Hong Kong J Radiol. 2013;16:270-7 | DOI: 10.12809/hkjr1313176

ORIGINAL ARTICLE

Treatment Outcomes of Primary Pulmonary Lymphoepithelioma-like Carcinoma: a Series of 22 Patients and Treatment Strategy Review

FST Mok[1], OSH Chan[2], ATY Chang[2], LLK Chan[2], IS Soong[2], WT Ng[2], FY Cheung[2], RMW Yeung[2]

[1]Department of Clinical Oncology, Prince of Wales Hospital, Shatin, Hong Kong; [2]Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, Chai Wan, Hong Kong

ABSTRACT

Objectives: *Primary pulmonary lymphoepithelioma-like carcinoma (LELC) is a rare subgroup of non–small-cell lung cancer. Limited published series suggested that it might be associated with more favourable survival than ordinary non–small-cell lung cancer. We set out to review the treatment outcomes of patients with primary pulmonary LELC treated in our institution since 1994.*

Methods: *All patients with pathologically confirmed primary pulmonary LELC treated between 1994 and 2012 were retrospectively reviewed. Treatment modalities and outcomes — including local control rate, disease-free and overall survival — were analysed.*

Results: *Twenty-two patients with primary pulmonary LELC were identified. Their median follow-up duration was 33 months (range, 1 day to 106 months). Surgery was the mainstay of treatment for patients with stage I to II diseases. Those with advanced non-metastatic disease (n = 5) treated with high-dose radiotherapy (EQD2 60 Gy) with or without platinum-based chemotherapy had a local control rate of 100% after a median follow-up of 68 months. The 5-year progression-free survival (PFS) and overall survival (OS) were 53% and 80%, respectively. Their median PFS and OS had not reached at the time of publication. For patients with stages III and IV disease beyond radical radiotherapy portals, palliative platinum doublets gave a median disease-free survival of 10 months in 12 patients. The 5-year OS of stage I-II, III, and IV patients were 41%, 38%, and 25%, respectively (p = 0.61). Their median OS durations were 58, 30, and 19 months, respectively.*

Conclusion: *Our series echoed prior suggestions that primary pulmonary LELC achieves favourable outcomes.*

Key Words: *Carcinoma, non-small-cell lung; Epstein-Barr virus infections; Lung neoplasms; Radiotherapy; Survival*

中文摘要

原發性肺淋巴上皮瘤樣癌的治療效果：22個病例以及其治療策略回顧

莫小婷、陳少康、張天怡、陳麗君、宋崧、吳偉棠、張寬耀、楊美雲

目的：原發性肺淋巴上皮瘤樣癌（LELC）是非小細胞肺癌的一種罕見亞型。一系列有限的文獻提示原發性肺淋巴上皮瘤樣癌可能會比一般非小細胞肺癌的生存率高。本文回顧自1994年以來，於我們醫院診治的原發性肺LELC患者的治療效果。

Correspondence: *Dr Florence ST Mok, Department of Clinical Oncology, Pamela Youde Nethersole Eastern Hospital, 3 Lok Man Road, Chai Wan, Hong Kong.*
Tel: (852) 2595 4175; Fax: (852) 2904 5216 ; Email: siutinggreen@gmail.com

Submitted: 7 Mar 2013; Accepted: 2 Jul 2013.

方法：回顧性分析所有1994至2012年期間經病理學證實的原發性肺LELC的患者紀錄。分析治療方式和結果，包括局部控制率、無病生存率和總體生存率。

結果：發現原發性肺LELC22例。病例的隨訪期中位數為33個月（範圍：1日至106個月）。對於第I至第II期的患者來說，手術是主要的治療方法。於中位隨訪期68個月後，接受高劑量放療（EQD2為60 Gy）的晚期無轉移瘤患者（n = 5）局部控制率達100%；伴或不伴以鉑類藥物為基礎的化療均如此。五年無進展生存率（PFS）和總體生存率（OS）分別為53%和80%。至本文發表時，尚未獲得PFS和OS的中位數數據。至於無法施以根治性放療第III及第IV期患者，有12例因接受含鉑類雙藥聯合方案的姑息性化療而無瘤中位生存期達至10個月。第I-II、III和IV期的五年OS分別為41%、38%和25%（p = 0.61），其中位生存期分別為58、30和19個月。

結論：本系列研究結論呼應之前的報道，即原發性肺LELC的治療效果是樂觀的。

INTRODUCTION

Lymphoepithelioma-like carcinoma (LELC) of the lung is a rare entity worldwide, with limited case series or case reports having been published. It was first reported by Bégin et al in 1987,[1] and categorised as a form of large cell carcinoma according to World Health Organization classification.[2] It is more prevalent in Asia,[2] notably in Southeast Asia. In the past two decades, studies reported its histological resemblance to undifferentiated nasopharyngeal carcinoma (NPC),[2,3] which is associated with Epstein-Barr virus (EBV) and occurs almost exclusively in Asians[2,4-6] and exhibits specific radiological features.[7,8] Limited case series comparing treatment outcomes of patients with LELC and non-LELC non–small-cell lung cancer (NSCLC),[2,9-12] reported that the former had superior chemo- and radio-sensitivity[2,9-11] and was associated with statistically significant better survival of patients with stages II to IV disease.[12] The objective of this study was to evaluate the treatment outcomes in a series of 22 patients with primary pulmonary LELC treated at our institution, and compare them to other reported series. Systemic treatment strategies effective against NPC that could have a role in this rare disease entity were also explored.

METHODS

The medical records (both paper and electronic) of 22 patients with pathologically confirmed primary pulmonary LELC treated in the Pamela Youde Nethersole Eastern Hospital from 1994 to 2012 were reviewed. Primary pulmonary LELC was defined pathologically as having a characteristic morphology. It entailed presence of undifferentiated carcinoma cells with ill-defined cytoplasmic borders arranged in syncytial sheets and nests separated by broad areas of lymphocytic reaction, and tumour cells growing in a diffuse manner and mimicking malignant lymphoma.[2,6] The diagnosis was confirmed by in-situ hybridisation for EBV-encoded small nuclear RNA (EBER) status.[4] Clinical (with computed tomography [CT]) or pathological restaging was performed according to the International Union Against Cancer (UICC) / American Joint Committee on Cancer (AJCC) 6th edition. For operable disease, final pathology reports were studied and restaging performed. For patients with surgically or medically inoperable disease, their initial CT films and reports were reviewed and restaged. To exclude metastasis from primary NPC, initial presenting symptoms were documented. All patients had no upper aerodigestive symptoms including nasal congestion, hearing loss, neck mass etc. Of 22 patients, 15 had nasopharyngoscopy to rule out NPC. Two others had positron emission tomography ruling out nasopharyngeal involvement. Patient characteristics, including age, gender, and smoking status, were evaluated. Treatment modalities including surgery, chemotherapy schemes and radiation techniques, doses and fractionation were explored. Patients who completed radical treatment were followed up every 3 to 4 months in the first 2 years, then every 4 to 6 months in the 3rd to 5th year and yearly after 5 years according to department policy, with physical examination and chest radiograph done at every visit and contrast CT 3 to 12 months post-treatment that was repeated about 1 year after the first post-treatment image. This imaging was to confirm disease in remission. Patients treated with palliative intent were followed up according to clinical needs. For those given a primary radical dose of radiotherapy (i.e. biologically equivalent total dose applied in 2 Gy fractions [EQD2] = 60 Gy or above), their chest radiographs and contrast CT images were re-

evaluated according to Green et al's criteria[13] to exclude local disease. These entailed complete disappearance of all evidence of malignant disease, or residual radiographic abnormalities assessed by CT 3 and 6 months after completion of radiotherapy, which then remained stable for an additional 6 months or more. Treatment response to palliative chemotherapy was re-evaluated according to RECIST criteria version 1.1.[14]

Table 1. Summary of treatment details of 22 patients with primary pulmonary lymphoepithelioma-like carcinoma treated at Pamela Youde Nethersole Eastern Hospital from 1994-2012.

Patient No.	Stage	Primary treatment	Tumour response to primary treatment	Second-line treatment	Status at last follow-up	Survival time to last follow-up (months)*
1	IB	Surgery	N/A	-	Died of postoperative complications	1 day
2	IB	Surgery then RT 46 Gy / 23 Fr / 4.5 weeks	CR	PF x 2	Died of disease	58.0
3	IIA	Surgery	CR	chemoRT (RT 60 Gy / 30 Fr / 6 weeks, concurrent with EP x2)	Disease-free	74.0
4	IIA	Surgery (R1 resection) then RT 55 Gy / 22 Fr / 4.5 weeks	CR	-	Died of disease	33.7
5	IIB	Surgery (R2 resection), then EP x 4, then RT 60 Gy / 30 Fr / 6 weeks	CR	-	Disease-free	67.9
6	IIB	Palliative RT	N/A	-	Lost FU	1.7
7	IIIA	Surgery	CR	GJ x 6, then RT 40 Gy / 20 Fr / 4 weeks Capecitabine x 3 cycles	Died of disease	39.0
8	IIIA	EP x 2, then surgery, then EP x 4, then RT 50 Gy / 25 Fr / 5 weeks	CR	-	Disease-free	58.4
9	IIIA	GP x 2 then concurrent CRT with EP x 2, then RT 60 Gy / 30 Fr / 6 weeks	CR	-	Died of disease	22.7
10	IIIB	GJ x 4 then RT 60 Gy / 30 Fr / 6 weeks	CR	RT to relapsed paraaortic node 45 Gy / 18 Fr / 3.5 weeks Distant relapse (lung) treated with GJ x 4 cycles and capecitabine x 2 cycles	Active disease	106.2
11	IIIA	PF x 1 then palliative RT	SD	-	Died of disease	19.9
12	IIIA	GJ x 4 then palliative RT	PR	Erlotinib x 1.8 months	Deceased	18.6
13	IIIB	GJ x 4 then palliative RT	SD	Pemetrexed x 6 cycles Erlotinb x 1.4 months	Died of disease	19.1
14	IIIA	Symptomatic care	N/A	Erlotinib x 2 weeks	Died of disease	30.9
15	IV	MIC x 4	PR	-	Died of disease	33.5
16	IV	PF x 2	PD	-	Died of disease	52.4
17	IV	EP x 6	PD	Capecitabine x 6 cycles	Died of disease	19.7
18	IV	JF x 6	SD	-	Died of disease	16.2
19	IV	GJ x 4 then palliative RT	PR	Capecitabine x 8 cycles Retry GJ x 6 cycles Retry capecitabine x 2 cycles	Active disease	51.8
20	IV	GJ x 6	PR	Capecitabine x 1 cycle Retry GJ x 6 cycles Taxotere x 2 cycles Retry GJ x 3 cycles Pemetrexed x 1 cycle	Died of disease	17.6
21	IV	GJ x 6 then palliative RT	PR	GJ x 3 cycles Capecitabine x 6 cycles	Active disease on treatment	68.8
22	IV	Palliative RT	N/A	-	Died of disease	3.4

Abbreviations: CR = complete remission; CRT = chemoradiotherapy; FU = follow-up; N/A = not applicable; PD= progressive disease; PR = partial remission; RT = radiotherapy; SD = static disease.

Chemotherapy regimens: EP = etoposide 100 mg/m^2 intravenous (IV) day 1-3, cisplatin 25 mg /m^2 IV day 1-3; GJ = gemcitabine 1200 mg/m^2 IV day 1 and 8, carboplatin IV AUC 5 day 1; GP = gemcitabine 1200 mg/m^2/day IV day 1 and 8, cisplatin 80 mg/m^2 IV day 1; JF = carboplatin AUC 5 IV day 1, 5FU 1000 mg/m^2 IV day 1-3; MIC = mitomycin 6 mg/m^2 IV day 1, ifosfamide 3000 mg/m^2 IV day 1, cisplatin 50 mg/m^2 IV day 1; PF = cisplatin 80 mg/m^2 day 1 , 5FU 1000 mg/m^2/day IV day 1-3.

* Unless otherwise specified.

Patient statistics and response rates were calculated using the Statistical Package for the Social Sciences (Windows version 12.0; SPSS Inc, Chicago [IL], US). Overall survival (OS) was measured from the date of diagnosis to death. Progression-free survival (PFS) was calculated from the start of treatment to disease progression or death. We censored at the follow-up date if there was no radiological / clinical progression or death. PFS and OS were calculated by the Kaplan Meier method.

RESULTS

Among the 22 patients, the numbers with stage I, II, III, and IV (AJCC 6th edition) were 2, 4, 8, and 8, respectively. The male-to-female ratio was 6:16. The mean age at diagnosis was 59 (range, 39-78) years. The majority (n=20, 90%) were EBER stain–positive after the year 1995 (after journals published the association of EBV with pulmonary LELC). In all, 59% were never-smokers, whereas 22% were smokers and in 18% the status was unknown. The median follow-up duration was 33 months (range, 1 day to 106 months). Treatment summaries of each patient are shown in Table 1.

For early staged patients (stages I-II, patient Nos. 1-6), five were treated surgically. Only one received palliative radiotherapy due to suboptimal clinical status. Three out of the five patients relapsed; one had a local and regional relapse after 18 months (patient No. 3) and two had distant relapses both after 29 months (patient Nos. 2 and 4). The one with local-regional relapse was successfully salvaged with definitive chemoradiotherapy and remained disease-free after 67.9 months of follow-up.

Of the 22 patients, 12 had unresectable non–metastatic disease at primary presentation (n = 11) or relapse (n = 1), based on UICC 6th edition IIB-IIIB staging. Six patients were treated radically with a combination of surgery, radiotherapy, and chemotherapy; the other six had a poor clinical status or their disease was deemed beyond radical radiotherapy, and thus they were treated palliatively. Five out of the six patients (patient Nos. 3-5, 9, and 10) were treated with a primary radical radiotherapy dose of EQD2 60 Gy that covered the gross disease including the tumour and lymph nodes. Four out of five patients were given 3D conformal radiotherapy, while only one received 2D radiotherapy (in the 1990s). Four out of five patients received either sequential or concurrent platinum doublets chemotherapy. Their median follow-up duration was 68 months (range, 33-106) months. All five patients (100%) achieved control of local disease on serial imaging until the last follow-up. Three patients remained disease-free on last follow-up while two relapsed with distant lesions after 29 and 18 months. The median PFS and OS had not been reached at publication of this series. The 5-year PFS and 5-year OS were 53% and 80%, respectively (Figures 1 and 2).

Twelve patients with stage III-IV disease at presentation or relapse who were not amenable for radical radiotherapy or surgery (patient Nos. 2, 7, 11-13, 15-21) were given first-line palliative chemotherapy with platinum doublets, which included cisplatin or carboplatin combined with gemcitabine (n=6), 5-fluorouracil (n=4), etoposide (n=1), mitomycin plus ifosphamide (n=1) from 1 to 6 cycles. The median time to progression was 10 (range, 1-23) months. Second-line treatment included retrying platinum doublets (n=3), capecitabine (n=7), pemetrexed (n=1), and erlotinib (n=3). The time to progression of patients treated with platinum doublets, pemetrexed, and erlotinib were 5-14 months, 5 months, and 0.5-1.8 months, respectively. For the seven patients treated with capecitabine, three patients survived 0.3-17 months; the other four were still having active treatment at the time of data collection.

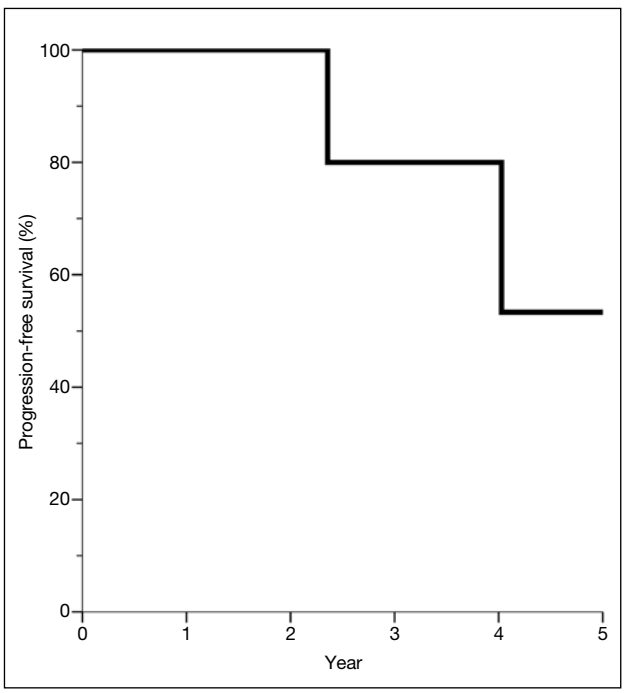

Figure 1. Progression-free survival curve of the five patients with unresectable non-metastatic pulmonary lymphoepithelioma-like carcinoma received radical radiotherapy with or without chemotherapy.

The median OS values for patients having stages I-II, III, and IV disease were: 58, 30, and 19 months, respectively. The 5-year OS values were 41%, 38%, and 25%, respectively (p = 0.61). The survival curves are shown in Figure 3.

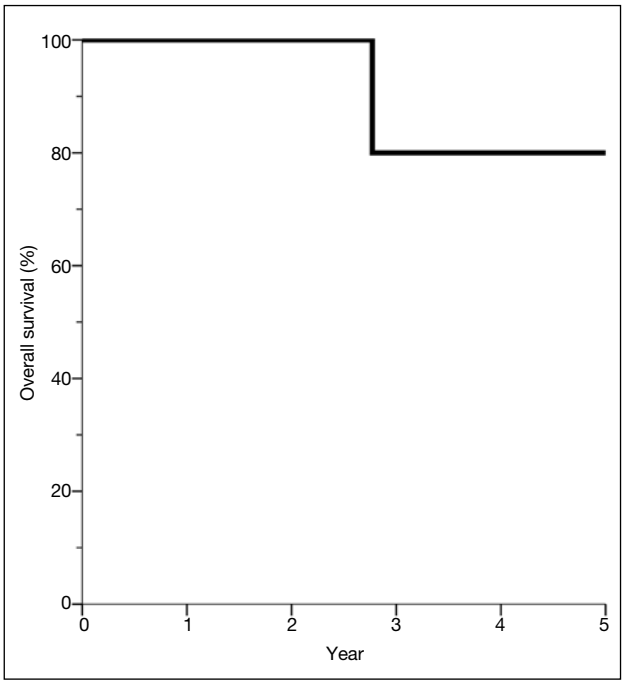

Figure 2. Overall survival curve of the five patients with unresectable non-metastatic pulmonary lymphoepithelioma-like carcinoma received radical radiotherapy with or without chemotherapy.

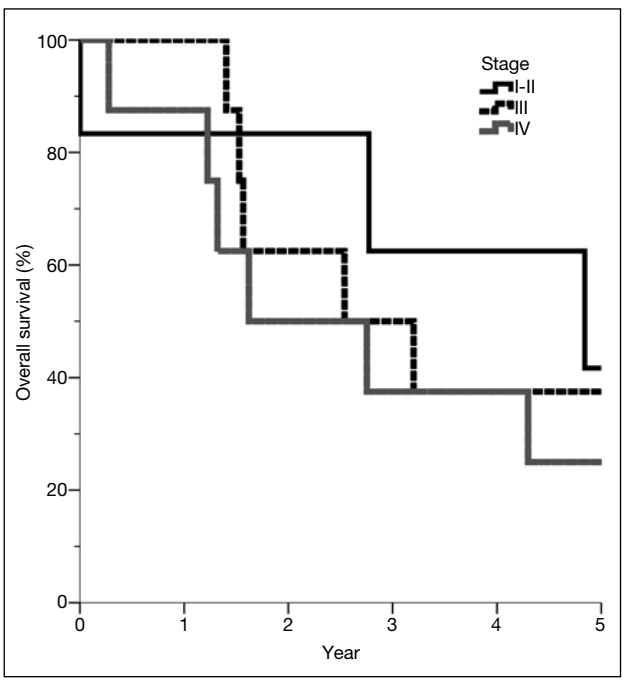

Figure 3. Overall survival curves of stage I/II, III, and IV primary pulmonary lymphoepithelioma-like carcinoma patients in this series (n=22).

DISCUSSION

The favourable local control rate and survival outcomes exhibited in the current study echoed with those of previous series as shown in Table 2.[9-12,15,16] However, prospective randomised trials are warranted to validate this hypothesis because of the intrinsic limitations of retrospective analysis and limited patient numbers.

Treatment strategies implemented in previous series were largely similar to those used for NSCLC. Reviewing available series on PubMed and the Cochrane review (Table 2) found that primary pulmonary LELC was usually treated using a multimodality approach. Stage I-II diseases were mainly treated with surgery with or without adjuvant chemotherapy. Meanwhile, there are inadequate data to infer whether early stages pulmonary LELC can be treated with radiotherapy alone. A recent series published by Liang et al[15] did not show survival benefit for adjuvant chemotherapy in stage II patients with complete resection, but the number of patients was small. Further studies are again warranted for confirmation.

Advanced non-metastatic diseases were treated with combined modality treatment including various platinum doublet chemotherapy regimens and radiotherapy. Chemotherapy included platinum combined with 5-fluorouracil[9,10] gemcitabine, taxane, etoposide, ifosphamide and vinorelbine,[15,16] in which various doses of radical radiotherapy from 40-70 Gy, 2-2.5 Gy per fraction were used. The 2-year OS in several series was around 60 to 80% (Table 2). In our series, the local control rate and OS of patients with advanced non-metastatic disease treated with radiotherapy of EQD2 60 Gy combined with platinum doublets was excellent. However, it is worth highlighting that the radiotherapy techniques used in various pulmonary LELC series were heterogeneous, owing to the scanty number of cases encountered over more than 10 years. There have been further advancements in radiotherapy techniques, including intensity-modulated radiotherapy, rapid-arc or hybrid rapid-arc techniques,[17] and the use of different respiration motion techniques including respiratory gating and 4D CT.[18] Currently, we are therefore able to deliver radiotherapy to lung tumour with a more stringent margin, a more favourable dose coverage, and tolerable mean lung dose. Thus, more favourable outcomes for this specific disease entity are anticipated

Table 2. Summary of treatment details and outcomes of pulmonary LELC in major series available on PubMed search (n ≥ 5).[9-12,15,16]

Study	No. of patients	Mean age (years)	M:F	Disease stage distribution	Treatment strategy	Follow-up	Survival
Current study, 2013	22	58.5	6:16	I: 2 II: 4 III: 8 IV: 8	Stage I-II: surgery Advanced non-metastatic: RT 60 Gy + platinum doublet chemotherapy Advanced beyond radical radiotherapy: platinum doublets +/- palliative RT Second-line chemotherapy with retrying platinum doublets, capecitabine etc	Median 33.1 months	5-year OS: Stage I/II: 50% Stage III: 37.5% Stage IV: 25.0%
Huang et al,[16] 2012	21	55.6	5:16	I-II: 4 IIIA: 7 IIIB: 6 IV :4	Early: surgery +/- platinum doublet chemotherapy Advanced: platinum doublet chemotherapy +/- RT (50-70 Gy) +/- surgery	Median 5.9 year	Median OS: Stage I / II: not reached Stage III/ IV: 3.4 years
Liang et al,[15] 2012	52	51	29:23	I: 16 II: 9 IIIA: 18 IIIB-IV: 9	Resectable: surgery +/- chemotherapy / RT Incomplete resection / relapse: platinum chemotherapy +/- RT	Median 31.55 months	Median OS not reached 2-year OS 88% 5-year OS 62%
Ho et al,[10] 2004	10	47	5:5	IIIA: 1 IIIB: 4 IV: 5	Chemo PF* x 4 +/- RT 40 Gy / 16 Fr	Median 22 months	PR: 60% SD: 10% Median OS: 23.4 ± 4.7 months
Chang et al,[11] 2002	23	57	7:16	I: 8 II: 3 III: 8 IV: 4	Stage I - selected IIIA: surgery Stage IIIB - IV: chemotherapy or CRT (details of RT / chemotherapy not mentioned)	2.5-74 months	Stage I: 8/9 alive after median FU 31.4 month Stage II: 2/3 alive after 2 years Stage III: 7/8 alive after mean FU 21 months Stage IV: 4/4 alive after mean FU of 13 months
Han et al,[12] 2001	32	54	22:10	I: 12 II: 8 III: 11 IV: 1	Surgery +/- RT +/- chemotherapy (details of RT / chemotherapy not mentioned)	Mean 45 months	2- & 5-year OS: I: 75% and 37.5% II: 100.0% and 62.5% III and IV: 80.8% and 60.6%
Chan et al,[9] 1998	9	58 (median)	5:4	I-II: 2 IIIB-IV: 7	Stage I - IIIA: surgery Stage IIIB-IV: chemotherapy PF† or RT 60 Gy / 30 Fr / 6 weeks or both +/- intraluminal brachytherapy 15 Gy	Over 3 years	Chemotherapy RR 71.4%, early stage (I-II): recurrence-free at 18 & 20 months Late stage (IIIB-IV): OS 5-26 months

Abbreviations: CRT = chemoradiotherapy; FU = follow-up; OS = overall survival; PR = partial remission; RR = response rate; RT = radiotherapy; SD = static disease.

* 5-fluorouracil (5-FU 1000 mg/m^2/day intravenous (IV) on days 1-4), leucovorin (200 mg/m^2 IV on days 1-4), and cisplatin (100 mg/m^2 IV on day 1).

† Cisplatin 100 mg/m^2 IV on day 1 with hydration, 5-fluorouracil (5-FU) 1 g/m^2 IV on days 2, 3, and 4 given as 24-hour infusions. Cisplatin was substituted with carboplatin at area under curve 6 in patients with a creatinine clearance of 50 ml/min.

in the coming years. On the other hand, the 5-year survival stage III ordinary NSCLC remains less than 20%,[19] despite better radiotherapy planning techniques in recent years.

For advanced disease beyond radical radiotherapy portal or metastatic diseases, different treatment options were attempted in previous series.[9-12,15,16] First-line platinum chemotherapy apparently gave a more favourable PFS compared with ordinary NSCLC. In our current study, the time to progression for first-line platinum double was 10 months, as compared with 5 months for first-line pemetrexed / cisplatin in stage IIIB / IVA non-squamous lung cancers.[20] Second-line treatment options remain controversial. Physicians attempted the second-line chemotherapy agents as used in NPC owing to the histological resemblance of NPC and pulmonary LELC. The beneficial use of capecitabine, which is also used in NPC,[21,22] was reported by Ho et al[23] and was echoed by our series. Apart from capecitabine, retrying platinum

doublets may be another treatment option if the patient's tumour is platinum-sensitive at initial presentation, as shown by the satisfactory time to progression (5-14 months) in our series. Further studies are awaited to confirm the effectiveness of different systemic agents.

The role of serum EBV-DNA has been investigated in previous series. In terms of disease monitoring, good correlation of disease status with serum EBV-DNA level in pulmonary LELC was reported in two previous studies published by Ngan et al[24,25] For predictive or prognostic factors, in those who underwent complete resection, Liang et al[15] found that early tumour stage, a normal serum lactate dehydrogenase level, a normal serum albumin level, and absence of lymph node metastasis had significantly better OS ($p < 0.05$). The serum albumin level was also an independent prognostic factor ($p = 0.005$) in this series. However, it is difficult to draft a prognostic score for decisions on treatment strategy based on the available literature. It may be meaningful for future studies to explore the use of serum EBV-DNA to predict relapses and prognosis as for in NPC.[26,27] This approach may give more clues on the use of adjuvant chemotherapy in early stage disease.

To improve future treatment outcomes, it will be necessary to recruit patients into randomised control trials with standardised treatments, follow-up intervals and other management modalities.

CONCLUSION

Our series of patients with primary pulmonary LELC achieved favourable outcomes, echoing previous findings. Patients having early stage disease should be treated surgically. Radical chemoradiotherapy with EQD2 60 Gy and platinum doublets gives excellent survival outcomes in those with unresectable non-metastatic disease. Chemotherapy agents used in advanced or metastatic NPC, including platinum doublets or single agent capecitabine, can be attempted in pulmonary LELC patients. Serum EBV-DNA may be useful in disease monitoring. Further randomised studies are warranted.

ACKNOWLEDGEMENTS

We thank all our clerical and statistical staff for retrieving and analysing data for this study and the other members of our team for their academic support.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Bégin LR, Eskandari J, Joncas J, Panasci L. Epstein-Bar virus related lymphoepithelioma-like carcinoma of lung. J Surg Oncol. 1987;36:280-3. cross ref
2. Ho JC, Wong MP, Lam WK. Lymphoepithelioma-like carcinoma of the lung. Respirology. 2006;11:539-45. cross ref
3. Iezzoni JC, Gaffey MJ, Weiss LM. The role of Epstein-Barr virus in lymphoepithelioma-like carcinomas. Am J Clin Pathol. 1995;103:308-15.
4. Wong MP, Chung LP, Yuen ST, Leung SY, Chan SY, Wang E, et al. In situ detection of Epstein-Barr virus in non-small cell lung carcinomas. J Pathol. 1995;177:233-40. cross ref
5. Castro CY, Ostrowski ML, Barrios R, Green LK, Popper HH, Powell S, et al. Relationship between Epstein-Barr virus and lymphoepithelioma-like carcinoma of the lung: a clinicopathologic study of 6 cases and review of the literature. Hum Pathol. 2001;32:863-72. cross ref
6. Han AJ, Xiong M, Zong YS. Association of Epstein-Barr virus with lymphoepithelioma-like carcinoma of the lung in southern China. Am J Clin Pathol. 2000;114:220-6. cross ref
7. Ooi GC, Ho JC, Khong PL, Wong MP, Lam WK, Tsang KW. Computed tomography characteristics of advanced primary pulmonary lymphoepithelioma-like carcinoma. Eur Radiol. 2003;13:522-6.
8. Huang CJ, Chan KY, Lee MY, Hsu LH, Chu NM, Feng AC, et al. Computed tomography characteristics of primary pulmonary lymphoepithelioma-like carcinoma. Br J Radiol. 2007;80:803-6. cross ref
9. Chan AT, Teo PM, Lam KC, Chan WY, Chow JH, Yim AP, et al. Multimodality treatment of primary lymphoepithelioma-like carcinoma of the lung. Cancer. 1998;83:925-9. cross ref
10. Ho JC, Lam WK, Wong MP, Wong MK, Ooi GC, Ip MS, et al. Lymphoepithelioma-like carcinoma of the lung: experience with ten cases. Int J Tuberc Lung Dis. 2004;8:890-5.
11. Chang YL, Wu CT, Shih JY, Lee YC. New aspects in clinicopathologic and oncogene studies of 23 pulmonary lymphoepithelioma-like carcinomas. Am J Surg Pathol. 2002;26:715-23. cross ref
12. Han AJ, Xiong M, Gu YY, Lin SX, Xiong M. Lymphoepithelioma-like carcinoma of the lung with a better prognosis. A clinicopathologic study of 32 cases. Am J Clin Pathol. 2001;115:841-50. cross ref
13. Green MR, Cox JD, Ardizzoni A, Arriagada R, Bureau G, Darwish S, et al. Endpoints for multimodal clinical trials in stage III non-small cell lung cancer (NSCLC): a consensus report. Lung Cancer. 1994;11 Suppl 3:S11-3. cross ref
14. Response Evaluation Criteria In Solid Tumors. Available from: http://www.eortc.be/recist/. Accessed Nov 2013.
15. Liang Y, Wang L, Zhu Y, Lin Y, Liu H, Rao H, et al. Primary pulmonary lymphoepithelioma-like carcinoma: fifty-two patients with long-term follow-up. Cancer. 2012;118:4748-58. cross ref
16. Huang CJ, Feng AC, Fang YF, Ku WH, Chu NM, Yu CT, et al. Multimodality treatment and long-term follow-up of the primary pulmonary lymphoepithelioma-like carcinoma. Clin Lung Cancer. 2012;13:359-62. cross ref
17. Chan OS, Lee MC, Hung AW, Chang AT, Yeung RM, Lee AW. The superiority of hybrid-volumetric arc therapy (VMAT) technique over double arcs VMAT and 3D-conformal technique in the treatment of locally advanced non-small cell lung cancer — a planning study. Radiother Oncol. 2011;101:298-302. cross ref
18. Korreman S, Persson G, Nygaard D, Brink C, Juhler-Nøttrup T. Respiration-correlated image guidance is the most important radiotherapy motion management strategy for most lung cancer patients. Int J Radiat Oncol Biol Phys. 2012;83:1338-43. cross ref

19. Curran WJ Jr, Paulus R, Langer CJ, Komaki R, Lee JS, Hauser S, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452-60. cross ref
20. Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26:3543-51. cross ref
21. Chua DT, Sham JS, Au GK. A phase II study of capecitabine in patients with recurrent and metastatic nasopharyngeal carcinoma pretreated with platinum-based chemotherapy. Oral Oncol. 2003;39:361-6. cross ref
22. Chua D, Wei WI, Sham JS, Au GK. Capecitabine monotherapy for recurrent and metastatic nasopharyngeal cancer. Jpn J Clin Oncol. 2008;38:244-9. cross ref
23. Ho JC, Lam DC, Wong MK, Lam B, Ip MS, Lam WK. Capecitabine as salvage treatment for lymphoepithelioma-like carcinoma of lung. J Thorac Oncol. 2009;4:1174-7. cross ref
24. Ngan RK, Yip TT, Cheng WW, Chan JK, Cho WC, Ma VW, et al. Circulating Epstein-Barr virus DNA in serum of patients with lymphoepithelioma-like carcinoma of the lung: a potential surrogate marker for monitoring disease. Clin Cancer Res. 2002;8:986-94.
25. Ngan RK, Yip TT, Cheng WW, Chan JK, Cho WC, Ma VW, et al. Clinical role of circulating Epstein-Barr virus DNA as a tumor marker in lymphoepithelioma-like carcinoma of the lung. Ann N Y Acad Sci. 2004;1022:263-7. cross ref
26. Chan AT, Ma BB, Lo YM, Leung SF, Kwan WH, Hui EP, et al. Phase II study of neoadjuvant carboplatin and paclitaxel followed by radiotherapy and concurrent cisplatin in patients with locoregionally advanced nasopharyngeal carcinoma: therapeutic monitoring with plasma Epstein-Barr virus DNA. Clin Oncol. 2004;22:3053-60. cross ref
27. An X, Wang FH, Ding PR, Deng L, Jiang WQ, Zhang L, et al. Plasma Epstein-Barr virus DNA level strongly predicts survival in metastatic/recurrent nasopharyngeal carcinoma treated with palliative chemotherapy. Cancer. 2011;117:3750-7. cross ref