ERJ Express. Published on June 18, 2009 as doi: 10.1183/09031936.00039309

Clinical characteristics and prognostic factors of pulmonary MALT lymphoma

Raphaël Borie[1, 2], Marie Wislez[1], Gabriel Thabut[3], Martine Antoine[4], Antoine Rabbat[5], Louis-Jean Couderc[6], Isabelle Monnet[7], Hilario Nunes[8], François-Xavier Blanc[9], Hervé Mal[3], Anne Bergeron[10], Daniel Dusser[11], Dominique Israël-Biet[12], Bruno Crestani[2], Jacques Cadranel[1].

1. Service de Pneumologie et Réanimation, Centre de Compétence Maladies Rares Pulmonaires, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris and Faculté de Médecine Pierre et Marie Curie, Université Paris VI, France

2. Service de Pneumologie A, Centre de Compétence Maladies Rares Pulmonaires, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France

3. Service de Pneumologie B, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France

4. Service d'Anatomie-Pathologique, Hôpital Tenon, Assistance Publique-Hôpitaux de Paris, Paris, France

5. Service de Pneumologie et Réanimation, Hôpital Hôtel-Dieu, Assistance Publique-Hopitaux de Paris and Université René Descartes Paris V, France

6. Service de Pneumologie, Hôpital Foch, Suresnes and Faculté Paris-Ile de France-Ouest, Versailles, France

7. Service de Pneumologie, Centre Hospitalier Intercommunal de Créteil, France.

8. Service de Pneumologie, Centre de Compétence Maladies Rares Pulmonaires, Hôpital Avicenne, Assistance Publique-Hôpitaux de Paris and UPRES EA 2363, Université Paris 13, Bobigny, France

9. Unité de Pneumologie, Service de Médecine Interne, Hôpital Bicêtre, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France

10. Service de Pneumologie, Hôpital Saint-Louis, Assistance Publique-Hôpitaux de Paris, France

11. Service de Pneumologie, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, France

12. Service de Pneumologie, Centre de Compétence Maladies Rares Pulmonaires, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris, France

Address for correspondence : Pr Jacques Cadranel, Service de Pneumologie et Réanimation, Hôpital Tenon, 4 rue de la Chine 75970 cedex 20, Paris, France.

Phone : 331 56 01 65 31 ; Fax : 331 01 56 01 69 91 ;

mail : jacques.cadranel@tnn.aphp.fr

There were no potential conflicts of interest and no financial support

Running head: Pulmonary MALT Lymphoma

Number of word: **3577**

Abstract

MALT lymphoma, a low grade B-cell extranodal lymphoma, is the most frequent subset of primary pulmonary lymphoma. Our objective was to evaluate the initial extent of disease and to analyze the characteristics and long-term outcome of these patients.

All chest and pathological departments of teaching hospitals in Paris were contacted to identify patients with a histological diagnosis of primary pulmonary lymphoma of the MALT subtype.

Sixty-three cases were identified. The median age was 60 years. Thirty-six percent of cases had no symptoms at diagnosis. Forty-six percent of patients had at least one extra-pulmonary location of lymphoma. The estimated 5- and 10-year overall survival rates were 90% and 72%, respectively. Only two of the nine observed deaths were related to lymphoma. Age and performance-status were the only 2 adverse prognostic factors for survival. Extra-pulmonary location of lymphoma was not a prognostic factor for overall survival nor progression-free survival. Treatment with cyclophosphamide or anthracyclin was associated with shorter progression-free survival, when compared to chlorambucil.

The survival data confirm the indolent nature of pulmonary MALT lymphoma. Better progression-free survival was observed with chlorambucil when compared to cyclophosphamide or anthracyclin.

Abstract word count 186

Key words: pulmonary lymphoma, MALT lymphoma, prognostic, chorambucil

Introduction

Mucosa-associated lymphoid tissue-derived (MALT) lymphoma is the most frequent subset of primary pulmonary lymphoma. Gastro-intestinal tract involvement is the most frequent primary location, with lung location representing 15% of cases [1]. Gastric MALT lymphoma is a disseminated disease in less than 25% of cases [2]. The frequency of disseminated disease in pulmonary MALT lymphoma seems to be higher [1, 3], even if it has not been specifically evaluated.

MALT lymphoma is a low grade B-cell extranodal lymphoma characterized by a proliferation of clonal marginal zone lymphocytes (MZL) [4, 5] that invade epithelial structure and form characteristic lymphoepithelial lesions. Numerous evidences demonstrate that MZL are associated with chronic antigenic stimulation either by autoantigen or pathogen, leading to the accumulation of lymphoid tissue in involved organs [6, 7]. *Helicobacter pylori* (HP) is the best characterized causative pathogen and is responsible for gastric MALT lymphoma [8]. Other chronic infections seem associated with MALT-derived lymphoma at other sites, even if their roles in pathogenesis are not as firmly established as for HP [7]. However, an association between a specific pathogen and lung MALT lymphoma has never been shown.

Patients with MALT lymphoma have a favorable outcome with a 5-year overall survival of more than 85%. Survival does not differ between gastro-intestinal and non-gastrointestinal lymphoma and between localized and disseminated disease [1, 3, 9]. HP eradication leads to the regression of gastric lymphoma in 35 to 75% of cases [10-12] while the standard of care for other MALT lymphomas has not been defined.

We therefore undertook this retrospective study to evaluate the initial dissemination of pulmonary MALT lymphoma and the long-term outcomes for these

patients according to their clinical presentation and treatment. We also evaluated whether our patients shared some characteristics leading to a common pathogenesis in pulmonary MALT lymphoma.

Patients and Methods

All chest departments in adult teaching hospitals in Paris were contacted (n=15), in order to identify patients who had been diagnosed as having pulmonary MALT lymphoma, between January 1993 and February 2008. Moreover, the pathological departments attached to each hospital were asked to report their cases of histological pulmonary MALT lymphoma diagnosed during the same period of time.

Inclusion criteria

To be included in the study, patients had to have an initial pulmonary lesion assessed by CT scan without extra-pulmonary node involvement or chronic lymphocytic leukaemia, the diagnosis of MALT being histologically proven according to the WHO classification [4, 13], on a pathological lung lymphoma specimen. Exclusion criteria were as follows: 1) presentation of another histological type of lymphoma, including diffuse large B-cell lymphoma; 2) pulmonary relapse of MALT lymphoma without any evidence of an initial pulmonary lesion.

The clinical charts of the patients were reviewed by one of us (RB) to check all the inclusion criteria. Data were collected on a standardized and anonymous collection form. For this retrospective, observational, non-interventional analysis of medical records, French law does not require a specific approval of an Internal Review Board or the consent of patients.

Data collection

The following data were collected at the time of diagnosis: clinical parameters (age, gender, other diseases, presence of “B“ symptoms, delay between first symptoms and diagnosis, complete physical examination), Performance Status (PS) evaluated according to the Eastern Cooperative Oncology Group (ECOG), and biological parameters (serum lactic dehydrogenase (LDH), serum protein electrophoresis and blood cell count).

Staging was evaluated by computed tomography (CT) scan of the thorax, abdomen, and pelvis, endoscopic examination of the gastrointestinal tract with systematic biopsies including evaluation of HP infection status, and bone marrow biopsy. All chest CT-scans were analyzed by radiologists attending to the various chest departments from the teaching hospitals and were reviewed by one of us (RB). Pulmonary abnormalities were interpreted as previously described [14]. Pathological reports were centrally reviewed by a pathologist expert in oncology (MA).

Outcome data were collected at 3, 6 and 12 months and every 6 months thereafter until death or the last scheduled visit. Responses to treatment were based on the original data recorded by the local physician. Evaluation after treatment was classified as recommended by the 2007 International Working Group criteria for malignant lymphoma [15]. Complete remission was defined as the disappearance of all clinical, biological and morphological evidence of lymphoma. Partial remission was defined as a decrease in tumor volume higher than 50%, assessed by CT-scan evaluation. Disease control was defined as the sum of partial and complete remission. Progression was defined as the appearance of any new lesion or at least a 50% increase in tumor volume [15]. The transformation of MALT lymphoma to diffuse large B-cell lymphoma had to be demonstrated histologically, and referred to

the presence of 50% blast cells or the presence of sheets of large cells associated with high mitotic activity [1]. For statistical analysis, treatments were regrouped as follows: 1) chlorambucil group : patients treated by chlorambucil-based chemotherapy (chlorambucil alone or combined with rituximab); 2) cyclophosphamide group : patients treated by cyclophosphamide-based chemotherapy (cyclophosphamide alone or combined with vincristine and/or rituximab); 3) anthracycline/fludarabine group : patients treated by anthracycline- or fludarabin-based chemotherapy with or without rituximab; 4) local therapy group : patients treated by surgery or radiotherapy; and 5) abstention.

Statistical analysis

Continuous variables were expressed as the median (range) and compared by the Mann-Whitney U test. Categorical variables were expressed as counts and proportions and compared by the Fisher's exact test. Progression-free survival (PFS) was defined from diagnosis until lymphoma progression, relapse or death. Overall survival (OS) was defined as the time from diagnosis (first biopsy) to death or the last follow-up [15]. Survival was assessed using the Kaplan-Meier estimator. We used the Cox proportional hazard model to assess the impact of variables on survival, in univariate and multivariate analysis. For the multivariate model, we considered all variables significant in the univariate analysis at the 20% level, as well as all variables known to be clinically relevant (age and PS). All tests were two-sided, with $p<0.05$ indicating statistical significance. All the analyses involved use of the software R (www.r-project.org, Bell Laboratories).

Results

All 15 centers participated in the study. Four of the fifteen centers did not have any eligible cases. Ninety-six cases of pulmonary lymphoma were reported between January 1, 1993 and February 1, 2008, of which thirty-three were excluded: seventeen because of incomplete initial data (histology or initial thorax CT-scan missing), three because of lack of lung involvement evidenced at initial diagnosis, and thirteen because of inadequate histology. Sixty-three patients completed the inclusion criteria and were therefore evaluated.

Clinical characteristics of the population at initial presentation

Table 1 shows the main clinical characteristics of the patients at presentation. Ten patients had autoimmune disease at diagnosis, including systemic lupus erythematosus (n=2), rheumatoid arthritis (n=1), Sjogren's syndrome (n=5), and four more patients had undifferentiated connective tissue disease close to Sjogren's syndrome [16]. None of the evaluated patients were infected by HIV (0/42 tested), HBV (0/38 tested) or HCV (0/38 tested).

Twenty-three patients (36%) had radiological abnormalities without respiratory or B symptoms. Dry cough and dyspnea were the most frequent respiratory symptoms, found in 26 (41%) and 22 (35%) patients, respectively. Nine patients had prior history of pulmonary infection including tuberculosis in four of them. Weight loss was observed in eight patients (12%), fever in six (9%) and night sweats in three (5%). The median duration between the first symptoms (or radiological abnormalities) and diagnosis was 9.0 months (range: 0.4-229.2). However, the median duration for diagnosis was significantly longer in patients without symptoms (27.4 months, range: 0.4-229.2) than those with symptoms (4.7 months, range: 0.5-62.2 p=0.001).

Blood cell counts and LDH serum level were available for all patients. Sixteen patients had cytopenia at diagnosis, including ten with anemia (range: 8.6-11.9 g/dl), four with thrombocytopenia (range: 131000-149000/ml), and two with mixed thrombocytopenia and anemia. Two patients had elevated LDH serum levels more than 2 times the upper limit. Serum protein electrophoresis was available in 62 cases, of which 20 (32%) showed a monoclonal immunoglobulin, with a median weight of the monoclonal peak of 4.5 g/l (range: 1-20 g/l). Monoclonal immunoglobulin was characterized in 19 cases among which there were, 16 kappa and 3 lambda light chains and 12 mu, 6 gamma and 1 alpha heavy chains, respectively.

Pathological diagnosis of pulmonary MALT lymphoma

Pathological diagnosis of pulmonary MALT lymphoma was obtained by bronchial biopsies in 19 cases (19/61 performed), transbronchial biopsies in 23 cases (23/26 performed), CT-scan guided percutaneous lung biopsies in 8 cases (8/10 performed), and surgical biopsy in 18 cases (18/18 performed). Surgical supplementary specimens were obtained in 9 more cases because of curative surgery (Figure 1). Finally, a pathological specimen from an extra-thoracic MALT lesion was also obtained in 26 out of 63 patients (see below).

All pathological samples showed dense proliferation of small lymphocytes infiltrating the lung and the architecture was deeply reworked in 30 cases. The characteristic lymphoepithelial lesions containing B cells (CD20 or CD19 expression) was observed in 61 cases (96%). B cells was confirmed in 27 cases by a negative CD3 staining and lymphoepithelial lesion was better identified by cytokeratin staining in 17 cases. The neoplastic cells were morphologically centrocyte-like in 75% of samples and monocytoid in 25% of samples. Plasma cells were observed in 44% of

cases. Large cells were absent in 42 samples (66%) and less than 20% in the other samples. Evaluation of monotypic expression was interpretable in 15 cases among which there were 9 kappa and 5 lambda light chains, 6 mu and 2 gamma heavy chains, and 1 and 7 uninterpretable results, respectively. When performed CD5 (0/37), CD10 (0/27), CD23 (0/15), IgD (0/10) and CD30 (0/6) staining were always negative. Expression of bcl2 was performed in 12 cases and positive in 9 (75%).

In this series, EBV expression evaluated by In Situ Hybridization for EBER was always negative (n=5).

Thoracic and extra-thoracic evaluation

All patients underwent thoracic CT scan among which 33 revealed unilateral disease involvement (52%), limited to one lobe in 25 cases (39%). There was no topographic predominance. Mediastinal centrimetric lymph nodes were observed in 10 cases (16%) and pleural effusion in 7 (11%), respectively. According to CT scan analysis, 53 patients (84%) presented multi-pattern abnormalities, consolidations (n=35, 55%), nodules (n=35, 55%) and masses (n=34, 54%) being the most frequent patterns. Fifty-four (86%) patients had airways within the lesions, and the air bronchogramm seemed to be dilated in 42 of them (77%). Micronodules (22%), ground glass opacities (27%), septal lines (12%) were less frequent. Of note CT scan pattern was a solitary pulmonary nodule in only 5 patients (8%).

Twenty-nine patients (46%) had at least one extra-pulmonary location of lymphoma, which was unique for twenty-two of them (Table 2). An extra-pulmonary location of lymphoma was observed more frequently in patients with serum monoclonal immunoglobulin (14/20) than in patients without monoclonal immunoglobulin (14/42, p=0.01). Fifty-seven patients had systematic gastric

endoscopies with histological examination, showing lymphoma involvement in 15 cases (36%). Prevalence of histological HP infection was not significantly different in cases with gastric involvement (5/15, 33%) than in those without (10/42, 24%, p=0.7). Fifty-eight patients had bone marrow biopsies, showing lymphoma involvement in 8 cases (14%).

Fifteen patients had a 18F-fluorodeoxyglucose (FDG) PET-scan. A mild uptake was identifiable in the lung location for 12 (80%) patients. In three patients, no uptake was identifiable in the place of the lymphoma lesion. The PET-scan identified an ignored lymphoma location in two patients, which was confirmed by histology (nodal, n=1 and skin, n=1).

Treatment and outcomes

Treatments and the results of these treatments are summarized in Table 3. Six patients (9.5%) did not receive any treatment. Twenty patients were treated only by local therapy (32%) (surgical resection, n=19; radiotherapy, n=1) and thirty-seven (58.5%) only by chemotherapy. Anthracyclin based-chemotherapy was administered for almost 5 months, cyclophosphamide and chlorambucil for almost 15 months. The disease control rate was significantly better in patients from the chlorambucil group compared to those from the cyclophosphasmide group (p=0.02 vs. chlorambucil), but not significantly different to those from the anthracyclin/fludarabin group (p=0.07 vs. chlorambucil).

With a median follow-up for patients of 47 months (1-192), the estimated 5- and 10-years PFS rates were 51% and 36%, respectively (Figure 2). Proportion of patients with relapse and/or progression by treatment groups are shown in Table 4. It occurred in a known primary involved site in 16 cases (66%) and in a new site in 7

cases (33%). Factors associated with an increased probability of shorter PFS are shown in Table 4. The presence of mediastinal adenopathy was associated with a higher probability of shorter PFS in the univariate analysis (HR=3.5, 95% confidence interval (95%CI):[1.3-9], p=0.01), but was not confirmed in multivariate analysis (p=0.99). Patients from the cyclophosphamide group (HR=6.1, 95%CI:[2-18.6], p=0.001) and the anthracyclin/fludarabin group (HR=4.4, [95% CI:1.3-15.0], p=0.02) had a higher probability of relapse than those from the chlorambucil group (HR=1). Multivariate Cox analysis confirmed that treatments by non-chlorambucil chemotherapy were independent factors associated with shorter PFS (Table 4). Neither age, sex, PS, extra-pulmonary nor medullar location, nor a delay of diagnosis were predictors of PFS.

The median PFS was not achieved in the abstention and local therapy groups with a median of follow-up of 12.5 and 68.2 months, respectively. The median PFS was 8.2 years in the chlorambucil group while it was only 0.7 years in both cyclophosphamide (HR=6.1, 95%CI:[2-18.6] p=0.001) and fludarabin/anthracyclin (HR=4.4, 95%CI:[1.3-15.0] p=0.02) groups, respectively (Table 3).

Death occurred in nine patients but was related to diffuse large B-cell lymphoma transformation of MALT in only two cases. However, it is noteworthy that four of the seven lymphoma-unrelated deaths were due to secondary solid tumors (urinary bladder, kidney, gastric, and colonic). The estimated 5- and 10-year overall survival rates were 90% and 72%, respectively (Figure 3). Age>60 year-old (HR=12.5, 95%CI:[1.5-104.0]) and PS (PS 2 and 3, HR=38.6, 95%CI:[4-374]) were the only two variables associated with shorter survival in the univariate analysis (Table 5). Overall survival was not statistically modified by extra-pulmonary location or the type of treatment (Table 5). Multivariate Cox analysis (including age, PS and

extra-pulmonary location) confirmed that age>60 year-old and PS were independently associated with shorter overall survival (p=0.01 and p=0.02, respectively).

Discussion

This study describes the largest clinical series of pathologically proven pulmonary MALT lymphoma, the most frequent type of non-Hodgkin lymphoma involving the lung. Comparatively to older series [17, 18], most of our patients (71.4%) were diagnosed by a minimal invasive procedure including fiberoptic bronchoscopy bronchial, and transbronchial biopsies and CT-scan guided percutaneaous transthoracic biopsies. This minimal diagnosis approach seems justified as most patients had multi-lobar (61%) or disseminated disease (44%) and an excellent prognosis whatever the therapeutic strategy including abstention, surgery or single agent chemotherapy (see below). Furthermore, it has been facilitated by the use of new biomarkers including anti-cytokeratin antibody to identify lymphoepithelial lesions and CD20/CD19 and CD5 antibodies to identify marginal zone B-cell that may be done on paraffin-embedded tissue specimens [19]. Indeed in the present series, almost all pathological reports showed lymphoepithelial lesion containing dense proliferation of B-cells. The neoplastic cells were morphologically described as centrocyte-like or monocytoid aspect in almost all cases and large cells were either absent or less than 20%. Plasma cells were also found in 44% of cases.

In this study population of 63 patients, 44% of patients had a disseminated disease at diagnosis, which appears greater than the 10% to 34% previously observed in non-gastric MALT lymphoma [1, 3, 20]. By contrast, gastric MALT lymphoma seems a confined disease in approximately 90% of patients [2]. According

to Isaacson, the MALT concept relies on a particular behavior [5] in which dissemination occurs late and after many local relapses. Indeed, the great incidence of disseminated disease in MALT lymphoma of the lung could be explained by the long delay in diagnosis, which can reach more than 25 months in clinically asymptomatic patients.

There is still a controversy about the utility of the PET-scan in evaluating dissemination in MALT lymphoma. MALT lymphoma with indolent growth was expected to have little FDG uptake. In this series, the FDG-PET-scan was positive in 12 of 15 patients with lung location, 2 of 4 with gastric location, and 0 of 2 with medullar location, suggesting that FDG uptake might be site-specific [18]. Indeed, its sensitivity has been reported between 50-89% [21, 22] and 83%-100% [18] for stomach and lung involvement, respectively. However, the PET-scan also detected unsuspected extra-pulmonary lymphoma lesions in 2 patients (nodal and cutaneous). Altogether, these findings suggest the need for prospective evaluation of PET-scan for the initial staging and medical management of pulmonary MALT lymphoma.

Marginal zone lymphoma is considered as a model of antigen-driven lymphoma either by auto-antigen or by microbial pathogen [7]. The risk of developing lymphoma is estimated to be from 6.6 to 44 times higher in Sjogren's syndrome compared to the normal population [23, 24], with marginal zone lymphoma being the most frequent histological subtype of lymphoma [6, 24]. In this series, ten patients had an auto-immune disease, confirming the frequent association between these two disorders [6]. Chronic infections also seem responsible for site-specific marginal zone lymphomas, such as with HP for stomach, *Campylobacter jejuni* for small intestine, *Borrelia burgdorferi* for skin, *Chlamydiae psittaci* for ocular adnexa, and hepatitis C virus (HCV) for spleen. Moreover, other infections, i.e. *Mycobacterium tuberculosis*

[25], EBV [26], and HHV8 [27], are involved in high grade lymphoma with primary thoracic location. However, none of our cases were associated with HIV, hepatitis B virus or HCV infection, and only a few of them had a prior pulmonary infection, including tuberculosis sequel. Prevalence of HP infection was not significantly different in patients with gastric involvement (33%) compared to those without (24%). As the prevalence of HP infection in the general population is only 18% [28], we cannot definitively exclude that few of our patients had HP-driven primary gastric MALT lymphoma with secondary pulmonary dissemination. In this series, histological examination revealed absence of EBV, for every patient tested. This result is in accordance with previously published series of gastric MALT lymphoma showing the absence of an association with EBV, in the absence of a large B-cell lymphoma component [29]. At the present time, pulmonary MALT remains orphaned from a specific driving pathogen or perhaps does not depend on chronic infection to maintain lymphomagenesis.

Although a recent series of MALT lymphoma among which only 10 cases with lung location has suggested a lower overall survival in this setting [30] the present series confirms the favorable course of pulmonary MALT lymphoma, with an estimated 72% 10-year survival [1, 17]. Since only two of the nine deaths were related to lymphoma, only age and ECOG status were associated with poor outcome. Indeed, none of the lymphoma characteristics were associated with worse survival. PFS, reflecting tumor growth in indolent disease, is probably more useful to predict treatment efficacy than OS [15]. The 10-year PFS was estimated at 36%, and the factors associated with shorter PFS were mediastinal adenopathy and chemotherapy containing anthracyclin or cyclophosphamide. The mediastinal adenopathy designation in our patients could confer a behavior closer to nodal MZL rather than

MALT lymphoma, in accordance with a previous report [31]. Although, there are conflicting results regarding the influence of dissemination on survival [1, 32] an extra-pulmonary location was not associated with a shorter PFS or OS in this series. Indeed, the impact of extensive evaluation at diagnosis including bone marrow biopsy and endoscopic examination of the gastrointestinal tract should be better evaluated in patients that cannot be cured by local therapy.

Two previous large retrospectives studies did not show evidence of different outcomes between patients receiving different treatment modalities, i.e. local therapy, chemotherapy or combined therapy [33, 34]. ESMO guidelines for gastric non-HP MALT lymphoma recommend treatment with radiotherapy for localized lymphoma and chemotherapy using an alkylating agent (chlorambucil, cyclophosphamide) or purin analogs (fludarabine, cladribine) with or without the anti-CD20 monoclonal antibody, rituximab [35], for disseminated lymphoma. In the present series, patients treated by anthracyclin had worse PFS. However, anthracyclin based-chemotherapy was administered for almost 5 months, while MALT lymphoma with indolent growth may need a maintenance therapy as recently suggested with rituximab [36]. This treatment regimen reflects that 3 patients were treated in 1993 during a period when anthracyclines were recommended [1, 37]. Other patients from the group anthracyclin based-chemotherapy were treated since 2000. Therapy was chosen by local physician not always in accordance with newer recommendations. Cyclophosphamide resulted in a lower disease control rate than chlorambucil (70 vs. 87%, p=0.02), while both drugs were administered for a similar prolonged duration of almost 15 months. This was corroborated by the lower PFS observed in patients receiving cyclophosphamide-based chemotherapy. For five of the six patients without initial treatment, abstention was chosen because of a limited disease without possible

curative radiotherapy. None of these patients presented progression during the median follow-up of 12.5 months, confirming the feasibility of the previously published watch-and-wait policy [38]. Since our study is retrospective and multicentric, conclusions about treatment should be made with caution, however almost half of the patients (46%) were treated in the same hospital.

This series confirms the disseminated but indolent nature of pulmonary MALT lymphoma and supports the therapeutic recommendation of chlorambucil chemotherapy for disseminated lymphoma. Prospective studies should be done to confirm that chlorambucil is the best first-line therapy and to determine its place in the new therapeutic arsenal including rituximab, fludarabin, cladribin and bortezomib. Further works (i.e. FISH analysis for API2-MALT1 translocation [39] and universal 16S ribosomal RNA PCR for microbial infection) are in progress to better understand pulmonary MALT lymphomagenesis, which will hopefully lead to improvements in the therapeutic strategy.

Acknowledgments

The authors thank Jean-Pierre L'huiller (La Varenne St Hilaire), Eric Oksenhendler, (Hôpital Saint Louis, Paris) who provided outcome data and Thierry Chinet, Marc Humbert, Christophe Cracco, Christos Chouaid who provided grateful help.

References

1. Thieblemont C, Berger F, Dumontet C, Moullet I, Bouafia F, Felman P, Salles G, Coiffier B. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. *Blood* 2000: 95(3): 802-806.
2. Montalban C, Castrillo JM, Abraira V, Serrano M, Bellas C, Piris MA, Carrion R, Cruz MA, Larana JG, Menarguez J, et al. Gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma. Clinicopathological study and evaluation of the prognostic factors in 143 patients. *Ann Oncol* 1995: 6(4): 355-362.
3. Zucca E, Conconi A, Pedrinis E, Cortelazzo S, Motta T, Gospodarowicz MK, Patterson BJ, Ferreri AJ, Ponzoni M, Devizzi L, Giardini R, Pinotti G, Capella C, Zinzani PL, Pileri S, Lopez-Guillermo A, Campo E, Ambrosetti A, Baldini L, Cavalli F. Nongastric marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Blood* 2003: 101(7): 2489-2495.
4. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Delsol G, De Wolf-Peeters C, Falini B, Gatter KC, et al. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood* 1994: 84(5): 1361-1392.
5. Isaacson P, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. *Cancer* 1984: 53(11): 2515-2524.
6. Royer B, Cazals-Hatem D, Sibilia J, Agbalika F, Cayuela JM, Soussi T, Maloisel F, Clauvel JP, Brouet JC, Mariette X. Lymphomas in patients with Sjogren's syndrome are marginal zone B-cell neoplasms, arise in diverse extranodal and nodal sites, and are not associated with viruses. *Blood* 1997: 90(2): 766-775.
7. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. *Blood* 2006: 107(8): 3034-3044.
8. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, Isaacson PG. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. *Lancet* 1993: 342(8871): 575-577.
9. Thieblemont C, Bastion Y, Berger F, Rieux C, Salles G, Dumontet C, Felman P, Coiffier B. Mucosa-associated lymphoid tissue gastrointestinal and nongastrointestinal lymphoma behavior: analysis of 108 patients. *J Clin Oncol* 1997: 15(4): 1624-1630.
10. Roggero E, Zucca E, Pinotti G, Pascarella A, Capella C, Savio A, Pedrinis E, Paterlini A, Venco A, Cavalli F. Eradication of Helicobacter pylori infection in primary low-grade gastric lymphoma of mucosa-associated lymphoid tissue. *Ann Intern Med* 1995: 122(10): 767-769.
11. Montalban C, Manzanal A, Boixeda D, Redondo C, Alvarez I, Calleja JL, Bellas C. Helicobacter pylori eradication for the treatment of low-grade gastric MALT lymphoma: follow-up together with sequential molecular studies. *Ann Oncol* 1997: 8 Suppl 2: 37-39.
12. Savio A, Franzin G, Wotherspoon AC, Zamboni G, Negrini R, Buffoli F, Diss TC, Pan L, Isaacson PG. Diagnosis and posttreatment follow-up of Helicobacter pylori-positive gastric lymphoma of mucosa-associated lymphoid tissue: histology, polymerase chain reaction, or both? *Blood* 1996: 87(4): 1255-1260.
13. Isaacson PG M-HH, Piris MA. Extranodal marginal zone B-cell lymphoma of maucosa-associated lymphoid tissue (MALT lymphoma). *In:* Press I, ed. Jaffe ES, Harris NL, Stein H, Vardiman JW Pathology and Genetics: Tumours of Haematopoietic Tissues World Health Organization Classification of Tumours, Lyon, France, 2001; pp. 157-160.

14. Wislez M, Cadranel J, Antoine M, Milleron B, Bazot M, Mayaud C, Carette MF. Lymphoma of pulmonary mucosa-associated lymphoid tissue: CT scan findings and pathological correlations. *Eur Respir J* 1999: 14(2): 423-429.
15. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007: 25(5): 579-586.
16. Kinder BW, Collard HR, Koth L, Daikh DI, Wolters PJ, Elicker B, Jones KD, King TE, Jr. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? *Am J Respir Crit Care Med* 2007: 176(7): 691-697.
17. Cordier JF, Chailleux E, Lauque D, Reynaud-Gaubert M, Dietemann-Molard A, Dalphin JC, Blanc-Jouvan F, Loire R. Primary pulmonary lymphomas. A clinical study of 70 cases in nonimmunocompromised patients. *Chest* 1993: 103(1): 201-208.
18. Bae YA, Lee KS, Han J, Ko YH, Kim BT, Chung MJ, Kim TS. Marginal zone B-cell lymphoma of bronchus-associated lymphoid tissue: imaging findings in 21 patients. *Chest* 2008: 133(2): 433-440.
19. Campo E, Chott A, Kinney MC, Leoncini L, Meijer CJ, Papadimitriou CS, Piris MA, Stein H, Swerdlow SH. Update on extranodal lymphomas. Conclusions of the Workshop held by the EAHP and the SH in Thessaloniki, Greece. *Histopathology* 2006: 48(5): 481-504.
20. de Boer JP, Hiddink RF, Raderer M, Antonini N, Aleman BM, Boot H, de Jong D. Dissemination patterns in non-gastric MALT lymphoma. *Haematologica* 2008: 93(2): 201-206.
21. Hoffmann M, Wohrer S, Becherer A, Chott A, Streubel B, Kletter K, Raderer M. 18F-Fluoro-deoxy-glucose positron emission tomography in lymphoma of mucosa-associated lymphoid tissue: histology makes the difference. *Ann Oncol* 2006: 17(12): 1761-1765.
22. Radan L, Fischer D, Bar-Shalom R, Dann EJ, Epelbaum R, Haim N, Gaitini D, Israel O. FDG avidity and PET/CT patterns in primary gastric lymphoma. *Eur J Nucl Med Mol Imaging* 2008.
23. Kassan SS, Thomas TL, Moutsopoulos HM, Hoover R, Kimberly RP, Budman DR, Costa J, Decker JL, Chused TM. Increased risk of lymphoma in sicca syndrome. *Ann Intern Med* 1978: 89(6): 888-892.
24. Ekstrom Smedby K, Vajdic CM, Falster M, Engels EA, Martinez-Maza O, Turner J, Hjalgrim H, Vineis P, Seniori Costantini A, Bracci PM, Holly EA, Willett E, Spinelli JJ, La Vecchia C, Zheng T, Becker N, De Sanjose S, Chiu BC, Dal Maso L, Cocco P, Maynadie M, Foretova L, Staines A, Brennan P, Davis S, Severson R, Cerhan JR, Breen EC, Birmann B, Grulich AE, Cozen W. Autoimmune disorders and risk of non-Hodgkin lymphoma subtypes: a pooled analysis within the InterLymph Consortium. *Blood* 2008: 111(8): 4029-4038.
25. Nakatsuka S, Yao M, Hoshida Y, Yamamoto S, Iuchi K, Aozasa K. Pyothorax-associated lymphoma: a review of 106 cases. *J Clin Oncol* 2002: 20(20): 4255-4260.
26. Katzenstein AL, Peiper SC. Detection of Epstein-Barr virus genomes in lymphomatoid granulomatosis: analysis of 29 cases by the polymerase chain reaction technique. *Mod Pathol* 1990: 3(4): 435-441.
27. Boulanger E, Gerard L, Gabarre J, Molina JM, Rapp C, Abino JF, Cadranel J, Chevret S, Oksenhendler E. Prognostic factors and outcome of human herpesvirus 8-associated primary effusion lymphoma in patients with AIDS. *J Clin Oncol* 2005: 23(19): 4372-4380.
28. Hansen JM, Wildner-Christensen M, Hallas J, Schaffalitzky de Muckadell OB. Effect of a community screening for Helicobacter pylori: a 5-Yr follow-up study. *Am J Gastroenterol* 2008: 103(5): 1106-1113.

29. Chan WY, Chan EK, Chow JH. Epstein-Barr virus-associated gastric lymphomas are distinct from mucosa-associated lymphoid tissue-type lymphomas: genetic abnormalities of p53 gene. *Diagn Mol Pathol* 2001: 10(3): 153-160.
30. Kalpadakis C, Pangalis GA, Vassilakopoulos TP, Kyrtsonis MC, Siakantaris MP, Kontopidou FN, Korkolopoulou P, Bobotsis P, Sahanas S, Tzenou T, Anagnostou D, Dimitriadou E, Yiakoumis X, Patsouris E, Roussou P, Panayiotidis P, Papadaki E, Angelopoulou MK. Non-gastric extra-nodal marginal zone lymphomas--a single centre experience on 76 patients. *Leuk Lymphoma* 2008: 49(12): 2308-2315.
31. Thieblemont C. Non-MALT marginal zone lymphomas. *Ann Oncol* 2008: 19 Suppl 4: iv70-73.
32. Arcaini L, Burcheri S, Rossi A, Passamonti F, Paulli M, Boveri E, Brusamolino E, Orlandi E, Molteni A, Pulsoni A, Cox MC, Orsucci L, Fabbri A, Frezzato M, Voso MT, Zaja F, Montanari F, Pascutto C, Morra E, Cortelazzo S, Lazzarino M. Nongastric marginal-zone B-cell MALT lymphoma: prognostic value of disease dissemination. *Oncologist* 2006: 11(3): 285-291.
33. Pinotti G, Zucca E, Roggero E, Pascarella A, Bertoni F, Savio A, Savio E, Capella C, Pedrinis E, Saletti P, Morandi E, Santandrea G, Cavalli F. Clinical features, treatment and outcome in a series of 93 patients with low-grade gastric MALT lymphoma. *Leuk Lymphoma* 1997: 26(5-6): 527-537.
34. Thieblemont C, Dumontet C, Bouafia F, Hequet O, Arnaud P, Espinouse D, Felman P, Berger F, Salles G, Coiffier B. Outcome in relation to treatment modalities in 48 patients with localized gastric MALT lymphoma: a retrospective study of patients treated during 1976-2001. *Leuk Lymphoma* 2003: 44(2): 257-262.
35. Zucca E, Dreyling M. Gastric marginal zone lymphoma of MALT type: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 2008: 19 Suppl 2: ii70-71.
36. Hainsworth JD, Litchy S, Burris HA, 3rd, Scullin DC, Jr., Corso SW, Yardley DA, Morrissey L, Greco FA. Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. *J Clin Oncol* 2002: 20(20): 4261-4267.
37. Coiffier B, Thieblemont C, Felman P, Salles G, Berger F. Indolent nonfollicular lymphomas: characteristics, treatment, and outcome. *Semin Hematol* 1999: 36(2): 198-208.
38. Troch M, Streubel B, Petkov V, Turetschek K, Chott A, Raderer M. Does MALT lymphoma of the lung require immediate treatment? An analysis of 11 untreated cases with long-term follow-up. *Anticancer Res* 2007: 27(5B): 3633-3637.
39. Remstein ED, James CD, Kurtin PJ. Incidence and subtype specificity of API2-MALT1 fusion translocations in extranodal, nodal, and splenic marginal zone lymphomas. *Am J Pathol* 2000: 156(4): 1183-1188.

Figure legends

Figure 1: Strategy for pathological diagnosis in pulmonary MALT lymphoma. Sixty-three patients were referred for diagnosis of pulmonary opacity(ies). Sixty-one had bronchial biopsies during fiberoptic bronchoscopy among wich transbronchial biopsies were performed in the same procedure in 26 cases (42.6%). In a second step, 10 patients had CT scan guide percutaneous transparietal biopsies. One supplementary patient had CT scan biopsies, whereas re-reading of the bronchial biopsy revealed MALT lymphoma. In a third step, the diagnosis was made by open lung biopsy in 18 patients.

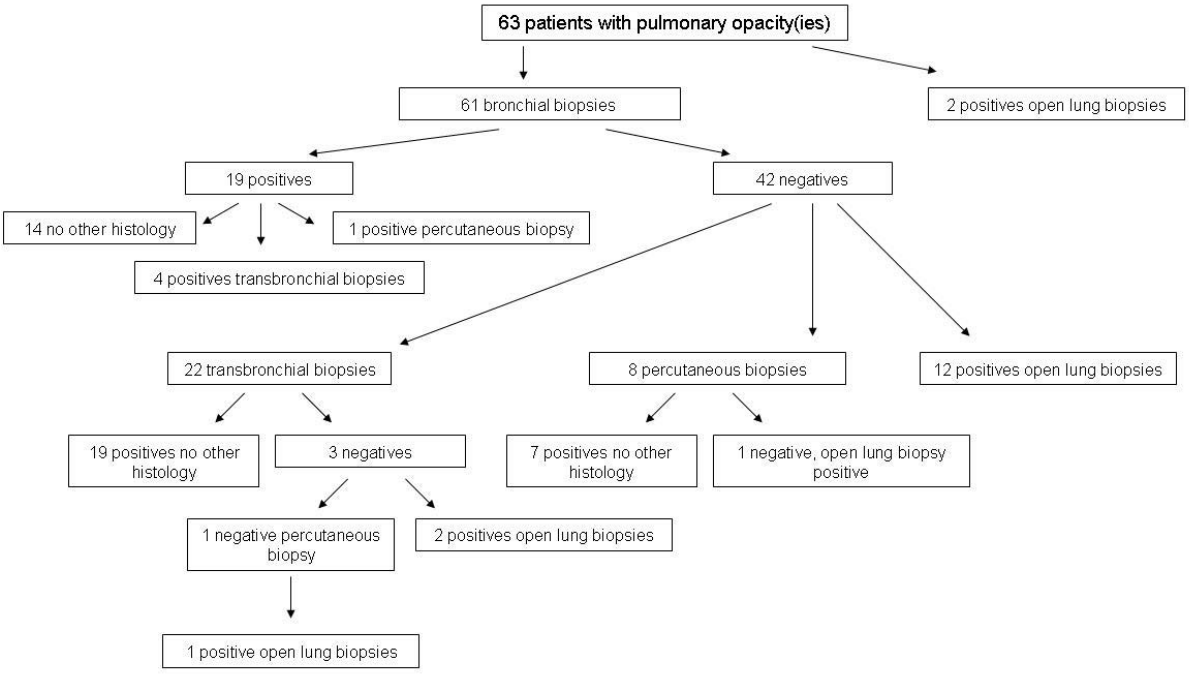

Figure 2: Kaplan-Meier estimate of the progression-free survival of 63 patients with pulmonary MALT lymphoma. Dotted lines indicate the 95% CI. The estimated PFS was 36% [19%-52%] at 10 years.

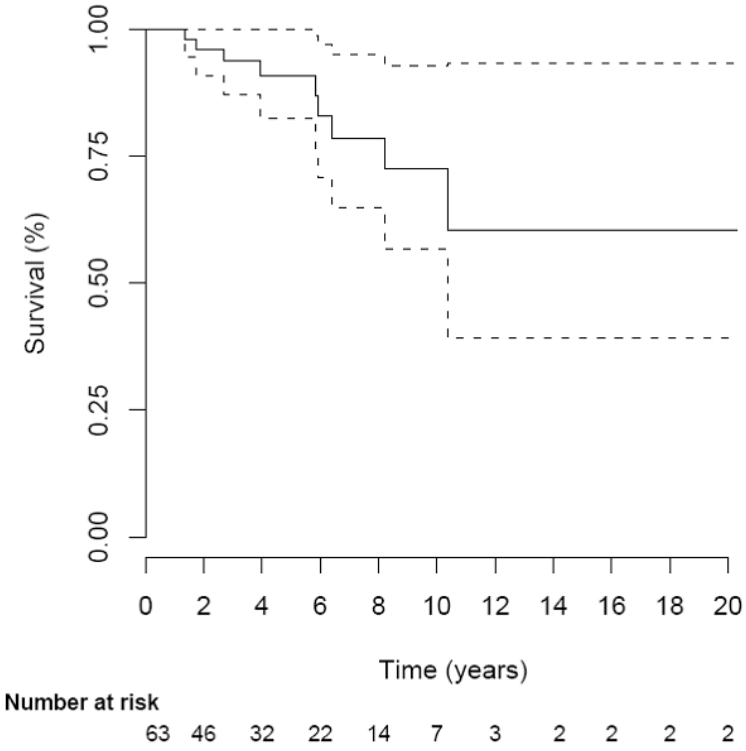

Figure 3: Kaplan-Meier estimate of the overall survival of 63 patients with pulmonary MALT lymphoma. Dotted lines indicate the 95% CI. The estimated overall survival of patients was 72% [50-86] at 10 years.

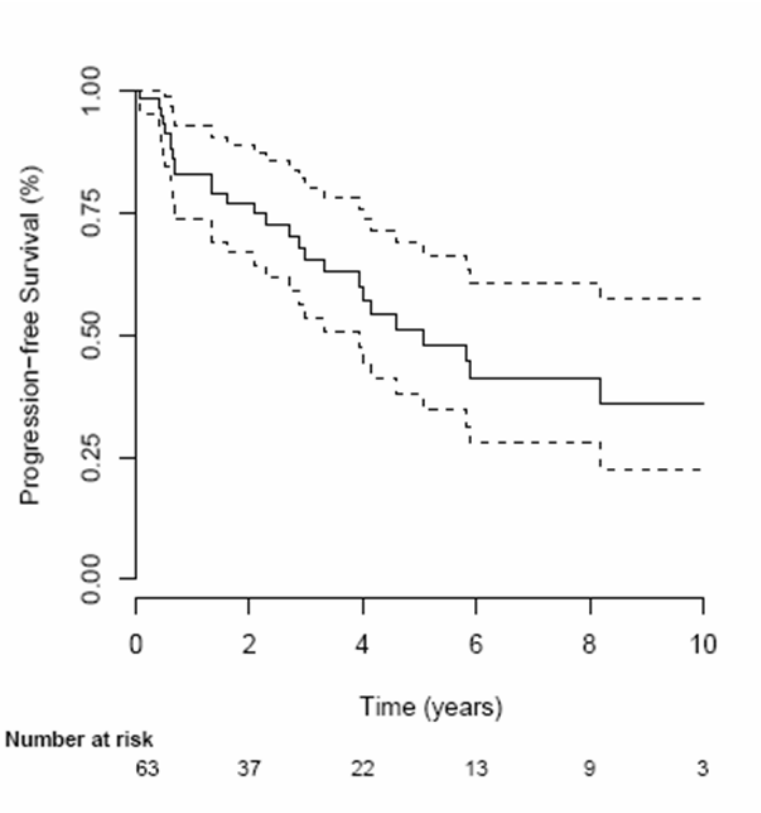
Progression−free Survival (%)
0.00
0.25
0.50
0.75
1.00
0
2
4
6
8
10
Time (years)
Number at risk
63
37
22
13
9
3

Table 1. Main clinical and biological characteristics of the 63 patients

Characteristics	Value
Age (range)	60 (24-83)
Female sex	29 (47)
Active or former tobacco use	24 (37)
Respiratory tract infection	6 (9)
including tuberculosis	4 (6)
Autoimmune background	10 (16)
Respiratory symptoms	37 (58)
B symptoms	14 (22)
Cytopenia	12 (19)
LDH level more than 2 times the upper limit	2 (3)

Data are reported as N (%) or median (range). B symptoms include weight loss, fever and night sweats.

Table 2. Staging of the 63 patients with pulmonary MALT lymphoma

	N (%)
Pulmonary CT scan evaluation*	
Unilateral	33 (52)
- one lobe	*25 (39)*
Mediastinal adenopathy	10 (16)
Pleural effusion	7 (11)
Extra-pulmonary evaluation**	
Total	29 (46)
Mucosal site	19 (30)
- stomach	*15 (19)*
- skin	*2 (3)*
- bowel	*2 (3)*
- conjunctiva	*1 (1.5)*
- cavum	*1 (1.5)*
- parotid	*1 (1.5)*
Lymphoid organs	14 (22)
- bone marrow	*8 (13)*
- nodal	*4 (6)*
- spleen	*4 (6)*

The sum of each location is higher than the total because 7 patients had more than one extra-pulmonary location.
*Mediastinal adenopathy or pleural effusion were assessed by CT scan, and not histologically proven.
**Except for spleen, all extra-pulmonary locations of MALT were histologically proven.

Table 3. Remission and outcome according to type of therapy

Treatment group	N (%)	DCR N (%)	Death N (%)	Relapse or Progression N (%)	PFS Median in years	3-year PFS % [CI]
Abstention	6 (9)	0 (0)	1 (16)	0 (0)	NA	66 [0-94]
Local therapy*	20 (32)♦,◊	20 (100)	1 (5)	7 (35)	NA	83 [55-94]
Clorambucil*	19 (30)	17 (87)	2 (10)	3 (15)	8.2	75 [41-91]
Cyclophosphamide*	10 (16)	7 (70)	2 (20)	8 (80)	0.7	40 [12-67]
Anthracyclin/Fludarabin*	8 (13)∞	8 (100)	3 (37)	6 (75)	0.7	25 [0-63]

***All treatment groups were compared to chlorambucil *Treatment groups are defined in the Methods section. ♦Only one patient was treated by radiotherapy without relapse. ◊One patient received chlorambucil adjuvant therapy after surgery. ∞ One patient received Fludarabin in combination with rituximab. DCR: disease control rate; PFS: progression-free survival; NA: not achieved. CI 95% confidence interval.

Table 4. Hazard ratio for progression-free survival

	Univariate analysis Hazard ratio [CI]		P	Multivariate analysis Hazard ratio [CI]		P
Age >60	1.0	[0.5-2.2]	0.9	0.8	[0.3-1.7]	0.52
Male sex	0.7	[0.3-1.5]	0.3			
ECOG						
0	1			1		
1	2.0	[0.8-5.0]	0.1	1.9	[0.7-5.1]	0.22
2-3	1.99	[0.8-5]	0.1	3.0	[1.0-9.5]	0.05
Diagnosis delay (per 1 month increase)	1.0	[0.99-1.01]	0.8			
Extra-pulmonary location	1.4	[0.7-3.0]	0.4	0.9	[0.4-2.2]	0.86
Gastric	1.3	[0.6-3.0]	0.6			
Nodal	0.7	[0.1-5.1]	0.7			
Medullar	1.1	[0.3-3.7]	0.9			
Pulmonary extension						
Mediastinal adenopathy	3.5	[1.3-9.0]	0.01	1.0	[0.3-3.3]	0.99
Bilateral involvement	1.8	[0.9-3.9]	0.6			
Pleural effusion	1.7	[0.6-4.9]	0.7			
Treatment						
Chlorambucil *	1			1		
Cyclophosphamide based Chemotherapy *	6.1	[2-18.6]	0.001	6.1	[1.6-23.7]	0.01
Anthracyclin or Fludarabin based Chemotherapy *	4.4	[1.3-15.0]	0.02	4.9	[1.3-17.6]	0.02
Local therapy *	1.0	[0.3-3.2]	0.9	1.1	[0.3-3.8]	0.96
Abstention *	1.2	[0.1-10.1]	0.8	1.2	[0.1-11]	0.84

All treatment groups were compared to chlorambucil. Multivariate Cox analysis was performed using significant clinical variables.
CI: 95% confidence interval. *Treatment groups are defined in the Methods section.

Table 5. Hazard ratio for overall survival

	Univariate analysis Hazard ratio [CI]		P
Age >60	12.5	[1.5-104.0]	0.02
Male sex	0.7	[0.2-2.5]	0.5
ECOG			
0	1		
1	20.3	[2.1-190.4]	0.008
2-3	38.6	[4-374]	0.002
Diagnosis delay (per 1 month increase)	1.0	[0.99-1.02]	0.8
Extra-pulmonary location	2.2	[0.6-8.4]	0.2
Gastric	1.8	[0.4-7.8]	0.4
Nodal	6.0	[0.6-58.8]	0.1
Medullar			0.52**
Pulmonary extension			
Mediastinal adenopathy	2	[0.2-17.7]	0.5
Bilateral involvement	1.7	[0.4-6.4]	0.4
Pleural effusion	5.4	[0.9-30.6]	0.1
Treatment			
Chlorambucil *	1		
Cyclophosphamide based Chemotherapy *	0.9	[0.1- 6.6]	0.9
Anthracyclin or Fludarabin based Chemotherapy *	2.6	[0.4-6]	0.3
Local therapy *	0.2	[0.02-2.7]	0.2
Abstention *	4.6	[0.4-54]	0.2

*Treatment groups are defined in the Methods section. All treatment groups were compared to chlorambucil.

** By log-rank test, because no death was observed in case of medullar location, the hazard ratio cannot be estimated.