Diagnostic and prognostic factors for patients with primary pulmonary non-Hodgkin's lymphoma: A 16-year single-center retrospective study

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Abstract. Primary pulmonary non-Hodgkin's lymphoma (PP-NHL) is a rare entity with non-specific symptoms and radiographic findings, as well as a difficult preoperative diagnosis. A limited number of studies have described PP-NHL in Chinese patients. The goal of the present study was to improve early diagnosis by examining prognostic factors in patients with PP-NHL. Therefore, a total of 29 patients with PP-NHL were included in the study between January 2001 and June 2017, including 14 with aggressive-type and 15 with indolent-type lymphomas (10 male, 19 female; median age, 50.3 years; range, 19-87 years). Pulmonary nodules and masses (55.2%) were the most common radiographic features. The diagnostic yield was 80% (12/15) by endobronchial biopsy or transbronchial lung biopsy and 100% by computed tomography (CT)-guided percutaneous needle lung biopsy (11/11) or surgery (8/8). Elevated lactate dehydrogenase levels and systemic symptoms were observed considerably more often in patients with aggressive disease than in those with indolent disease. The 1-, 3- and 5-year overall survival (OS) rates were 42, 32, and 21%, respectively, for all patients, 72, 57 and 43%, respectively, for patients with indolent lymphomas, and 13, 6 and 0%, respectively, for patients with aggressive lymphomas. The median OS rate for all patients was 12.0 months; however, the OS rate for patients with aggressive lymphomas was significantly shorter compared with those with indolent lymphomas (7.1 months vs. 16.6 months; P=0.002). Aggressive vs. indolent lymphoma status was indicated to be an independent prognostic factor for poor 5-year OS rate (hazard ratio, 5.98; P=0.014). In conclusion, bronchoscopic and CT-guided percutaneous needle lung biopsies were the most useful and least invasive procedures for diagnosing PP-NHL. Furthermore, aggressive PP-NHL was highly associated with poor 5-year OS rate and a poor prognosis.

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Introduction

Primary pulmonary lymphoma (PPL) is defined as a clonal lymphoid proliferation affecting one or both lungs in patients with no detectable extrapulmonary involvement or bone marrow disease at the time of diagnosis and during the subsequent 3 months (1). This disease is a rare entity that accounts for 1% of malignant lymphomas (2) and 3.6% of extranodal lymphomas worldwide (3). The rarity of PPL may be attributed to the relatively low levels of lymphoid tissue in pulmonary tissue compared with the levels at other sites (4). The most frequent subtypes are MALT-type lymphoma, and other subtypes are commonly identified in immunocompromised patients (5). Pulmonary MALT lymphoma is referred to as nodal marginal-zone B-cell lymphoma, with similar cytopathological features to other MALT lymphomas, especially gastric lymphoma, 70 to 90% of PPL cases are classified as mucosa-associated lymphoid tissue (MALT)-type non-Hodgkin's lymphomas (NHLs) (5). The male to female ratio of patients with PPL varies from 1:1 to 1:2 (6), and the mean age of patients with NHL is 53±12 years (6). In general, NHL can be divided into two types according to World Health Organization (WHO) criteria: i) Indolent-type lymphomas, which include follicular lymphoma (FL) grade I-II, marginal zone B-cell lymphoma, small lymphocytic lymphoma and hairy cell leukemia, and ii) aggressive-type lymphomas, which include diffuse large B-cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma unspecified (PTCL-U), mantle cell lymphoma (MCL) and natural killer/T-cell lymphoma (NK/T-L) (7).

To the best of our knowledge, few PP-NHL cases have been reported in China. Therefore, a 16-year retrospective study was conducted that focused on the clinical features and prognostic factors of 29 patients with PP-NHL at a single institution-Guangdong Provincial People's Hospital/Guangdong Academy of Medical Sciences, and the majority of patients were from Southern and Central China Region, to provide awareness and useful diagnostic and prognostic indicators of PP-NHL. It was indicated that minimally invasive procedures, including bronchoscopy and computed tomography (CT)-guided percutaneous needle lung biopsy, serve an important role in obtaining a definitive diagnosis for the majority of patients with PP-NHL, as aggressive PP-NHL was highly associated with a poor 5-year OS rate and poor prognosis.

Patients and methods

Patients. The present retrospective study included a total of 29 patients with PP-NHL diagnosed between January 2001 and June 2017 in Guangdong Provincial People's Hospital/Guangdong Academy of Medical Sciences who met the following criteria (8): Unilateral or bilateral pulmonary involvement, no previous diagnosis of extrathoracic lymphoma, no evidence of extrathoracic disease by clinical staging workup, including thorough physical examination, CT scans of the chest, abdomen or pelvis, positron emission tomography-computed tomography (PET-CT) scans of the whole body or bone marrow biopsy, and no evidence of extrathoracic disease up to 3 months after the initial diagnosis. In accordance with previous reports, 12 patients with hilar or mediastinal lymphadenopathy were included (9,10). Primary clinical data were collected from the medical records of all patients.

Definitive diagnosis and histopathology. All patients were diagnosed by pathological analysis of samples collected through various invasive procedures, including bronchoscopic biopsy, CT-guided percutaneous needle lung biopsy, video-assisted thoracic surgery (VATS), open lung biopsy and pleural membrane biopsy. Histological specimens were evaluated and classified by hematopathologists using the updated WHO guidelines (7). In addition to morphology and growth pattern analysis, based on hematoxylin-eosin (HE) staining, immunohistochemistry or in situ hybridization (ISH) staining was performed to support the diagnosis of suspected subtypes based on unique markers. The tissue samples were fixed in 10% buffered formalin for 6 h at room temperature and embedded in paraffin, processed routinely, 4-μm sectioned and stained with hematoxylin (for 5 min at room temperature) and eosin (for 1 min at room temperature). Then, sections were deparaffinized and subsequently rehydrated in a descending alcohol series (100% alcohol for 5 min, 95% alcohol for 4 min, 85% alcohol for 2 min). Antigens were heat-retrieved at 98˚C in EDTA solution. Following cooling to room temperature, the tissue sections were quenched with 3% hydrogen peroxidase, and non-specific binding sites were blocked with 5% goat serum (Thermo Fisher Scientific, Inc.) at 37˚C for 30 min. Immunohistochemical staining was performed on 4-μm sections using a Real Envision Kit (K5007; Dako, Carpinteria, CA, USA) on an automated immunostaining module (Leica Bond III), according to the manufacturer's protocol. All primary antibodies were diluted to the manufacturer's recommendations or to previously optimized dilution and were incubated at room temperature for 30 min. The immunohistochemical staining was observed under the Olympus light microscope at x40, x100 and x400 magnification after dehydrating and stabilizing with mounting medium. Immunohistochemical staining was performed using commercially available antibodies (mouse anti-human monoclonal, Dako, Glostrup, Denmark) to the following antigens: CD3, CD5, CD10, CD19, CD20, CD30, CD45, CD56, CD79a, Ki-67. CD3 (clone F7.2.38, dilution, 1:200; M725401-2), CD5 (clone 4C7, dilution, 1;100; M3641), CD10 (clone 56C6, dilution, 1:100; IS64830-2), CD19 (clone LE-CD19, dilution, 1:200; M729629-2), CD20 (clone L26, dilution, 1:800; M0755), CD45 (clones 2B11+PD7/26, dilution, 1:200; IS75130-2), CD56 (clone 123C3, dilution, dilution, 1:100; M730429-2) and CD79a (clone JCB117, dilution, 1:200; M7050), Ki-67 (clone MIB1, dilution, 1:100; F726801-8). In-situ hybridization (ISH) for EBER was detected in all cases, according to the manufacturer's protocol. Tumor cells that only appeared to have distinct nuclear staining were recorded as positive. The paraffin sections were detected for EBER by a peptide nucleic acid probe (Dako-Y5200) labeled with fluorescein isothiocyanate, followed by anti-rabbit immunoglobulin (Ig)G with horseradish peroxidase. 3,30-Diaminobenzidine was used to detect the hybridization signal of chromogen detection. EBV positive nasopharyngeal carcinoma paraffin specimens were used for positive controls. The entire pathological tissue slices of immunostaining of Ki-67 were observed under a light microscope (magnification, x100; Olympus BX51; Olympus Corporation, Tokyo, Japan), regions of active growth of tumor cells were chosen and observed (magnification, x400; Olympus BX51; Olympus Corporation), at least 5 high power fields were further randomly selected, then the percentage of ki-67 positive tumor cells (ki-67 index) was recorded as a proliferation fraction.

Staging, treatment and treatment response. Disease stages were defined according to the Ann Arbor system (11). Updated National Comprehensive Cancer Network guidelines were consulted for patient treatments (12). Treatment responses were defined according to previously reported criteria (13). Overall survival (OS) was measured from the time of diagnosis to the date the patient succumbed from any cause or to the date of the last follow-up.

Statistical analysis. For statistical analyses, the patients were divided into indolent and aggressive lymphoma groups based on their pathological results. The clinical characteristics of all PP-NHL cases were summarized using the median and percentages, and were compared using Fisher's exact test. Survival curves were analyzed using the Kaplan-Meier method. Univariate analyses were performed to examine the survival of patients with different prognostic factors, including age, sex, symptoms, comorbidities, treatment, stage, hilar or mediastinal lymphadenopathy, histology, lactate dehydrogenase (LDH) levels, and unilateral or bilateral lesions. Cox proportional hazards regression analysis with a forward stepwise selection procedure was used to estimate OS and was adjusted for a number of independent

Table I. Demographics and clinical characteristics of the 29 subjects.

Characteristics	Indolent lymphoma	Aggressive lymphoma	Total	P-value
Total patients, n	15	14	29	-
Age, years				-
Mean (range)	51.73 (31-72)	47.93 (19-87)	50.3 (19-87)	0.45
>60, n (%)	7 (46.7)	5 (35.7)	12 (41.4)	0.31
Sex, n				-
Male	8 (53.3)	11 (78.6)	19 (65.5)	0.63
Female	7 (46.7)	3 (21.4)	10 (34.5)	0.57
Symptoms, n (%)				-
Asymptomatic	4 (26.7)	0 (0.0)	4 (13.8)	-
B symptoms	2 (13.3)[a]	10 (71.4)[a]	12 (41.4)	0.02
Respiratory	11 (73.3)	14 (100.0)	25 (86.2)	0.73
High serum LDH level, n (%)	3 (20.0)[a]	10 (71.4)[a]	13 (44.8)	0.01
Bone marrow involvement, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	-
EBERs, n (%)	0 (0.0)	6 (42.9)	6 (20.7)	-
Comorbidity[b], n (%)	1 (6.7)	3 (21.4)	4 (13.8)	-
Ann Arbor stage, n (%)				-
IE	11 (73.3)	6 (42.9)	17 (58.6)	0.50
II (1E-2E)	4 (26.7)	8 (57.1)	12 (41.4)	0.44
Initial clinical diagnosis, n (%)				
Pneumonia	4 (26.7)	5 (35.7)	9 (31.0)	-
Tuberculosis	1 (6.7)	2 (14.3)	3 (10.3)	-
Pulmonary abscess	2 (13.3)	1 (7.1)	3 (10.3)	-
Lung cancer	8 (53.3)	6 (42.9)	14 (48.3)	-

B symptoms included fever (9/25), weight loss (3/25), and night sweats (1/25). Respiratory symptoms included cough (23/25), sputum (13/25), chest pain (6/25), hemoptysis (2/25) and dyspnea (11/25). [a]P<0.05. [b]Comorbidity was mainly associated with autoimmune disorders, including dermatomyositis, SLE, systemic sclerosisandpolyarteritis nodosa. LDH, lactate dehydrogenase; EBERs, EBERs, EBV-encoded mRNAs.

factors with P<0.1 by univariate analysis. Two-tailed tests with P<0.05 were considered to indicate a statistically significant difference. Statistical analyses were performed using SPSS 13.0 (SPSS, Inc.).

Results

Demographic and clinical characteristics at initial clinical diagnosis. As presented in Table I, this study included a total of 29 patients with PP-NHL (10 female and 19 male; mean, 50.3 years; range, 19-87 years), including 15 patients with indolent disease and 14 with aggressive disease. Of these, 4 patients (13.8%) were asymptomatic and were incidentally diagnosed during radiographic examination. Patients with aggressive lymphoma were approximately 3-4 times more likely to exhibit elevated LDH levels and systemic symptoms (B symptoms) at diagnosis compared with patients with indolent lymphoma (71.4% vs. 20.0%; P=0.01; and 71.4% vs. 13.3%; P=0.02, respectively). There were no significant differences in respiratory symptoms, age or stage between the two groups. The rate of initial clinical misdiagnosis was 100% prior to biopsy or surgery, including false diagnoses of lung cancer (48.3%; 14/29), pneumonia (31.0%; 9/29), tuberculosis (10.3%; 3/29), and pulmonary abscess (10.3%; 3/29).

Chest radiographic findings. As presented in Table II and Fig. 1, the radiographic findings were both diverse and non-specific. The most common radiological finding was pulmonary nodules/masses (55.2%; 16/29), followed by pulmonary consolidation (41.4%; 12/29), mediastinal/hilar lymph node involvement (41.4%; 12/29), pleural effusion (24.1%; 7/29), air bronchogram (17.2%; 5/29) and cavitation (6.9%; 2/29).

Diagnostic procedures. As presented in Table II, while endobronchial biopsy and transbronchial lung biopsy (TBLB) resulted in diagnostic yields of 80% (12/15), CT-guided percutaneous needle lung biopsy (11/11) and surgery (8/8) obtained diagnostic yields of 100%. In addition, 3 patients received the same final diagnosis from two different procedures, with 2 patients receiving the same diagnosis by bronchoscopic biopsy and CT-guided percutaneous needle lung biopsy, and 1 patient receiving the same diagnosis by TBLB and pleural biopsy. The diagnoses of the remaining 8 patients were validated by either open lung biopsy (n=3) or VATS (n=5).

Histopathological outcomes. As presented in Table II and Fig. 2, the present study consisted of 15 cases of indolent lymphoma (MALT lymphoma, n=13; FL, n=2) and 14 cases of aggressive lymphoma (DLBCL, n=6; ALCL, n=4; PTCL-U,

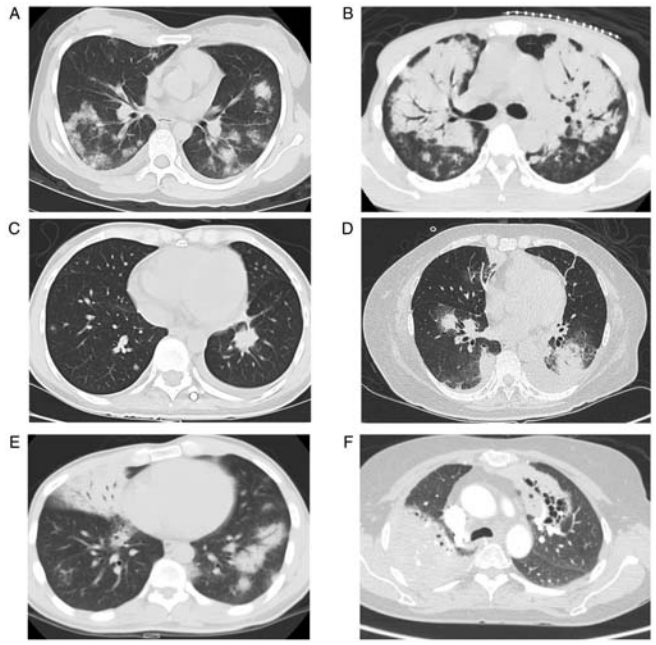

Figure 1. Thoracic computed tomography scans of patients with primary pulmonary non-Hodgkin's lymphoma. (A) Anaplastic large-cell lymphoma with multiple bilateral pulmonary infiltrates. (B) Peripheral T-cell lymphoma-unspecified with bilateral pulmonary consolidation, with air bronchogram. (C) Diffuse large B-cell lymphoma with multiple bilateral pulmonary nodules. (D) Natural killer/T-cell lymphoma with multiple masses, with a halo of ground-glass opacities, air bronchogram and a non-specific 'crazy paving' pattern in both lungs, plus small left pleural effusions. Mucosa-associated lymphoid tissue with (E) multiple bilateral pulmonary nodules and consolidation with air bronchogram, and (F) a mass with calcification in the right upper lobe, as well as patchy shadows with a honeycomb pattern in the left upper lobe.

n=1; extranodal nasal NK/T-L, n=3). No lymphoma cells were identified in any patient by bone marrow biopsy or aspiration. The diagnosis of NHL was first confirmed by morphological and growth pattern characterization based on HE staining. For example, diffuse small and medium-sized lymphoid cells were observed to have infiltrated the area surrounding the bronchus, lymphoepithelial lesions were observed and mitoses were rare in primary pulmonary MALT lymphoma; neoplastic cells were medium to large in size, with abundant pale cytoplasm and ovoid or irregular nuclei in primary pulmonary diffuse large B-cell lymphoma; diffuse lymphoid infiltration in the bronchial mucosa was observed, the neoplastic cells appeared homogeneous and were medium-sized with irregular nuclei, coagulative necrosis and apoptotic bodies were common in primary pulmonary NK/T-cell lymphoma, nasal type. The diagnosis was further differentiated by immunohistochemistry or ISH staining to establish the lymphoma subtype. Normal IHC results were as follows: i) MALT lymphoma: $CD20^+$, $CD3^-$, $CD5^-$, $CD10^-$, $CD23^-$, $CyclinD1^+$ and λ light-chain restriction$^+$; ii) FL: $CD20^+$, $CD10^+$, $BCL2^{+/-}$, $BCL6^+$, $CD5^-$, $CD23^-$, $CyclinD1^-$; iii) DLBCL: $CD20^+$, high Ki-67 index; iv) ALCL: Positive for T-cell markers, strong punctate membranous and paranuclear CD30 staining, strong cytoplasmic anaplastic lymphoma kinase staining; v) PTCL: Positive for T-cell markers, with no other characteristic positive markers; and vi) NK/T: $CD2^+$, cytoplasmic $CD3\varepsilon^+$, $CD56^+$ and EBV-encoded mRNA positivity required for diagnostic confirmation.

Treatments and responses. The majority of patients were treated with first-line chemotherapy, either cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or CHOP-like, including etoposide, doxorubicin, vincristine, prednisone and cyclophosphamide (EPOCH), regimens. A total of 8 patients underwent partial or complete surgical resection of lung lesions followed by chemotherapy, while 2 patients received radiotherapy with subsequent chemotherapy and 10 patients received chemotherapy alone. Overall, 4 patients received rituximab combined with CHOP therapy (median, 5 cycles; range, 2-9 cycles) and 2 patients were treated with rituximab alone. The objective response rate to chemotherapy was higher in the indolent lymphoma group than in the aggressive lymphoma group (67% vs. 7.1%, respectively; $P<0.05$). A total of 7 patients diagnosed with primary pulmonary MALT lymphoma were under watchful waiting and clinical observation only.

Survival time. At the time of final contact (June 30, 2017), 7 patients with primary pulmonary MALT lymphoma remained alive. The respective 1-, 3- and 5-year OS rates were 42, 31 and 21% for all patients, 72, 57 and 43% for patients with indolent lymphoma, and 13, 6 and 0% for patients with aggressive lymphoma. The median OS time for all patients was 12.0 months (95% confidence interval, 4.1-19.9 months). The median OS of patients with aggressive lymphoma was significantly shorter compared with that of patients with indolent lymphoma (7.1 months vs. 16.6 months; $P=0.002$; Fig. 3). OS times were compared across the indolent lymphoma group to assess therapeutic efficacy, and it was indicated that surgery and subsequent chemotherapy was not superior to other treatment regimens (14.2 months vs. 9.3 months; $P=0.412$). These other treatments regimens included chemotherapy alone, chemoradiotherapy and observation. In the aggressive lymphoma group, the OS time was not significantly increased for patients receiving chemotherapy alone compared with that for patients receiving other therapies, including surgery and subsequent chemotherapy or chemoradiotherapy (4.0 months vs. 2.6 months; $P=0.856$).

Prognostic factors. As presented in Table III, univariate analyses were used to evaluate a number of factors that contributed to OS. A poor 5-year OS rate was indicated to be significantly associated with aggressive lymphomas ($P=0.005$), but it was not significantly associated with bilateral pulmonary lesions ($P=0.05$). Due to the relatively small number of cases, only factors, including pathological type, sex and pulmonary lesions, with $P<0.1$ were included in the multivariate Cox regression analysis. Aggressive pathological type was an independent prognostic factor for 5-year survival (hazard ratio, 5.98; $P=0.014$), suggesting poor prognoses for patients with aggressive lymphoma compared with patients with indolent lymphoma.

Discussion

The low early diagnosis rate of PP-NHL remains a serious issue and presents a challenge for clinicians. Three factors may be responsible for poor early diagnosis rates. First, patients with PP-NHL often have non-specific clinical manifestations.

Table II. Chest radiographic findings, diagnostic procedures and pathological types of the 29 subjects.

Group	Indolent lymphoma, n (%)	Aggressive lymphoma, n (%)	Total, n (%)
Total patients	15 (51.7)	14 (48.3)	29 (100.0)
Radiographic findings			
Unilateral	9 (60.0)	5 (35.7)	14 (48.3)
Bilateral	6 (40.0)	9 (64.3)	15 (51.7)
Nodule/mass	9 (60.0)	7 (50.0)	16 (55.2)
Consolidation	5 (33.3)	7 (50.0)	12 (41.4)
Air bronchogram	1 (6.7)	4 (28.6)	5 (17.2)
Pleural effusion	5 (33.3)	2 (14.3)	7 (24.1)
Cavitation	2 (13.3)	0 (0.0)	2 (6.9)
Mediastinal/hilar lymphadenopathy	4 (26.7)	8 (57.1)	12 (41.4)
Definitive diagnostic procedures			
Endobronchial or transbronchial biopsy	7 (46.6)	5 (35.7)	12 (41.4)
CT-guided percutaneous needle biopsy	2 (13.3)	9 (64.3)	11 (37.9)
Open lung biopsy	3 (20.0)	0 (0)	3 (10.3)
VATS	4 (26.7)	1 (7.1)	5 (17.2)
Pleural biopsy	1 (6.7)	0 (0)	1 (3.4)
Pathological types			
MALT	13 (86.7)	0 (0)	13 (44.8)
FL	2 (13.3)	0 (0)	9 (31.0)
DLBCL	0 (0)	6 (42.9)	6 (20.7)
ALCL	0 (0)	4 (28.6)	4 (13.8)
PTCL-U	0 (0)	1 (7.1)	1 (3.4)
Extranodal nasal NK/T	0 (0)	3 (21.4)	3 (10.3)

CT, computed tomography; VATS, video-assisted thoracic surgery; MALT, mucosa-associated lymphoid tissue; FL, follicular lymphoma; DLBCL, diffuse large B cell lymphoma; ALCL, anaplastic large cell lymphoma; PTCL-U, peripheral T-cell lymphoma, unspecified; NK/T, natural killer/T-cell lymphoma.

In the present study, 31% (4/13) of patients with primary pulmonary MALT lymphoma were asymptomatic at diagnosis. This rate was lower compared with the rates recorded in other reports (36 and 88%, respectively) (14,15). However, similar to previous reports, it was indicated that patients with aggressive lymphomas, including primary pulmonary DLBCL and ALCL, presented with elevated LDH levels and systemic symptoms more frequently compared with patients with indolent lymphoma (16-18).

Second, radiographic findings in patients with PP-NHL are generally non-specific (19). CT findings in pulmonary lesions may co-exist in a number of manifestations. The most common CT findings in the present patients were nodules/masses, followed by mediastinal/hilar lymph node enlargement, consolidation, pleural effusion, air bronchogram and cavitation. In the present study, the initial diagnoses of all patients were misleading. Although the radiographic findings were atypical, there were number of hints suggesting PP-NHL, including a fuzzy shadow at the edge of the lung mass with air bronchogram, long-term stability of the lung mass shadow and a pneumonia-like presentation without infectious clinical or lab manifestations. These radiographic findings resembled a spectrum of other pulmonary diseases, including lung cancer, metastatic tumors, pneumonia, pulmonary tuberculosis and pulmonary abscesses (20). We believe that PP-NHL should be considered in the differential diagnosis of a pulmonary lesion, in particular for patients with long-lasting pulmonary shadows, systemic symptoms, including fever, weight loss and night sweats, elevated LDH levels or poor responses to antibiotic treatments.

Third, it remains challenging to definitively pathologically diagnose certain patients. In the present study, the diagnostic yields of the bronchoscopy and CT-guided percutaneous needle lung biopsies were considerably higher compared with a number of previously reported yields (2,9). Based on our experience, the following is suggested: i) A thin spiral thoracic CT scan and bronchoscopy should be performed to determine the lesion location and size, as well as pathological changes in the bronchial mucous; ii) based on the results of the CT scan and bronchoscopy, endobronchial biopsy or TBLB is the optimal approach for central pulmonary lesions or bronchial mucosal lesions, whereas CT-guided percutaneous needle lung biopsy is more suitable for peripheral pulmonary lesions, particularly for lesions close to the chest wall; iii) ≥2 TBLB or CT-guided percutaneous needle lung biopsies may improve the diagnostic yield; iv) a combination of bronchoscopy and CT-guided percutaneous needle lung biopsies may also increase the diagnostic yield; and v) surgical procedures, including lobectomy under

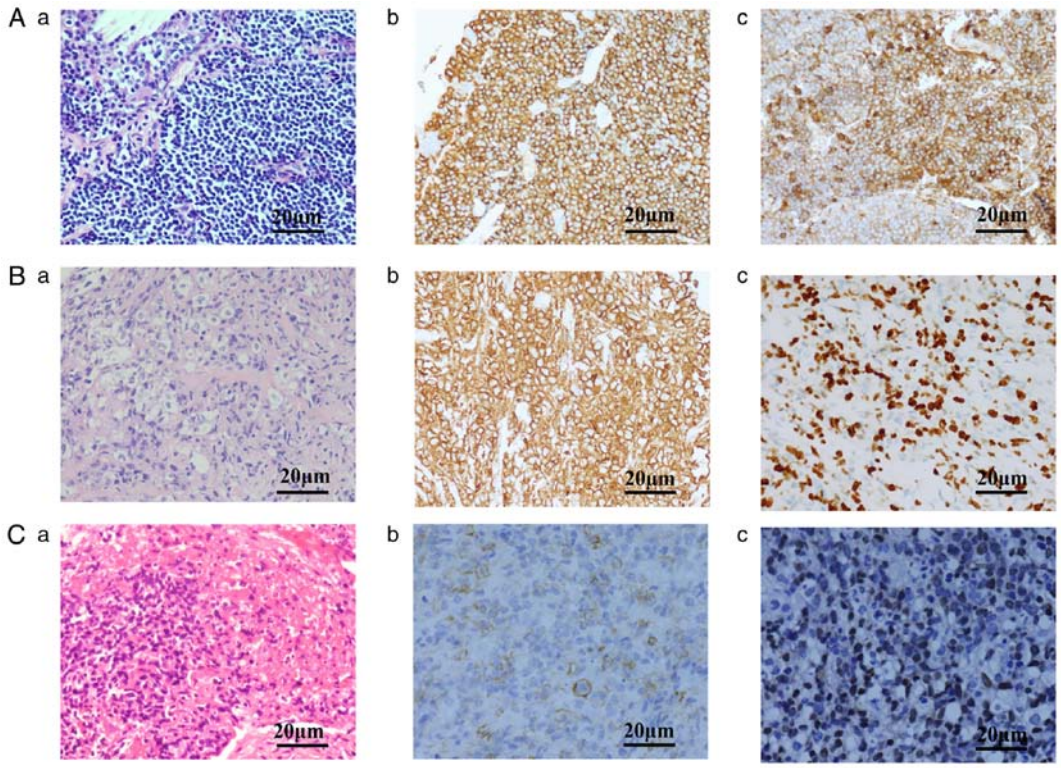

Figure 2. Hematoxylin-eosin, immunohistochemistry or *in situ* hybridization staining of specimens from patients with primary pulmonary non-Hodgkin's lymphoma. (A) Primary pulmonary mucosa-associated lymphoid tissue. (Aa) Diffuse small and medium-sized lymphoid cells were observed to have infiltrated the area surrounding the bronchus. Lymphoepithelial lesions were observed and mitoses were rare. Lymphoma cells indicated (Ab) strong CD20 staining and (Ac) λ light-chain restriction. (B) Primary pulmonary diffuse large B-cell lymphoma. (Ba) The neoplastic cells were medium to large in size, with abundant pale cytoplasm and ovoid or irregular nuclei. The neoplastic cells exhibited (Bb) strong CD20 staining and (Bc) a high Ki-67 proliferative index. (C) Primary pulmonary NK/T-cell lymphoma, nasal type. (Ca) Diffuse lymphoid infiltration in the bronchial mucosa was observed. The neoplastic cells appeared homogeneous and were medium-sized with irregular nuclei. Coagulative necrosis and apoptotic bodies were common. Except for the positive CD3 staining, the neoplastic lymphoid cells exhibited characteristics typical of NK/T-cell lymphoma, namely, (Cb) CD56 and (Cc) Epstein-Barr encoding region positivity. Magnification, x400. NK/T-cell lymphoma, natural killer/T-cell lymphoma.

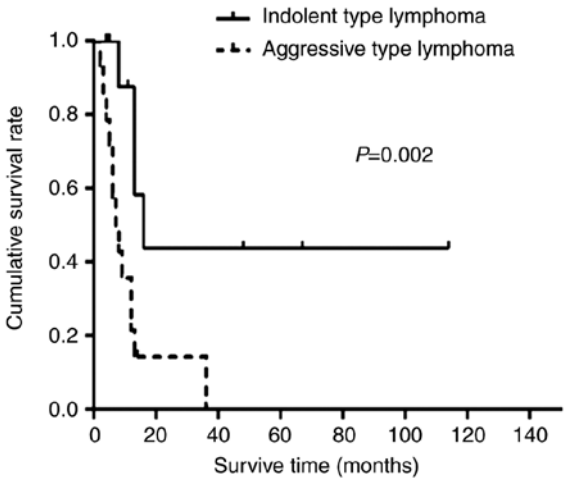

Figure 3. Cumulative survival curves for the 29 patients with primary pulmonary non-Hodgkin's lymphoma stratified by indolent vs. aggressive lymphoma classification.

VATS and conventional surgery, are more invasive and have a higher surgical risk compared with other procedures. Therefore, strict patient screening should be considered if only using these procedures for diagnosis. However, a large sample size and high diagnostic yield can be obtained by surgery. If positive specimens cannot be obtained, VATS should be selected, since it is safer and less invasive compared with conventional surgery. Clonal analysis of alveolar lymphocytes using bronchoalveolar lavage fluid (BALF) has been recently suggested to be helpful in diagnosing PP-NHL (21,22), although BALF alone may not be sufficient for morphological analysis (23). PET-CT may be helpful for initial staging and evaluation of the response to chemotherapy (24). In our opinion, without tissue pathology analysis, the initial false-positive rate can be as high as 100%; therefore, it is critical to determine the optimal procedure resulting in a definitive pathological diagnosis. Minimally invasive procedures, confirmed by flexible fiberoptic bronchoscopy and CT-guided percutaneous needle lung biopsy, were found to be helpful and reliable procedures, and should be preferentially considered to obtain pathological diagnoses in patients with PP-NHL. Additionally, diagnostic yields will increase with repeated biopsies. Each specimen collection method has its own advantages and disadvantages and therefore requires comprehensive consideration prior to use.

The optimal modality for managing PP-NHL has not yet been determined (10). For MALT, the most common indolent type of PP-NHL, the following should be considered: Complete surgical resection should be utilized for localized tumors (25,26), chemotherapy should be utilized for patients exhibiting diffuse involvement of one or both lungs (9), and a combination of radiotherapy and alkylating drug-based

Table III. Five-year survival rates of the 29 subjects in terms of various prognostic factors.

Factors	5-year survival rate, %	Univariate analyses P-value	Multivariate analyses P-value
Age			
≥60 years vs. <60 years	19 vs. 19	0.54	-
Sex			
Male vs. female	11 vs. 29	0.09	0.26
Asymptomatic at diagnosis			
Yes vs. no	0 vs. 19	0.56	-
B symptoms			
Yes vs. no	21 vs. 20	0.66	-
Histology			
Indolent vs. aggressive	43 vs. 0	0.005	0.014
Elevated serum LDH			
Yes vs. no	0 vs. 22	0.87	-
Hilar or hilar lymphadenopathy			
Yes vs. no	15 vs. 20	0.66	-
Lesions			
Bilateral vs. unilateral	19 vs. 21	0.05	0.39
Comorbidity			
Yes vs. no	16 vs. 25	0.49	-
EBERs			
Positive vs. negative	0 vs. 21	0.35	-
Stage			
I E vs. ≥II (1E-2E)	27 vs. 12	0.12	-
Surgery followed by chemotherapy			
Yes vs. no	20 vs. 18	0.22	-
Chemotherapy alone			
Yes vs. no	20 vs. 17	0.52	-

B symptoms included fever (9/25), weight loss (3/25) and night sweats (1/25). LDH, lactate dehydrogenase; EBERs, EBV-encoded mRNAs.

chemotherapy should be utilized to preserve lung function and reduce the risks associated with surgery (25). In addition, adjuvant chemotherapy followed by radical resection may not provide additional survival benefits (27). In the present study, the 6 patients with MALT lymphomas, who underwent surgery followed by chemotherapy, exhibited increased OS times compared with patients receiving other treatments; however, this difference was not significant. Furthermore, the role of rituximab remains controversial (15,16). Only 4 patients were treated with rituximab, and its efficacy could not be adequately evaluated in the present study due to the small sample size. Clinical observations of early-stage or indolent lymphomas are also advisable (26); therefore, a total of 7 patients diagnosed with primary pulmonary MALT lymphoma were under watchful waiting and clinical observation only in the present study. Regarding aggressive lymphomas, including DLBCL, combination chemotherapy regimens are often administered following attempts at curative surgical resection (23). CHOP or rituximab-CHOP combined with radiotherapy has previously been recommended for patients with aggressive lymphomas, radiotherapy was used to treat those patients who exhibited chemotherapeutic resistance, and dose-adjusted EPOCH was recommended as an alternative regimen (28). Although chemotherapy or radiotherapy should be considered for unfavorable primary pulmonary non-MALT lymphomas (2), in the present study, the objective response rate (7.1%) to the treatment of primary pulmonary aggressive lymphomas was inadequate. It was speculated that a combinatorial therapeutic regimen, including surgical resection, chemotherapy and radiotherapy, may be more efficacious for patients with a more aggressive form of the disease. The following two unusual phenomena were also observed in the present study: The complete response rate among the patients with aggressive PP-NHL was considerably lower compared with that observed in patients with systemic aggressive lymphoma, and ALCL cases constituted 14% of PP-NHL cases, which was considerably higher compared with the 2% ALCL cases observed among systemic NHL cases. It was also proposed that PP-NHL exhibits biological traits that are distinct from those of systemic NHL, and that a number of NHL pathological types tend to involve specific organs, including ALCLs, which tend to primarily involve the lung. A total of 75% (3/4) patients with ALCL

in the present study were <30 years old, which is consistent with the fact that ALCL usually occurs in young people or the elderly (29); thus, the small sample size of the present study may not truly reflect the real situation.

The survival times of patients with PP-NHL varied due to the heterogeneous patient groups. Overall, the median time to mortality was 7 years, the 3-year OS rate was 86% and the 5-year OS rate was 57-75% (2,30). For patients with indolent lymphomas, including MALT lymphomas, the survival rates were 68% at 5-year and 53% at 10-year (6). By contrast, aggressive lymphomas, including DLBCL, tended to be more diffuse and destructive, with 5-year survival rates ranging from 0-65% (31). In the present study, the respective 3-year and 5-year OS rates were 31 and 21% for all patients, 57 and 43% for patients with indolent lymphomas, and 6 and 0% for patients with aggressive lymphomas. Although the median survival time, 3-year OS rate and 5-year OS rate were poor in the present study compared with those in previous studies, the present study demonstrated that patients with indolent lymphomas exhibited an improved 5-year OS rate (43% vs. 0, P=0, 0.005) compared with patients with aggressive lymphomas, which is consistent with a previous report (8). The small sample size, the differences between Chinese and Caucasian patients, and the poor economic conditions may have contributed to the observed differences in disease control and survival.

Previous studies have not adequately defined the PP-NHL prognostic factors affecting patient survival. These studies reported that lymphoma stage, extent of resection and presence of mediastinal lymphadenopathy were not associated with poor prognosis (27). Another relevant report indicated that elevated serum LDH levels and hilar/mediastinal lymphadenopathy were independently associated with poor OS rate (18). In the present study of 29 cases, univariate analyses revealed that the 5-year OS rate of patients with aggressive lymphomas was significantly worse compared with that of patients with indolent lymphomas. Furthermore, the multivariate Cox regression analysis demonstrated that histological type was the only factor influencing OS and prognosis, i.e., patients with aggressive lymphomas presented with worse outcomes compared with patients with indolent lymphomas. These results are similar to the results of a French multicenter retrospective study (8). Therefore, attempts to procure adequate pathological tissue samples are critical in order to ensure accurate early diagnoses are made and to avoid misdiagnoses, thus directly affecting the therapeutic outcomes and prognosis of patients with PP-NHL.

In conclusion, PP-NHL is difficult to diagnose due to its rarity, non-specific clinical manifestations and atypical radiographic findings. Obtaining a suitable tissue sample is vital to making a definitive diagnosis. Endobronchial biopsy or TBLB and CT-guided percutaneous needle lung biopsy should be performed to facilitate a definitive diagnosis for the majority of patients with PPL. However, the optimal modality for managing PP-NHL has not yet been established. The present study is limited by its retrospective nature and small sample size. The study systematically assessed the clinical features, laboratory and imaging data, pathological characteristics, therapeutic outcomes and prognostic factors of PP-NHL, and indicated that pathological lymphoma type was highly associated with patient prognosis. Lymphoma aggressiveness was indicated to be an independent prognostic factor for 5-year OS, as patients with aggressive lymphomas had shorter 5-year OS rates and worse prognoses compared with patients with indolent lymphomas. Therefore, although further investigation is required, the present study may provide clinicians, pathologists and radiologists with useful guidance for the diagnosis and treatment of patients with PP-NHL.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JW, XG, XF, JD, HA, QL and WL collected the clinical records of all patients and participated in the design of the study. DL performed the pathological diagnosis of all cases. JZ analyzed the roentgenographic findings for all patients. JQ and JW summarized and analyzed the clinical data from all patients, and drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the clinical research Ethics committee of Guangdong Provincial People's Hospital/Guangdong Academy of Medical Sciences (Guangzhou, Guangdong, China). Informed consent was obtained from all subjects prior to participation in the study.

Patient consent for publication

Patient consent for publication was obtained for the thoracic computed tomography scans.

Competing interests

The authors declare that they have no competing interests.

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