO classification of lung cancer [18]. Along with 69 pulmonary LELC cases, a total of 1692 patients who were treated for lung malignancies from 2007 July to 2018 June were identified, including 1173 adenocarcinomas (AC), 245 squamous cell carcinomas (SCC) and 117 neuroendocrine tumors (NET). Tumor staging was determined according to the Eighth Edition of the American Joint Committee on Cancer staging system [19]. The stage distribution of LELC cases at initial diagnosis was stage IA in eight patients, IB in five, IIA in one, IIB in five, IIIA in seven, IIIB in 11, IIIC in three, IVA in 12, and IVB in 17.

Records of pulmonary LELCs were identified from hospital information systems using keyword-mining techniques. Records of other lung cancers were identified from a prospective database that has been collected by our multiple disciplinary team for lung malignancies. Every lung malignancy diagnosed in CHCSJ was first recorded and discussed in this MDT. All pulmonary LELC cases were confirmed by EBER positivity. Otolaryngologists consultations with nasopharyngoscope check-ups and imaging tests, including skull base magnetic resonance imaging (MRI), torso computed tomography (CT), or positron emission tomography (PET)/CT were applied to rule out nasopharyngeal cancer or other origin of LELCs.

Assessments of changes in tumor burden after treatments were determined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [20]. Progression-free survival (PFS) was calculated from the date of treatment to disease progression or death from any cause. Overall survival (OS) was calculated from the date of treatment to the date of death from any cause or last follow-up. This study was approved by the Ethics Committee of CHCSJ. Because strictly anonymous data were used, a waiver of consent was allowed by the Committee.

2.2. Statistical analysis

Continuous variables were compared using ANOVA. Chi-square and Fisher's exact tests were applied for categorical variable comparisons. Kaplan–Meier survival analysis and the log-rank test were performed to test differences in PFS and OS stratified by various variables. Univariate and multivariate survival analyses were conducted by the Cox proportional hazards model. Variables with $p < 0.2$ in univariate analysis and treatment-related variables were put into the multivariate analysis. All statistical analyses were performed using SPSS 19.0 (IBM Corporation, Armonk, NY, USA). Two-sided P values < 0.05 were considered statistically different.

3. Results

3.1. Demographic characteristics of LELCs and comparison to other histologic subtypes

Demographic characteristics of patients in the different histopathologic subgroups are reported in SubTable 1 . The median age of LELC patients was 55.3 ± 11.4 years, with 39 females and 30 males, 19 former or current smokers and 50 never-smokers. Patients with pulmonary LELCs were significantly younger than patients with other types of lung malignancies in terms of median age ($p < 0.001$). Compared with other histologic subtypes, significantly more females and non-smokers were found among LELCs (sex: LELC *vs*. AC $p = 0.012$, LELC *vs*. SCC and NET $p < 0.001$; smoking status: LELC *vs*. AC, SCC and NET $p < 0.001$). Furthermore, significantly more left lower lobe (29.0%) and right middle lobe (24.6%) tumors and fewer right upper lobe (4.3%) tumors were found in the LELC subgroup compared with all other subtypes ($p < 0.05$).

3.2. Survival analysis in LELCs and comparison to other subtypes

The median OS of LELCs was 40 months [95% confidence interval (CI), 25.5–54.5] which was superior to SCCs and NETs ($p = 0.003$ and < 0.001, respectively), but not to AC ($p = 0.062$). Kaplan–Meier curves of OS across different subtypes are displayed in Fig. 1A. The OS of LELC was not significantly different from that of AC across different stages (Fig. 1B and C).

In univariate survival, male LELC patients and patients who were older than 65 tended to have worse prognoses, but the p-value did not meet statistical significance (HR 1.886, 95%CI 0.957–3.716, $p = 0.067$, Fig. 1D; and HR 2.046, 95%CI 0.876–4.782, $p = 0.098$, respectively). Smoking status and primary site of the tumor were not associated with the OS of LELCs ($p = 0.172$ and $p = 0.385$, respectively). The median OS was not reached for patients with early stage LELCs but was significantly longer than those of patients with late-stage disease (HR

Table 1
Univariate and multivariate analysis of OS in all LELC cohort.

Variables	N	Median OS	Univariate analysis		Multivariate analysis	
			HR	*P* value	HR	*P* value
Age						
≤65	57	46.5(31.3–61.7)	1		1	
> 65	12	10.8(6.2–15.4)	2.046(0.876–4.782)	0.098	1.783(0.772–4.402)	0.210
Sex						
Female	39	52.4(0.0–112.2)	1		1	
Male	30	20.8(13.8–27.8)	1.886(0.957–3.716)	0.067	1.567(0.686–3.580)	0.287
Smoking						
No	50	49.0(0.0–104.8)	1		1	
Yes	19	33.8(9.9–57.7)	1.636(0.808–3.312)	0.172	1.118(0.489–2.555)	0.792
Locations						
Left	33	46.6(23.9–69.3)	1		–	–
Right	36	33.8(11.5–56.1)	1.348(0.688–2.642)	0.385	–	–
Stage						
I/II	19	Not reached	1		1	
III/IV	50	22.7(12.7–32.7)	0.114(0.034–0.379)	< 0.001	0.419(0.075–2.331)	0.321
Surgery						
Yes	25	Not reached	1		1	
No	44	18.1(11.2–25.0)	0.116(0.044–0.306)	< 0.001	0.206(0.051–0.838)	0.027

0.114, 95%CI 0.034–0.379, p < 0.001, Fig. 1E). Similarly, patients who underwent surgery for primary tumors had significantly longer OS than those without surgery (HR 0.123, 95%CI 0.047–0.324, p < 0.001, Fig. 1F). In multivariate analysis of survival, radical resection of primary tumor was the only independent prognostic factor for OS for all LELCs (p = 0.042) (Table 1).

3.3. The pattern and response of multimodality treatment in advanced LELCs

At the point of cutoff, nine relapses had occurred in patients whose primary tumors had been removed. Their initial stages were stage I in 3 patients, stage II in 2 and stage III in 4. Five of them received adjuvant chemotherapy with platinum doublets and two stage III cases received adjuvant radiation postoperatively. Adding those to the 14 unresectable stage III case and 29 genuine stage IV cases brought the total number of advanced LELCs to 52. One stage III and 10 stage IV LELCs received supportive care or symptom-relieving treatments (including radiofrequency ablation to liver metastases, palliative RT to bone metastases, tracheal stent against oppression, and traditional Chinese medicine). Forty-one patients received multimodality treatment in the advanced setting, which was defined as completing at least one cycle of systemic chemotherapy and/or RT with curative purpose. These patients received two lines of treatment on average (mean: 2.02, median: 2). In the upfront setting, 36 patients received platinum-based chemotherapy and three received Capecitabine alone. Among them, 16 received RT with chemotherapy. There were nine sequential RT, five concurrent RT, and two sandwich RT (dose range: 45–70 Gy). Another two patients underwent RT for mediastinal lymph node metastases without any chemotherapies.

Response rates of five patients were unavailable. The efficacy of the other 36 patients are listed in Fig. 2. In upfront settings, the response rate and disease-control rate (DCR) were 61.8% and 80.6%, respectively. There was no significant difference in response rates between taxane-containing and non-taxane combinations (p = 0.217), but response rates and DCRs of patients who received RT were significantly better than those of patients without (p < 0.05). The efficacy of platinum duplex in later lines of multimodality treatment for advanced LELCs was abysmal (Table 2). However, some LELCs treated with platinum-based chemotherapy in upfront setting still had the chance of responding to other combinations (primarily 5-FU-based) and single agent, which had never been used. It is noteworthy that one patient was treated with Pembrolizumab in the 4th line and achieved 15.6% reduction of tumor burden and stable disease for 12 months.

3.4. Survival analysis in advanced LELCs treated with multiple modalities

The median OS of LELCs experiencing multiple treatments was 31.4 months (95%CI, 14.1–48.7). The median PFS of upfront and 2nd line treatment was 10.1 months (95% CI, 8.2–12.0) and 7.1 months (95%CI, 0.1–14.1), respectively. There were no differences in PFS or OS between those who underwent taxane combination and non-taxane regimens among patients treated with platinum-based combination in upfront settings (Fig. 3A and B). The PFS of patients who received RT in upfront settings was significantly better than those who did not (Fig. 3C); however, these difference in OS did not reach statistical significance (Fig. 3D).

The median OS for the 52 advanced LELCs was 22.7 months (95% CI, 11.5–33.9). In Kaplan–Meier analysis, patients who received platinum-based combinations and curative RT had significantly better prognoses (p < 0.05, Fig. 3E and F). Furthermore, multivariate analysis revealed these two factors independently associated with superior OS in the advanced LELCs population (Table 3).

4. Discussion

In this Macau cohort, in which advanced stage patients accounted for the largest proportion, we found that LELC had unique demographic features among lung cancers. We then attempted to determine the ideal treatment for pulmonary LELCs using complex retrospective clinical data. Surgery of the primary tumor was independently associated with the OS of the whole LELC cohort. Systemic chemotherapy and radiation were both identified as true backbones for advanced LELCs.

The median age of LELCs was 55.4 (range 16–85), compatible with that of previous studies [10,15]. But age predilection varies across different studies; some have reported much older [8,17]. The male:female ratio of LELC was 1:1.3, and 72.5% of patients were never smokers. The gender distribution of LELC is quite the contrary to that of SCC and NET. Male preponderance in these two subtypes was owing to the huge differences of the proportion of smokers between men and women (76.4% *vs* 6.6%), as well as to the fact that small cell cancer made up majority of NETs (81.1%). By comparison with other subtypes of lung cancers, which were predominated by elder male smokers, LELC should be regarded as a disease with the opposite demographic characteristics. Curiously, we found LELCs seldom originated from the right upper lobe. This finding was also observed in the study by Yu et al.

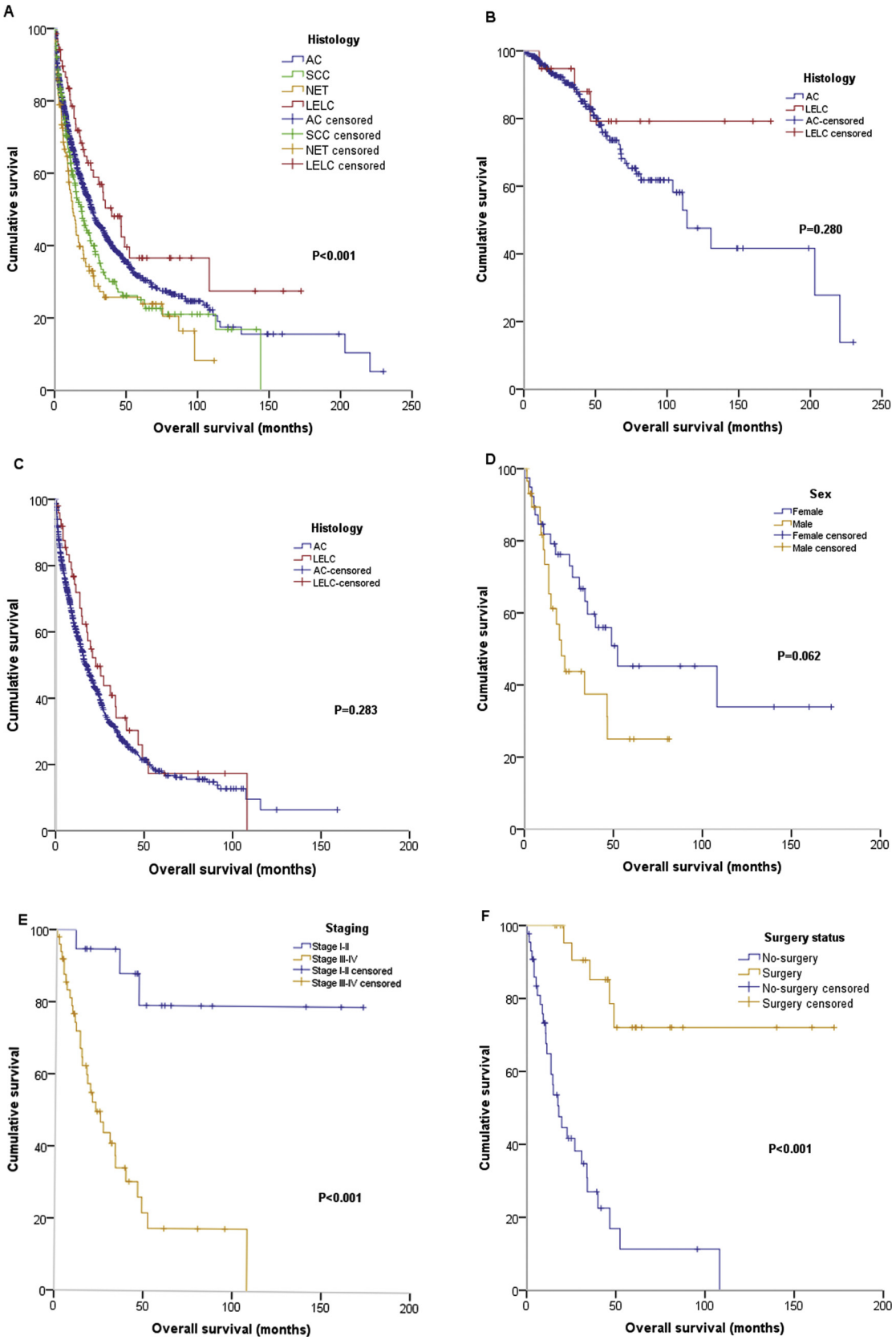

Fig. 1. Overall survival of LELC and other carcinoma types across all stages. (A) Overall survival of LELC and other common types of lung cancer. (B) Comparison of overall survival between LELC and adenocarcinoma patients in stage I-II diseases. (C) Comparison of overall survival between LELC and adenocarcinoma patients in stage III-IV diseases. (D) Overall survival of LELC patients by age groups. (E) Overall survival of LELC patients by stage groups. (F) Overall survival of LELC patients with or without operation.

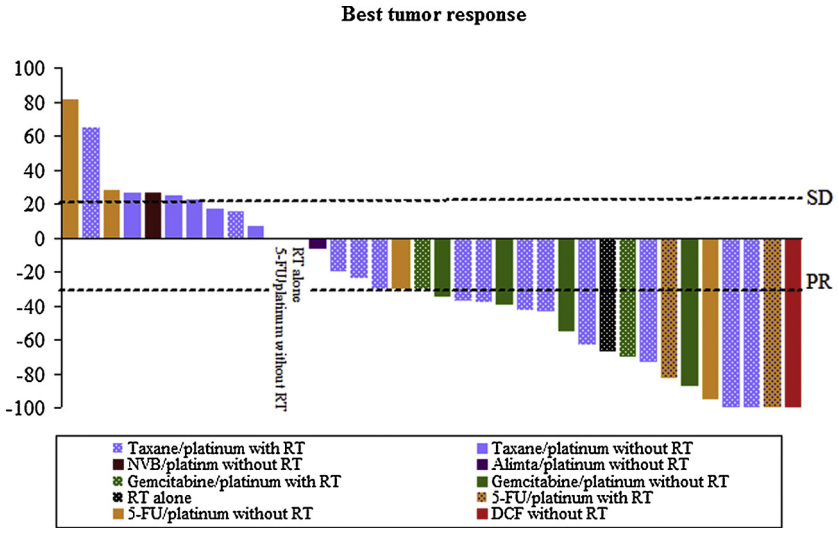

Fig. 2. Overall response rate of advanced LELCs treated with multimodality treatment.

Table 2
Response rate of advanced pulmonary LELCs.

	$N_{(Total)}$	$N_{(Available)}$	ORR (%)	DCR (%)
Upfront line	41	36	61.8	80.6
Chemotherapy	39	34		
Taxane-platinum	20	19	52.6$^{○}$	73.7$^{△}$
Non-taxane-platinum	16	15	73.3$^{○}$	86.7$^{△}$
Capetabine	3	0	n.a.	n.a.
Radiation	36	36		
Yes	18	18	77.8$^{●}$	94.4$^{▲}$
No	18	18	44.4$^{●}$	61.1$^{▲}$
2nd line	20	15	20.0	60.0
Platinum duplex	8	5	0	60.0
Other duplex	4	3	67.7	100.0
Single drug	8	7	14.3	57.1
3rd line and above	21	13	23.1	53.8
Platinum duplex	6	5	0.0	20.0
Other duplex	2	1	0.0	100.0
Single drug	10	6	50.0	66.7
Target or immunotherapy	3	1	0.0	100.0

$^{○}$&$^{△}$: $p > 0.05$; $^{●}$&$^{▲}$:$p < 0.05$($^{●}p = 0.040$; $^{▲}p = 0.041$).

[10], but not in others [8]. Further studies with larger case number are needed to clarify these discrepancies. The OS of LELC has been previously reported to be superior to other subtypes of lung cancers, including adenocarcinoma [8,15], but we did not find any significant differences between pulmonary LELC and adenocarcinoma, neither in ensemble OS nor in OS divided by staging. This lack of significance could be attributable to imprecise clinical staging, population changes according to the newest WHO classification, or the increasing adoption of tyrosine kinase inhibitors in mutation-driven neoplasms.

Radical surgery is the primary approach used to cure LELC. In the past, the role of surgery in multimodality treatment of LELC had not yet been tested because the majority of research had been focused on enrolling early stage LELCs. Accordingly, He et al. could not establish surgery as an independent predictor for OS in LELC [8]. However, patients who underwent radical resection f primary tumors had a significantly favorable OS in Cox-regression. Theoretically, patients with later stage LELC might have worse prognosis than those with early-stage disease. However, staging did not stand out as an independent predictor. Sensitivity to both chemotherapy and radiation may cloud the ultimate prognosis of the disease, alternatively a staging system that is dedicated to lung cancer may not be suitable for LELCs.

The most important finding of our study was the establishment of platinum-combined chemotherapy and RT with curative purpose as the mainstays of advanced LELC treatment. There have been only a handful of studies concentrated on the multimodality treatment of LELCs, and none have succeeded in establishing a treatment standard due to small case numbers and the heterogeneous manner of anti-neoplastic treatments. In patients who underwent multimodality treatment, those treated with RT had markedly more favorable response and PFS than patients who received only chemotherapy in upfront settings. There was also a trend of improved OS towards patients who had RT. In all advanced patients, curative RT was proven to be an independent predictor of OS. While there is the potential that this small group of patients only coincided with those who have locally advanced or limited metastatic lesions, staging status did not reach statistical significance in multivariate analysis. Because of limited cases, the optimal modality and dose of RT in chemoradiation remains unclear. Concurrent RT was inclined to offer the highest response (80.0%). Since primary pulmonary LELCs often present with sizable masses and extensive mediastinal lymph nodes metastases, induction chemotherapy is recommended before RT according to our clinical practice.

Multivariate analysis revealed platinum-based chemotherapy to be another independent predictor for OS in advanced LELCs, however, consensus has never been reached on the optimal chemotherapy regimen. 5-FU and docetaxel were suggested to be potential partners for platinum-based combinations [16,17], providing favorable responses and survival data. The most commonly used agents apart from platinum in our study were taxanes, 5-FU, and gemcitabine. We did not find significant differences in response or survival between taxane-based and non-taxane-based combinations, which is consistent with the findings of a meta-analysis of induction chemotherapy regimens in NPC [21] and by Lin et al. [17]. It is worth mentioning that cases treated with gemcitabine initially achieved full responses. Response and survival data in our study seemed less encouraging than those reported by Lin et al. [17], which might be attributed to diversities of characteristics of included cases and anti-neoplastic managements. Notably, a smaller proportion of our patients underwent RT and surgery after tumor downstaging. Three patients with unsatisfactory performance status received Capecitabine alone (1–3 cycles), and were excluded from analysis of multimodality treatment because of unknown drug compliance.

Several studies have revealed frequent PD-L1 expression in LELCs, assuming it a potential biomarker and rational therapeutic target. However, only few case reports have examined the effect of newly-listed checkpoint inhibitors in LELCs, predominantly Nivolumab [22,23]. We also attempt to test the actual effect of immunotherapy in LELCs. One female patient who was proven to have high PD-L1 expression (90%) in tumor cells took Pembrolizumab after failing three

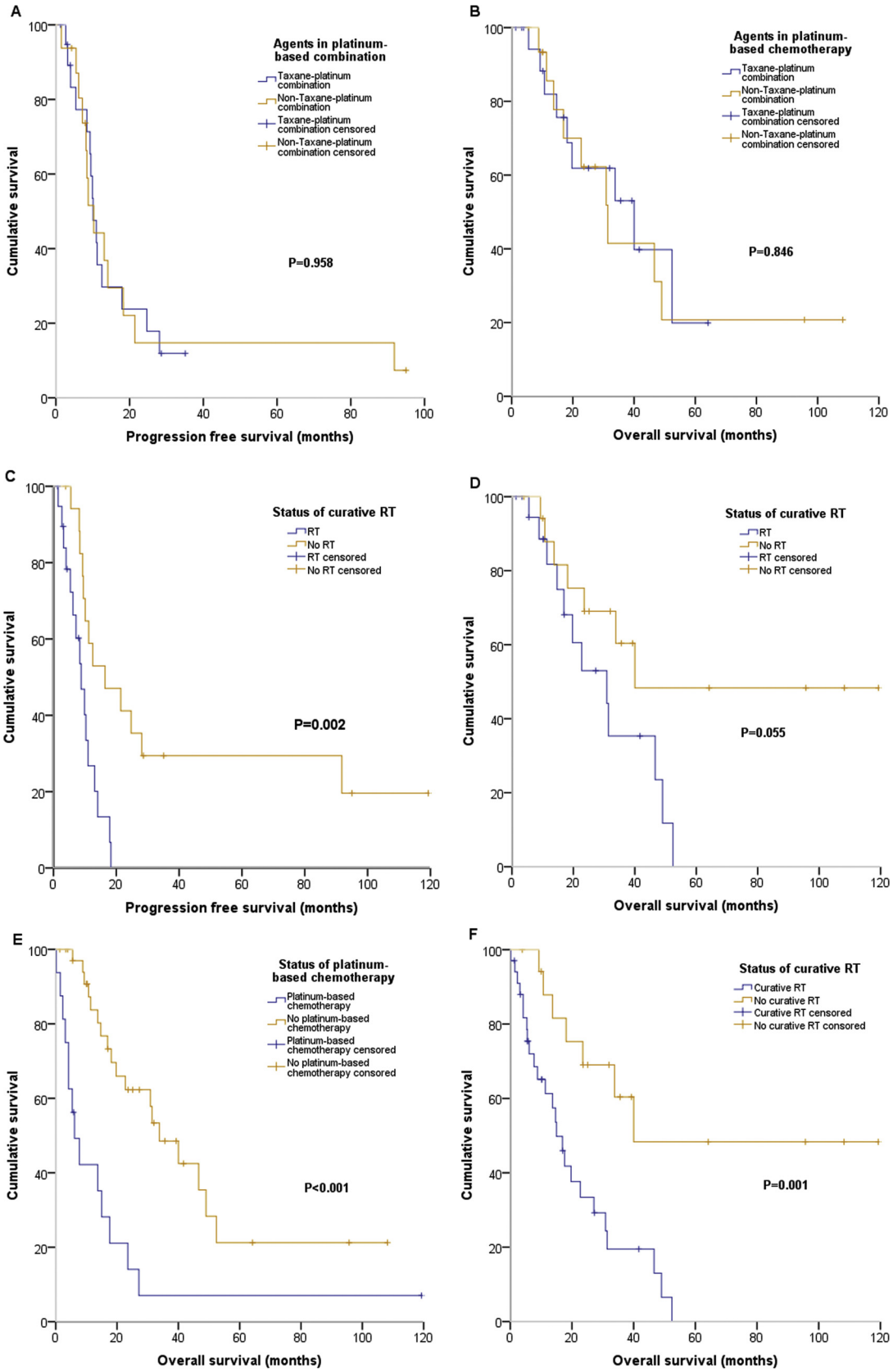

Fig. 3. Progression free survival and overall survival in advanced LELC patients. (A, B) Comparison of progression free survival and overall survival regarding different chemotherapy regimens in advanced LELCs who received multimodality treatment. (C, D) Comparison of progression free survival and overall survival regarding radiotherapy in advanced LELCs who received multimodality treatment. (E) Overall survival of total advanced LELC population with cisplatin-based chemotherapy or without. (F) Overall survival of total advanced LELC population with curative radiation or without.

Table 3
Univariate and multivariate analysis of OS in advanced LELCs.

Variables	N	Median OS	Univariate analysis		Multivariate analysis	
			HR	*P* value	HR	*P* value
Age						
≤65	43	27.1(12.3–41.9)	1		1	
> 65	9	10.7(3.4–18.0)	2.045(0.814–5.141)	0.128	1.825(0.660–5.046)	0.247
Sex						
Female	25	30.9(20.1–41.7)	1		–	
Male	27	15.0(7.8–22.2)	1.471(0.725–2.984)	0.285	–	–
Smoking						
No	36	23.5(8.4–38.6)	1		–	
Yes	16	17.6(7.3–27.9)	1.445(0.695–3.003)	0.324	–	–
Stage						
III	15	33.8(0–72.4)	1		1	
IV	37	18.1(7.4–28.8)	1.824(0.807–4.125)	0.149	1.256(0.527–2.994)	0.607
Platinum chemotherapy						
Yes	36	33.8(22.2–45.4)	0.274(0.134–0.561)		0.313(0.141–0.695)	
No	16	6.1(2.0–10.2)	1	< 0.001	1	0.004
Curative radiation						
Yes	18	40.0	0.265(0.113-0.623)		0.255(0.105–0.620)	
No	34	15.0(10.4–19.6)	1	0.002	1	0.003

lines of platinum-combined chemotherapy and achieved tumor stabilization for 12 months. To our knowledge, this is the first time that a study has reported a favorable response to Pembrolizumab in advanced LELC. Tumor recurrence is still possible in LELCs whose primary tumors has been resected. Immunotherapy is to be a promising strategy for improving the cure rate and OS of patients with resectable LELC. This promise is based on the remarkable efficacy of checkpoint inhibitors in untreated locally advanced and metastatic NSCLCs when administered alone or following concurrent chemoradiation in stage III NSCLCs [24,25]. As mentioned before, LELC was one of NSCLCs proved to possess above-average PD-L1 expression, a predictor closely connected with even better clinical outcome [14,26]. Thus, immune therapy would act as a mainstay therapy for locally advanced LELCs or bring additional benefits for patients with early-stage LELCs in perioperative setting in the future. Additionally, two patients took Cetuximab in the 4^{th} line, but the efficacy of this therapy could not be assessed because of limited survival.

Prudence should be exercised when applying research results to other scenarios in daily clinical practice. First, the retrospective nature and relatively small scale of this study makes it prone to selection bias. Second, some of the data were lacking, which could also lead to bias. For example, patient fitness was untouched in this study due to incomplete data over long time span, but this would turn out to be an important factor for clinical outcomes of advanced LELCs and may have impact on multivariate analysis. And response rates of multimodality treatments, especially in later lines, should not be over-estimated because some cases fell off treatment regimens, and their responses were unavailable to be assessed. Third, during the long duration of this study, approaches and modes of certain therapeutic measures such as surgery and RT might have changed. The study was also crisscrossed with various chemotherapy regimens that were parallel to the drug revolution taking place at the time. Fourth, localized and distant advanced LELCs were mixed together in response and survival analysis and subdivided staging was not employed. Nevertheless, the investigation of this unprecedented cohort at Macau could still yield convincing evidence about associations between certain treatment modalities and outcomes in LELCs.

We conclude that patients who underwent radical resection for primary tumors had better prognoses. Patients with advanced LELC could achieve satisfactory survival by receiving multimodality treatment, including platinum-based chemotherapy and/or RT with curative purpose. Immune checkpoint inhibitors may join the therapeutic armory in the future. Most importantly, a well-organized clinical trial should be carried out to determine the optimal treatment regimen for this disease.

Contributions

Conception and design: N Zhou and Y Wang; Provision of study materials: Y Lin and X Peng; Collection and assembly of data, data analysis and manuscript writing: N Zhou; Statistics advisor, revision and final approval of manuscript: Y Wang.

Funding

This study was supported by grants from the Chinese Academy of Medical Sciences (CAMS) Initiative for Innovative Medicine (No. 2017-I2M-4-002), and National Natural Science Foundation of China (No. 81472785; No. 61435001).

Declaration of Competing Interest

The authors have declared no conflicts of interest.

Acknowledgments

We thank James P. Mahaffey, PhD, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

We thank all the members in Department of Medical Oncology, Peking Union Medical College Hospital for their help and valuable opinion.

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.2019.10.004.

References

[1] L.R. Bégin, J. Eskandari, J. Joncas, L. Panasci, Epstein-Barr virus related lymphoepithelioma- like carcinoma of lung, J. Surg. Oncol. 36 (4) (1987) 280–283.
[2] Y.C. Yeh, H.L. Kao, K.L. Lee, et al., Epstein-Barr virus-associated pulmonary carcinoma: proposing an alternative term and expanding the histologic spectrum of lymphoepithelioma- like carcinoma of the lung, Am. J. Surg. Pathol. 43 (2) (2019) 211–219.
[3] A.J. Han, M. Xiong, Y.S. Zong, Association of Epstein-Barr virus with lymphoepithelioma-like carcinoma of the lung in southern China, Am. J. Clin. Pathol. 114

(2) (2000) 220–226.
[4] Y.L. Chang, C.T. Wu, J.Y. Shih, Y.C. Lee, New aspects in clinicopathologic and oncogene studies of 23 pulmonary lymphoepithelioma-like carcinomas, Am. J. Surg. Pathol. 26 (6) (2002) 715–723.
[5] C.J. Huang, A.C. Feng, Y.F. Fang, et al., Multimodality treatment and long-term follow-up of the primary pulmonary lymphoepithelioma-like carcinoma, Clin. Lung Cancer 13 (5) (2012) 359–362.
[6] Y. Liang, L. Wang, Y. Zhu, et al., Primary pulmonary lymphoepithelioma-like carcinoma: fifty-two patients with long-term follow-up, Cancer 118 (19) (2012).
[7] W. Fang, S. Hong, N. Chen, et al., PD-L1 is remarkably over-expressed in EBV-associated pulmonary lymphoepithelioma-like carcinoma and related to poor disease-free survival, Oncotarget 6 (32) (2015) 33019–33032.
[8] J. He, J. Shen, H. Pan, et al., Pulmonary lymphoepithelioma-like carcinoma: a surveillance, epidemiology, and end results database analysis, J. Thorac. Dis. 7 (12) (2015) 2330–2338.
[9] Y.L. Chang, C.Y. Yang, M.W. Lin, et al., PD-L1 is highly expressed in lung lymphoepithelioma- like carcinoma: a potential rationale for immunotherapy, Lung Cancer 88 (3) (2015) 254–259.
[10] X. Yu, Y. Wen, R. Qin, et al., Prognosis and distribution of lymph nodes metastases in resectable primary pulmonary lymphoepithelioma-like carcionma: a large cohort from a single center, Thorac. Cancer 9 (3) (2018) 360–367.
[11] C.K. Tay, Y.C. Chua, A. Takano, et al., Primary pulmonary lymphoepithelioma-like carcinoma in Singapore, Ann. Thorac. Med. 13 (1) (2018) 30–35.
[12] L. Wang, Y. Lin, Q. Cai, et al., Detection of rearrangement of anaplastic lymphoma kinase (ALK) and mutation of epidermal growth factor receptor (EGFR) in primary pulmonary lymphoepithelioma-like carcinoma, J. Thorac. Dis. 7 (9) (2015) 1556–1562.
[13] Q. Liu, G. Ma, H. Yang, et al., Lack of epidermal growth factor receptor gene mutations in exons 19 and 21 in primary lymphoepithelioma-like carcinoma of the lung, Thorac. Cancer 5 (1) (2014) 63–67.
[14] L. Jiang, L. Wang, P.F. Li, et al., Positive expression of programmed death ligand-1 correlates with superior outcomes and might be a therapeutic target in primary pulmonary lymphoepithelioma- like carcinoma, Onco. Ther. 8 (2012) 1454–1457.
[15] Y.H. Sun, S.W. Lin, C.C. Hsieh, et al., Treatment outcomes of patients with different subtypes of large cell carcinoma of the lung, Ann. Thorac. Surg. 98 (3) (2014) 1013–1019.
[16] J.C. Ho, W.K. Lam, M.P. Wong, et al., Lymphoepithelioma-like carcinoma of lung: experience with ten cases, Int. J. Tuberc. Lung Dis. 8 (7) (2004) 890–895.
[17] C.Y. Lin, Y.J. Chen, M.H. Hsieh, et al., Advanced primary pulmonary lymphoepithelioma-like carcinoma: clinical manifestations, treatment, and outcome, J. Thorac. Dis. 9 (1) (2017) 123–128.
[18] W.D. Travis, E. Brambilla, A.G. Nicholson, et al., The 2015 world health organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification, J. Thorac. Oncol. 10 (9) (2015) 1243–1260.
[19] AJCC cancer staging manual. Springer international publishing ISBN 978-3-319-40617-6.
[20] E.A. Eisenhauer, P. Therasse, J. Bogaerts, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), Eur. J. Cancer 45 (2) (2009) 228–247.
[21] R. Tian, H.X. Ye, B.G. Zhang, et al., Use of taxane-containing induction chemotherapy in combination with concurrent chemoradiotherapy in Chinese patients with locally advanced nasopharyngeal carcinoma: a meta-analysis, Onco. Ther. 8 (2015) 3255–3263.
[22] M. Darrason, A. Martin, M. Soussan, et al., Immunotherapy for LELC: case report and a focused review, Clin. Lung Cancer (18) (2018) S1525–S7304 30332-2.
[23] V. Kumar, V. Dave, J. Harris, Y. Huang, Response of advanced stage recurrent lymphoepithelioma- like carcinoma to nivolumab, Immunotherapy. 9 (12) (2017) 955–961.
[24] T.S.K. Mok, Y.L. Wu, I. Kudaba, et al., KEYNOTE-042 Investigators. Pembrolizumab versus chemotherapy for previously untreated, PD-L2-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomized, open-lable, controlled, phase 3 trial, Lancet 393 (10183) (2019) 1819–1830.
[25] S.J. Antonia, A. Villegas, D. Daniel, et al., Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, N. Engl. J. Med. 379 (24) (2018) 2342–2350.
[26] E.J. Aguilar, B. Ricciuti, J.F. Gainor, et al., Outcomes to first-line pembrolizumab in patients with non-small cell lung cancer and very high PD-L1 expression, Ann. Oncol. 21 (August) (2019), https://doi.org/10.1093/annonc/mdz288 pii: mdz288.