Lung Cancer 132 (2019) 39–44

Contents lists available at ScienceDirect

Lung Cancer

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

Clinical features and outcomes of pulmonary lymphoma: A single center experience of 180 cases

Mu-Chen Zhang[a,1], Min Zhou[b,1], Qi Song[c,1], Shuo Wang[a], Qing Shi[a], Li Wang[a,d], Fu-hua Yan[c], Jie-Ming Qu[b,**], Wei-Li Zhao[a,d,*]

[a] State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, Shanghai Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Department of Respiration, Shanghai Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[c] Department of Radiology, Shanghai Rui Jin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[d] Pôle de Recherches Sino-Français en Science du Vivant et Génomique, Laboratory of Molecular Pathology, Shanghai, China

ARTICLE INFO

Keywords:
Pulmonary lymphoma
Primary
Secondary
Clinical features
Prognosis

ABSTRACT

Background: Pulmonary lymphoma arises primarily from the lung, which is extremely rare, or be secondarily involved by lymphoma. The clinical features, management, and prognostic factors have not been clearly identified.

Methods: Sixty-three patients with primary pulmonary lymphoma (PPL) and 117 patients with secondary pulmonary lymphoma (SPL) treated in our institution between June 2003 and December 2017 were retrospectively reviewed.

Results: MALT (67%) was the most common pathological subtype of PPL, while DLBCL (48%) was the most common subtype of SPL. Compared to the patients with PPL, the presence of B symptoms, advanced disease stage, intermediate-high or high risks of IPI and NCCN-IPI, elevated inflammatory parameters, and elevated cytokine levels were all observed in patients with SPL. Consolidation was the most frequent radiological finding in PPL cases, while nodules were the most frequent finding in SPL. With a median follow-up of 35 months (range 2–176), the estimated 3-year OS rates were 95%, 100%, 70% and 50% in indolent PPL, indolent SPL, aggressive PPL, and aggressive SPL, respectively. In indolent pulmonary lymphoma, none of the prognostic factors we studied significantly influenced survival of the patients. In aggressive pulmonary lymphoma, univariate analysis showed that NCCN-IPI was related to OS in PPL. Multivariate analysis showed that β2-MG was an independent prognostic factor for OS in SPL.

Conclusions: Primary and secondary pulmonary lymphoma differ in their clinical features and outcome. Furthermore, β2-MG is the independent prognostic factor for OS in patients with aggressive SPL.

1. Introduction

Primary pulmonary lymphoma (PPL) is extremely rare, accounting for only 0.4% of all lymphomas and less than 0.5% of all primary lung tumors [1,2]. PPL is defined as a lymphoma confined to the lung with or without hilar lymph node involvement at the time of diagnosis or up to 3 months thereafter, and predominantly affects adults with a median age of about 60 years [1,3–5]. Approximately 30% to 40% of patients are asymptomatic at initial presentation. Other patients may present non-specific clinical symptoms that are difficult to distinguish from

Abbreviations: PPL, primary pulmonary lymphoma; SPL, secondary pulmonary lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma; DLBCL, diffuse large B-cell lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; BL, burkitt lymphoma; SLL, small lymphocytic lymphoma; ECOG PS, eastern cooperative oncology group performance status; IPI, international prognostic index; NCCN-IPI, national comprehensive cancer network-IPI; LDH, lactate dehydrogenase; ALB, albumin; β2-MG, β2-microglobulin; CRP, C-reactive protein; NSE, neuron specific enolase; CA, carbohydrate antigen; IL, interleukin; TNF, tumor necrosis factor; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

* Corresponding author at: State Key Laboratory of Medical Genomics, Shanghai Institute of Hematology, Shanghai Rui Jin Hospital, 197 Rui Jin Er Road, Shanghai, 200025, China.
** Corresponding author at: Department of Respiration, Shanghai Rui Jin Hospital, 197 Rui Jin Er Road, Shanghai, 200025, China.
E-mail addresses: jmqu0906@163.com (J.-M. Qu), zhao.weili@yahoo.com (W.-L. Zhao).
[1] These authors contributed equally to this manuscript.

https://doi.org/10.1016/j.lungcan.2019.04.004
Received 14 January 2019; Received in revised form 3 April 2019; Accepted 6 April 2019

other lung cancers, such as cough, dyspnea, hemoptysis and chest pain. Fever, diaphoresis, or weight loss were reported in 15% to 27% of patients with PPL [1]. The radiological findings of PPL are heterogenous and present as solitary mass lesions, pulmonary infiltrates, and solitary/ multiple bilateral nodules [6,7]. The majority of PPL cases are of B-cell origin, among which mucosa-associated lymphoid tissue (MALT) lymphoma encompasses 70% to 80% [2]. The survival of PPL patients is favorable, with 68% 5-year survival rate and 53% 10-year survival rate in MALT lymphoma [1].

Secondary pulmonary lymphoma (SPL) is more frequent and defined as secondary involvement of pulmonary by a systemic lymphoma. The radiological features of SPL may present with solitary or multiple nodules, mass or mass-like consolidation, alveolar or interstitial infiltrates, pleural effusions and mediastinal lymph node enlargement. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of SPL, followed by mantle cell lymphoma (MCL), MALT, follicular lymphoma (FL), and Burkitt lymphoma (BL). The response and outcome of SPL are significantly worse compared to those without pulmonary involvement [8]. National Comprehensive Cancer Network-International Prognostic Index (NCCN-IPI) considered lung as one of the major extranodal organs [9].

The aim of this study is to analyze the clinical characteristics, treatment and outcome of pulmonary lymphoma and to identify prognostic factors.

2. Patients and methods

2.1. Patients

A total of 180 patients were included in this study, including 63 PP L [MALT, n = 42, DLBCL, n = 17, peripheral T-cell lymphoma (PTCL), n = 3, FL, n = 1] and 117 SPL [DLBCL, n = 56, PTCL, n = 37, MALT, n = 7, FL, n = 6, BL, n = 4, small lymphocytic lymphoma (SLL), n = 4, MCL, n = 3). Pulmonary tissue samples were obtained from surgical resection, bronchoscopic biopsies or computed tomography (CT)-guided percutaneous lung biopsies. The histological diagnosis was established according to the World Health Organization (WHO) 2008 classification [10].

2.2. Data collection

The following clinical data was collected: age, gender, presenting symptoms, Eastern Cooperative Oncology Group performance status (ECOG PS), clinical stage, extranodal involvement, IPI and NCCN-IPI. Laboratory data at diagnosis were reviewed, including hemoglobin level, neutrophil and platelet counts, absolute lymphocyte count (ALC), absolute monocyte count (AMC), lymphocyte-monocyte ratio (LMR), neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR); serum levels of lactate dehydrogenase (LDH), albumin (ALB), β2-microglobulin (β2-MG), C-reactive protein (CRP), ferritin; tumor markers such as neuron specific enolase (NSE), carbohydrate antigen (CA)12-5 and CA19-9; and levels of cytokines such as interleukin-2 receptor (IL-2R), IL-6, IL-8, IL-10 and tumor necrosis factor (TNF)-α.

All patients underwent a bone marrow biopsy, computed tomography (CT) scans of thorax, chest, abdomen and pelvic cavity, or fluorine-18-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) scans before treatment. Disease stage was assessed according to the Ann Arbor system. The stage of PPL was determined according to the Ann Arbor stages modified by Ferraro et al.: patients with unilateral or bilateral presentation of the lung were defined as stage IE; patients with lung presentation and hilar lymph node involvement were defined as stage IIE; patients with lung presentation and chest wall or diaphragm involvement were defined as stage IIEW; patients with lung presentation and abdominal lymph node involvement were defined as stage IIIE; and patients with lung presentation and extra-lymphatic organs or tissue involvement were defined as stage IVE [1]. The treatment response was evaluated according to WHO criteria for response [11]. Patient follow-ups were obtained through out-patient visits or by telephone interview.

Table 1
Clinical characteristics at diagnosis according to the type of pulmonary involvement.

	PPL (n = 63) n (%)	SPL (n = 117) n (%)	*P* value
Age			
Median age at diagnosis (range)	56 (15-81)	55 (15-83)	0.661
≤60 years	36 (57)	71 (61)	0.644
> 60 years	27 (43)	46 (39)	
Sex			
Male/female	29 (46)/34 (54)	71 (61)/46 (39)	0.059
Clinical symptoms			
Respiratory symptoms	35 (56)	38 (32)	0.003
B symptoms	17 (27)	66 (56)	< 0.001
Asymptomatic	23 (36)	21 (18)	0.006
Stage			
I-II	33 (52)	3 (3)	< 0.001
III-IV	30 (48)	114 (97)	
LDH			
Normal	50 (79)	42 (36)	< 0.001
Elevated	13 (21)	75 (64)	
ALB			
< 35 g/L	28 (44)	61 (52)	0.345
≥35 g/L	35 (56)	56 (48)	
β2-MG	n = 54	n = 106	
≤3500 ng/mL	6 (11)	39 (37)	0.001
> 3500 ng/mL	48 (89)	67 (63)	
Ferritin	n = 56	n = 107	
≤500 ng/mL	52 (93)	43 (40)	0.001
> 500 ng/mL	4 (7)	64 (60)	
IPI			
0–1	24 (38)	2 (2)	< 0.001
2	15 (24)	22 (19)	
3	17 (27)	45 (38)	
4–5	7 (11)	48 (41)	
NCCN-IPI			
0–1	0	1 (1)	< 0.001
2–3	39 (62)	36 (31)	
4–5	21 (33)	60 (51)	
6–8	3 (5)	20 (17)	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ALB, albumin; β2-MG, β2-microglobulin; IPI, International Prognostic Index; NCCN-IPI, National Comprehensive Cancer Network-International Prognostic Index.

2.3. Statistical analysis

All statistical analyses were performed with Statistical Package for the Social Sciences (SPSS) 23.0 software (SPSS Inc., Chicago, USA). Overall survival (OS) was calculated from the date of diagnosis to the date of death or the date of last follow-up (1 st October 2018). Progression-free survival (PFS) was measured from the date when treatment began to the date when the disease progression was recognized or the date of last follow-up. Patients with no progression or that were still alive at last follow-up date were considered right censored. Survival analyses were estimated by the Kaplan-Meier method. The log-rank tests were used to compare survival curves between groups. Categorical measures were compared by Fisher exact test or chi-square test. All *P* values were two-sided and *P* values of less than 0.05 were considered statistically significant.

3. Results

3.1. Clinical and laboratory characteristics

The median age at diagnosis was 55 (range 15–83) years, and 100

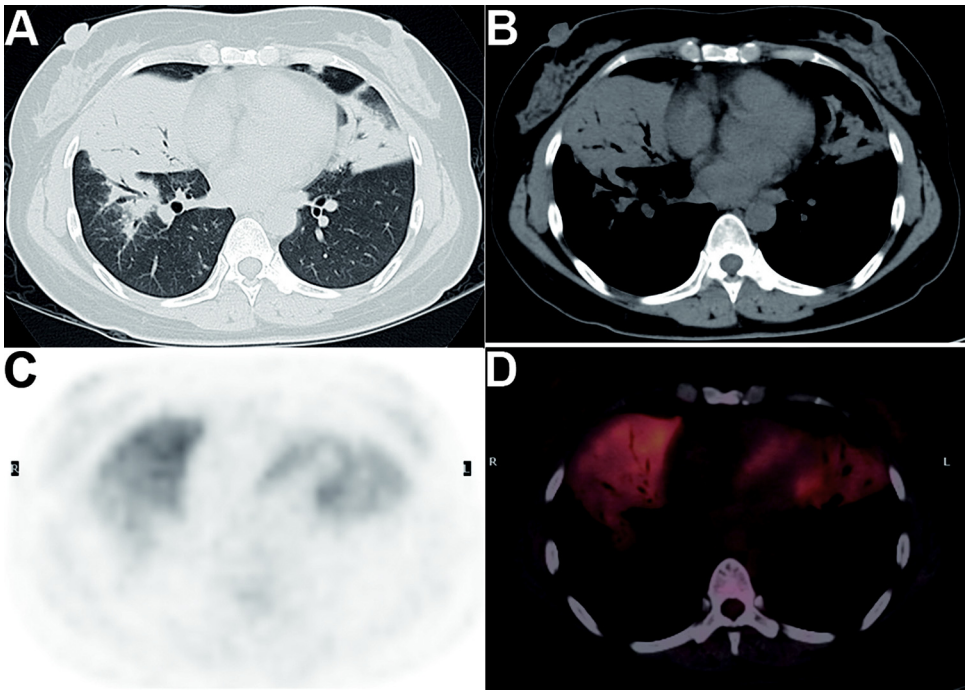

Fig. 1. Representative presentation of consolidation pattern of pulmonary lymphoma. Axial CT (A, B), axial PET (C) and axial PET/CT (D) images demonstrated two areas of consolidation with air bronchograms in middle lobe of right lung and upper lobe of left lung in a 46-year-old female, showing an FDG uptake with SUV max of 5.5–6.5, lesion-to-liver SUV max ratio of 1.6–1.9 and lesion-to-blood pool SUV max ratio of 3.4–4.1. Biopsy of the consolidation revealed MALT lymphoma.

patients were male. The main clinical characteristics at diagnosis are summarized in Table 1. Thirty-three (33/63, 52%) PPL patients presented with early stage (stages I-II), 50 patients (50/63, 79%) with normal serum LDH, 39 patients (39/63, 62%) with low or low-intermediate risks of IPI (IPI 0–2) and 39 patients (39/63, 62%) with low or low-intermediate risks of NCCN-IPI (NCCN-IPI 0–3). Thirty-five patients (35/63, 56%) had non-specific respiratory symptoms, such as cough, dyspnea, hemoptysis and chest pain. Twenty-three patients (23/63, 36%) were asymptomatic at diagnosis. The majority of SPL patients (114/117, 97%) presented advanced stage disease (stages III-IV), elevated LDH (75/117, 64%), intermediate-high or high risks of IPI (IPI 3–5, 93/117, 79%) and NCCN-IPI (NCCN-IPI 4–8, 80/117, 68%). B symptoms were more commonly presented in SPL compared to PPL (56% vs 27%, $P < 0.001$).

Inflammatory factors (LDH, AMC, CRP, β2-MG and ferritin), tumor marker (NSE), and cytokine (IL-2R, IL-6 and IL-10) levels were all significantly elevated in patients with SPL, as compared to those with PPL (Supplementary Table S1).

3.2. Radiological findings

Radiological features were shown in the non-contrast enhanced images. Tumor lesions of 25 cases (25/41, 61%) of primary pulmonary MALT lymphoma were multiple and 49% (20/41) were bilateral. On CT scans, the lesions presented as lobar consolidation (24/41, 58%) (Fig. 1), multiple nodules (12/41, 29%), lung mass (11/41, 27%) (Fig. 2), bronchiectasis (6/41, 15%), solitary nodule (4/41, 10%) and diffuse intestinal disease (5/41, 12%) (Fig. 3). Hilar or mediastinal lymph nodes were observed in 15 cases (15/41, 36%). Primary pulmonary DLBCL manifested as mass (7/17, 41%), consolidation (5/17, 29%), multiple nodules (4/17, 24%) and solitary nodule (2/17, 12%). All three cases of primary pulmonary PTCL presented as mass lesions. Primary pulmonary FL presented as multiple nodules. Most of the SPL cases presented as multiple nodules (70/117, 60%) (Fig. 4), followed by mass or mass-like consolidation (39/117, 33%), alveolar or interstitial infiltrates (25%), and solitary nodule (18/117, 15%).

3.3. Treatment and outcome

Except for 4 patients with primary MALT lymphoma who did not receive systemic treatment (two patients underwent surgery alone, one patient with radiotherapy and the other with observation), patients with B-cell lymphoma were treated with rituximab, either alone (n = 2) or combined with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone, n = 113), COP (cyclophosphamide, vincristine, and prednisone, n = 15), FC (fludarabine, and cyclophosphamide, n = 3), lenalidomide (n = 2), or ibrutinib (n = 1). Patients with PTCL received CHOP (n = 30) or CHOP with etoposide (n = 10). Treatment response was reported in Supplementary Table S2. The CR rate (CRR) and overall response rate (ORR) were 58% and 77% in PPL and 47% and 66% in SPL, respectively.

With a median follow-up of 35 months (range 2–176), 49 deaths were reported, including 1 case of indolent PPL, 5 cases of aggressive PPL, 2 cases of indolent SPL and 41 cases of aggressive SPL. The estimated 3-year OS rates were 95%, 70%, 100% and 50%, respectively (Fig. 5A and B, $P < 0.001$). Survival analyses were performed separately for indolent PPL, indolent SPL, aggressive PPL, and aggressive SPL. Indolent lymphoma included MALT, FL, and SLL. Aggressive lymphoma included DLBCL, PTCL, BL and MCL. The OS curves did not show significant difference in terms of IPI in all the four groups. Fig. 5C and D showed the OS curves of aggressive pulmonary lymphoma stratified by NCCN-IPI. Aggressive PPL patients with intermediate-high or high risks of NCCN-IPI (NCCN-IPI 4–8) experienced a worse prognosis than patients with low or low-intermediate risks of NCCN-IPI (NCCN-IPI 0–3) ($P = 0.023$). However, this tendency was not presented in patients with aggressive SPL ($P = 0.299$).

The following factors were included in our univariate analyses: Ann Arbor stage, LMR, NLR, PLR, and serum LDH, ALB, β2-MG, ferritin and cytokines. None of these factors were found to have a significant influence on OS in indolent pulmonary lymphoma. For univariate analysis of aggressive pulmonary lymphoma, patients older than 60 years had a worse OS both in PPL (3-year OS: 85% vs 50%, $P = 0.045$) and SPL (3-year OS: 56% vs 42%, $P = 0.049$). Univariate analysis of aggressive SPL showed that clinical characteristics significantly correlated with poor OS were patients older than 60 years, NLR > 4.6, decreased serum ALB, elevated serum β2-MG, and ferritin (Supplementary Table

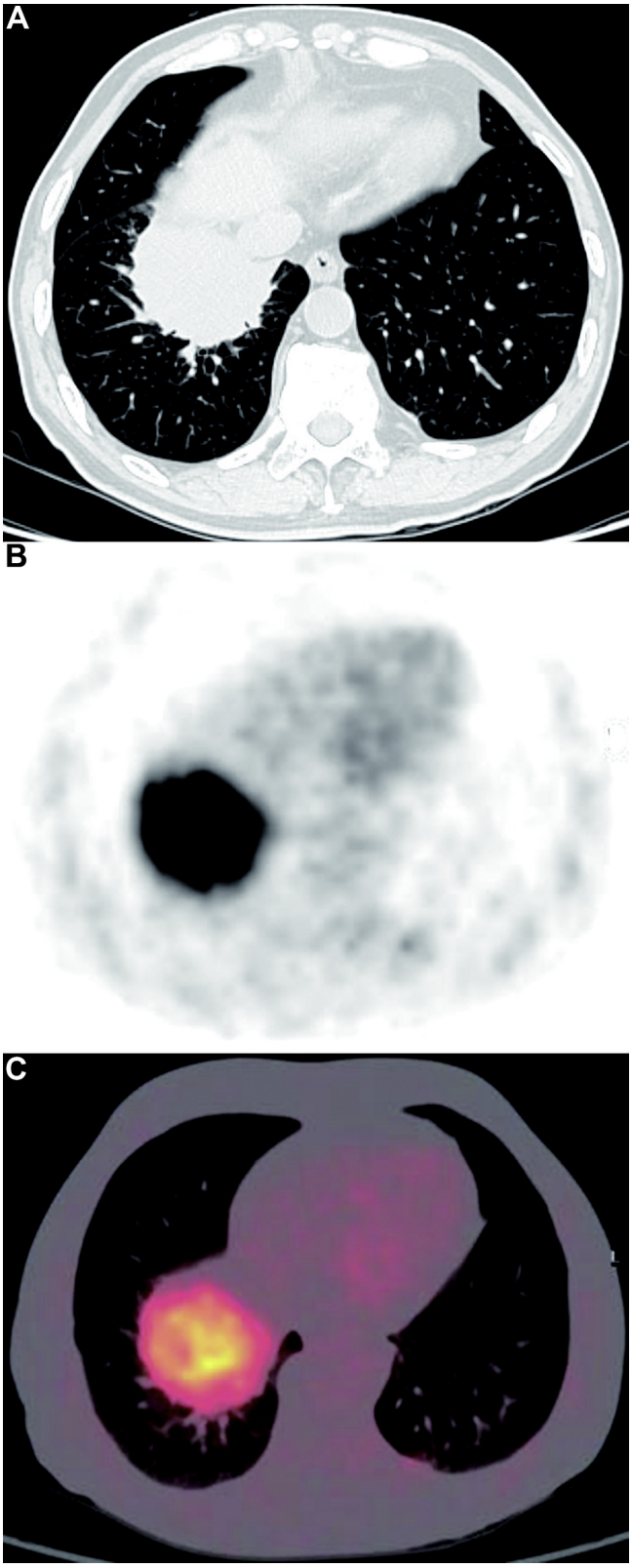

Fig. 2. Representative presentation of mass pattern of pulmonary lymphoma.
Axial CT (A), axial PET (B) and axial fused PET/CT (C) images in a 68-year-old male demonstrated a large, well-circumscribed mass of 6.9 cm of diameter in the lower lobe of right lung, showing an FDG uptake with a SUV max of 10.4, lesion-to-liver SUV max ratio of 2.5 and lesion-to-blood pool SUV max ratio of 4.5. The patient visited the clinic with no symptoms and percutaneous core needle biopsy revealed a diagnosis of MALT lymphoma.

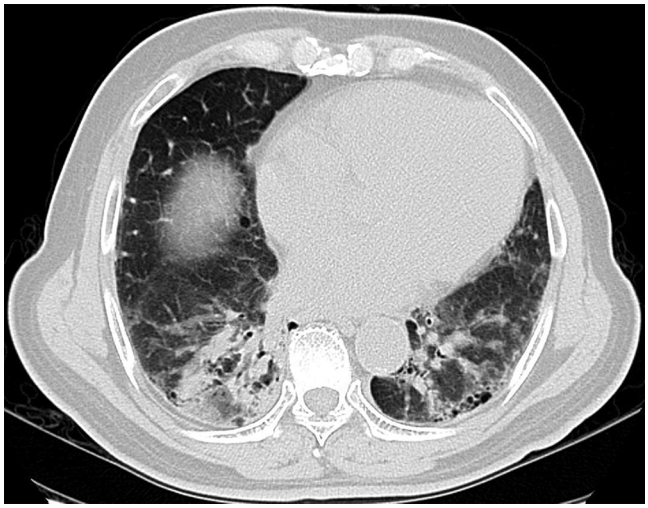

Fig. 3. Representative presentation of interstitial disease pattern of pulmonary lymphoma.
Axial CT scan of a 73-year-old male demonstrated ground-glass opacities and cysts. There was also an area of consolidation in the lower lobe of right lung. This was proven to be a MALT lymphoma on percutaneous core biopsy.

S3). From the multivariate analysis of aggressive SPL, the significant independent prognostic factor for OS was elevated serum β2-MG level (RR: 4.442, 95% *CI*: 1.567–12.591, $P = 0.005$).

4. Discussion

Approximately 25% of non-Hodgkin's lymphoma arises in extranodal sites, most often the gastrointestinal tract [12,13]. Primary pulmonary involvement is a very rare entity, accounting for only 3% of extranodal lymphoma [13]. The majority of PPL is of B-cell origin, accounting for more than 90% of cases, with MALT lymphoma as the most common subtype. In our study, 67% of PPL were MALT, 27% were DLBCL, 5% were PTCL, and 1% was FL, confirming the epidemiologic data previously reported [2]. Meanwhile, all histological subtypes of lymphoma may also secondarily involve the lung. Here, SPL patients were most commonly affected by DLBCL (48%), followed by PTCL (32%), MALT (6%), FL (5%), BL (3%), SLL (3%), and MCL (2%). As expected, we observed more frequent presence of B symptoms, advanced stage disease, intermediate-high or high risks of IPI and NCCN-IPI, elevated inflammatory parameters (AMC, CRP, β2-MG and ferritin) and cytokine levels (IL-2R, IL-6 and IL-10) in patients with SPL, compared to patients with PPL.

PPL is insufficient to be diagnosed with radiology alone. The imaging manifestations of pulmonary MALT lymphoma are various and often presented as multiple and bilateral disease. The most frequent findings are consolidations, followed by nodules and masses [14]. Similar results were confirmed in our study. In consolidative forms, bronchial dilatation is a common feature [6]. Unexpected persistence or progression of consolidation lesions during appropriate antibiotic therapy may indicate PPL. Moreover, although pneumonia may produce mediastinal or hilar nodal enlargement, internal mammary nodal enlargement is rare and is highly suggestive of lymphoma [15]. Imaging manifestations of SPL are similar to those of PPL. Nodules, masses, and mass-like consolidation are common and may cavitate, particularly in aggressive lymphoma [15]. Metabolic activity at PET/CT may also be helpful. Pulmonary lymphoma is FDG avid in most cases and FDG is correlated with tumor size [14,16,17]. Secondary pulmonary involvement should be considered in patients with known extrapulmonary lymphoma, particularly in the disseminated disease.

Various therapeutic modalities have been applied in clinical practice, such as surgery, chemotherapy, immunotherapy, and radiation

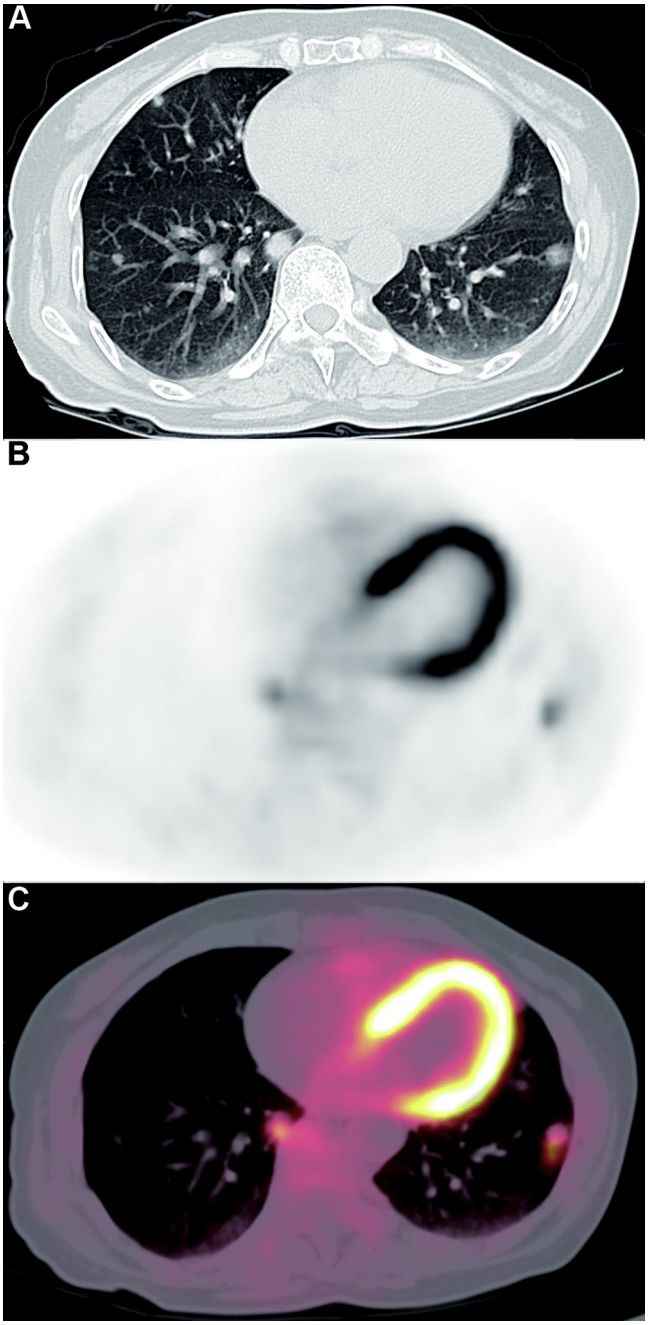

Fig. 4. Representative presentation of scattered small nodules pattern of pulmonary lymphoma.
Axial CT (A), axial PET (B) and axial fused PET/CT (C) images demonstrated small peripheral nodules in a 61-year-old female diagnosed with DLBCL. SUV max was 14.7, lesion-to-liver SUV max ratio was 4.0 and lesion-to-blood pool SUV max ratio was 6.1. Biopsy of the nodule was consistent with DLBCL.

therapy (alone or in combination), but currently no optimal management of pulmonary MALT lymphoma has been defined. Surgery may provide diagnostic purpose and therapeutic resection. Some investigators suggest surgical resection for patients with localized or peripherally located lesions [1,12]. In our study, the majority of enrolled cases presented with extensive disease or symptoms. Under these circumstances, patients received chemotherapy alone at diagnosis, or following partial surgical resection. Response to first-line treatment of primary MALT lymphoma was similar to a previous study reported by the International Extranodal Lymphoma Study Group (IELSG) [4], with a CRR of 54% and ORR of 78%. R-CHOP is recognized as the standard regimen for DLBCL, resulting in 70%–80% of CR [18,19]. Forty-two cases of primary pulmonary DLBCL with stage IE, age 65 years or younger were reported. All patients were IPI 0–2, of which 91% with IPI 0-1. Upon R-CHOP treatment, 83% of patients achieved CR [20]. To our knowledge, our study represents the first series of Chinese primary pulmonary DLBCL patients in the literature. More than 50% of patients presented with advanced stage (59%) and intermediate-high or high risks of IPI (IPI 3–5, 53%). The CRR and ORR were 76% and 82%, respectively, suggesting primary pulmonary DLBCL may respond well to R-CHOP. However, the response was poor in secondary pulmonary DLBCL, with a CRR and ORR of only 53% and 71%, respectively.

Because of the different clinical course of indolent NHL and aggressive NHL, we performed the survival analysis separately. Since pulmonary involvement is selected as a predictive factor in NCCN-IPI [9], whether NCCN-IPI can still perform well in pulmonary lymphoma is unknown. We found that NCCN-IPI only predicted survival in aggressive PPL. Patients with intermediate-high or high risks of NCCN-IPI experienced significantly worse outcomes than patients with low or low-intermediate risks of NCCN-IPI. This tendency was not presented in aggressive SPL. Our study further explored prognostic factors in aggressive SPL. Age is an important predictive factor in several clinical prognostic indexs, including IPI and NCCN-IPI. Elderly patients often experienced poor prognosis. Recent studies indicated that inflammatory status is essential on lymphoma progression and associated with inferior outcome in lymphoma. The inflammatory-IPI model was first proposed to predict prognosis in DLBCL based on inflammatory factors (LDH, ALC, serum ALB, CRP, β2-MG, and ferritin) [21]. In terms of β2-MG, it is related to tumor burden in many tumors and has been reported as an adverse prognostic factor in various subtypes of lymphoma [22,23]. β2-MG level was likely to add significant predictive information in aggressive SPL.

In conclusion, our study confirmed that the presence of B symptoms, more advanced disease stage, intermediate-high or high risks of IPI and NCCN-IPI, elevated inflammatory parameters (AMC, CRP, β2-MG and ferritin) and elevated cytokine levels (IL-2R, IL-6 and IL-10) were presented in SPL compared to PPL. Indolent pulmonary lymphoma presented favorable outcomes. In aggressive pulmonary lymphoma, univariate analysis showed that NCCN-IPI was related to OS in PPL, and multivariate analysis showed that β2-MG was an independent prognostic factor for OS in SPL.

Author contributions

M.-C.Z. collected and analyzed clinical data and wrote the article. M.Z. analyzed the data and wrote the article. Q.SONG reviewed the radiological findings and wrote the article. S.W. and Q.SHI collected study data. L.W. gathered detailed clinical information for the study. F.-H.Y. reviewed the radiological findings. W.-L.Z. and J.-M.Q. conceived the study and wrote the manuscript. All authors reviewed the manuscript and approved the final draft.

Declaration of interest

The authors declare no potential conflicts of interest.

Fundings

This study was supported, in part, by research funding from the National Natural Science Foundation of China (81520108003, 81830007, and 81670716), Chang Jiang Scholars Program, the Shanghai Commission of Science and Technology (16JC1405800), Shanghai Municipal Education Commission Gaofeng Clinical Medicine Grant Support (20152206 and 20152208), Clinical Research Plan of SHDC (16CR2017A), Multicenter Clinical Research Project by Shanghai Jiao Tong University School of Medicine (DLY201601), Collaborative Innovation Center of Systems Biomedicine, Samuel Waxman Cancer

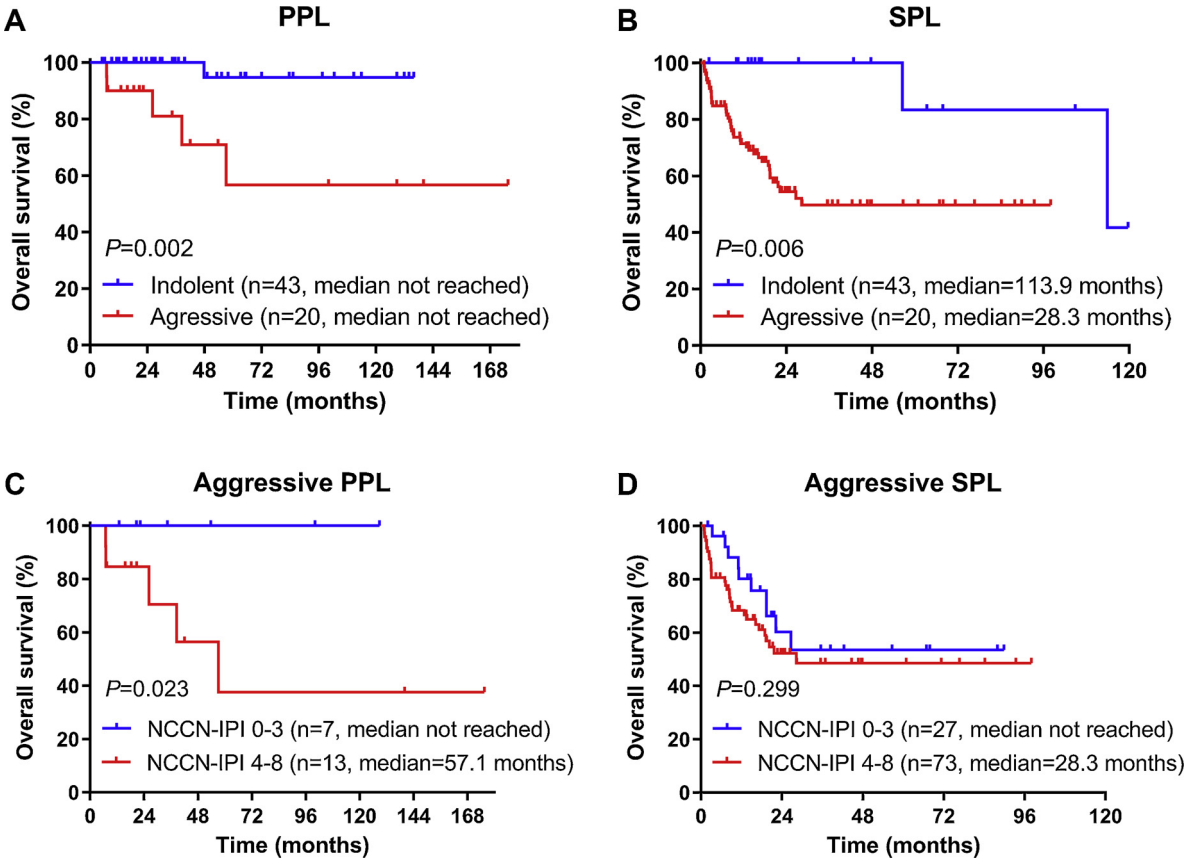

Fig. 5. Overall survival curve of pulmonary lymphoma.
(A) OS of PPL stratified by indolent and aggressive lymphoma. (B) OS of SPL stratified by indolent and aggressive lymphoma. (C) OS of aggressive PPL stratified by NCCN-IPI. (D) OS of aggressive SPL stratified by NCCN-IPI.

Research Foundation, Shanghai Key Discipline for Respiratory Diseases (2017ZZ02014) and Innovative research team of high-level local universities in Shanghai.

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.2019.04.004.

References

[1] P. Ferraro, V.F. Trastek, H. Adlakha, et al., Primary non-Hodgkin's lymphoma of the lung, Ann. Thorac. Surg. 69 (2000) 993–997.
[2] S. Pina-Oviedo, A. Weissferdt, N. Kalhor, et al., Primary pulmonary lymphomas, Adv. Anat. Pathol. 22 (2015) 355–375.
[3] M.O. Khalil, L.M. Morton, S.S. Devesa, et al., Incidence of marginal zone lymphoma in the United States, 2001–2009 with a focus on primary anatomic site, Br. J. Haematol. 165 (2014) 67–77.
[4] S. Sammassimo, G. Pruneri, G. Andreola, et al., A retrospective international study on primary extranodal marginal zone lymphoma of the lung (BALT lymphoma) on behalf of International Extranodal Lymphoma Study Group (IELSG), Hematol. Oncol. 34 (2016) 177–183.
[5] M.N. Koss, Malignant and benign lymphoid lesions of the lung, Ann. Diagn. Pathol. 8 (2004) 167–187.
[6] S.S. Hare, C.A. Souza, G. Bain, et al., The radiological spectrum of pulmonary lymphoproliferative disease, Br. J. Radiol. 85 (2012) 848–864.
[7] Y.A. Bae, K.S. Lee, J. Han, et al., Marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue: imaging findings in 21 patients, Chest 133 (2008) 433–440.
[8] M. Mian, I. Wasle, S. Gritsch, et al., B cell lymphoma with lung involvement: what is it about? Acta Haematol. 133 (2015) 221–225.
[9] Z. Zhou, L.H. Sehn, A.W. Rademaker, et al., An enhanced International Prognostic Index (NCCN-IPI) for patients with diffuse large B-cell lymphoma treated in the rituximab era, Blood 123 (2014) 837–842.
[10] S.H. Swerdlow, E. Campo, N.L. Harris, E.S. Jaffe, S.A. Pileri, H. Stein, J. Thiele, J.W. Vardiman, et al., WHO Classificaiton of Tumors of Haematopoietic and Lymphoid Tissues, 4th edn, World Health Organization classification of tumors, 2008.
[11] B.D. Cheson, B. Pfistner, M.E. Juweid, et al., Revised response criteria for malignant lymphoma, J. Clin. Oncol. 25 (2007) 579–586.
[12] S. Ahmed, S.J. Kussick, A.K. Siddiqui, et al., Bronchial-associated lymphoid tissue lymphoma: a clinical study of a rare disease, Eur. J. Cancer 40 (2004) 1320–1326.
[13] C. Freeman, J.W. Berg, S.J. Cutler, Occurrence and prognosis of extranodal lymphomas, Cancer 29 (1972) 252–260.
[14] D. Albano, A. Borghesi, G. Bosio, et al., Pulmonary mucosa-associated lymphoid tissue lymphoma: (18)F-FDG PET/CT and CT findings in 28 patients, Br. J. Radiol. 90 (2017) 20170311.
[15] M.P. Bligh, J.N. Borgaonkar, S.C. Burrell, et al., Spectrum of CT findings in thoracic extranodal non-hodgkin lymphoma, Radiographics 37 (2017) 439–461.
[16] K.P. Beal, H.W. Yeung, J. Yahalom, FDG-PET scanning for detection and staging of extranodal marginal zone lymphomas of the MALT type: a report of 42 cases, Ann. Oncol. 16 (2005) 473–480.
[17] S.H. Park, J.J. Lee, H.O. Kim, et al., 18F-Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography in mucosa-associated lymphoid tissue lymphoma: variation in 18F-FDG avidity according to site involvement, Leuk. Lymphoma 56 (2015) 3288–3294.
[18] P. Feugier, A. Van Hoof, C. Sebban, et al., Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte, J. Clin. Oncol. 23 (2005) 4117–4126.
[19] M. Pfreundschuh, L. Trumper, A. Osterborg, et al., CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group, Lancet Oncol. 7 (2006) 379–391.
[20] A. Aviles, M.J. Nambo, J. Huerta-Guzman, et al., Rituximab in the treatment of diffuse large B-cell lymphoma primary of the lung, Hematology 18 (2013) 81–84.
[21] C. Kim, H.S. Lee, J.-C. Jo, et al., Clinical usefulness of inflammatory factors based modified international prognostic index in diffuse large B cell lymphoma treated with rituximab combined chemotherapy, Blood 128 (2016) 4220-4220.
[22] T. Melchardt, K. Troppan, L. Weiss, et al., A modified scoring of the NCCN-IPI is more accurate in the elderly and is improved by albumin and beta2 -microglobulin, Br. J. Haematol. 168 (2015) 239–245.
[23] C. Montalban, A. Diaz-Lopez, I. Dlouhy, et al., Validation of the NCCN-IPI for diffuse large B-cell lymphoma (DLBCL): the addition of beta2 -microglobulin yields a more accurate GELTAMO-IPI, Br. J. Haematol. 176 (2017) 918–928.