Dissemination patterns in non-gastric MALT lymphoma

Jan Paul de Boer,[2] Reinier Frederik Hiddink,[2] Markus Raderer,[5] Ninja Antonini,[4] Berthe Mauricia Pauline Aleman,[3] Henk Boot,[1] and Daphne de Jong[4]

[1]Department of Gastroenterology, [2]Department of Medical Oncology, [4]Department of Pathology, [3]Department of Radiotherapy, [4]Department of Biometrics Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands, and [5]Department of Internal Medicine I, Division of Oncology, University of Vienna, Vienna, Austria

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Correspondence:
J.P. de Boer, MD, PhD
Dept. Of Medical Oncology
The Netherlands Cancer Institute
Plesmanlaan 121, 1066 CX
Amsterdam, the Netherlands.
E-mail: j.d.boer@nki.nl

ABSTRACT

Background
In contrast to gastric extranodal marginal zone mucosa associated lymphoid tissue (MALT) lymphomas, there is little consensus on the value and clinical consequences of extensive staging at diagnosis and during follow-up in non-gastric MALT lymphomas.

Design and Methods
Complete clinical information at presentation and during follow-up was collected for 72 patients with non-gastric MALT lymphoma treated at the Netherlands Cancer Institute between 1977 and 2005. Dissemination patterns at presentation were studied for nine primary dominant organ groups in our series of 72 patients and in a similar cohort treated at Vienna University (for a total of 106 patients).

Results
Twenty-three of our patients (32%) had more than one site of extranodal MALT lymphomatous disease, 13 patients (18%) had regional nodal involvement and 7 (10%) had bone marrow involvement. Site-specific dissemination was seen in paired organs (orbit, lung) and in the gastrointestinal tract (stomach, colon) and primary pulmonary MALT lymphoma was specifically related to gastric involvement ($p<0.0001$). These patterns of dissemination were retained during relapsed disease.

Conclusions
Primary extranodal non-gastric marginal zone MALT lymphoma frequently presents as stage IV disease (26%) and multifocal disease (32%) and with a site-specific dissemination pattern. After an extensive staging procedure at presentation, we recommend primary site-directed protocols during follow-up focused on the primary involved tract/organ system, regional lymph nodes and pulmonary and gastric relapses.

Key words: extranodal marginal zone lymphoma, MALT, dissemination patterns.

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Introduction

Marginal zone B-cell lymphoma mucosa associated lymphoid tissue (MALT) lymphoma is a distinct clinicopathological entity with characteristic histological features.[1-4] MALT lymphomas account for approximately 8% of all non-Hodgkin's lymphomas and usually arise from B cells that have undergone post-follicular differentiation in the context of chronic antigenic stimulation mediated by persistent infection and/or auto-immune mechanisms.[2,3] MALT lymphomas have been described in various extranodal sites, including stomach, intestine, conjunctiva, orbit, salivary glands, thyroid, larynx, lung, breast, kidney, liver, prostate, skin and dura mater.[5] Although nodal and bone marrow involvement are observed, MALT lymphomas preferentially disseminate to extranodal and often mucosal sites mediated by specific mucosal homing properties.[6-9]

MALT lymphomas behave clinically as indolent non-Hodgkin's lymphoma with a long disease-free survival and long overall survival. It is thought that this good prognosis is due to the tendency of MALT lymphomas to remain localized for long periods and to the low frequency of transformation to aggressive non-Hodgkin's lymphoma.[5;10;11] In contrast to the far more frequent gastric MALT lymphomas, thus far no controlled randomized trials have been published on treatment of primary MALT lymphomas outside the stomach and there is no consensus on the optimal approach to the management of such lymphomas. Various treatment modalities, including antibiotics, chemotherapy, immunotherapy, radiotherapy and surgery, are applied according to local preferences.[5;10;11] Despite controversy on the prognostic impact of localized versus disseminated disease at presentation, it is generally recommended that extensive staging is performed in this group of patients to guide treatment choices.[5,10-13] The value of extensive screening during follow-up is a matter of even stronger debate.

On the basis of 72 patients treated between January 1977 and December 2005 in the Netherlands Cancer Institute for primary MALT lymphoma outside the stomach with various primary localizations, cause-specific survival, transformation and site-specific dissemination patterns and relapse patterns were studied and analyzed in combination with previously published series to asses the value of extensive staging protocols at diagnosis and during follow-up.[13]

Design and Methods

Data were retrieved from the clinical files of the Antoni van Leeuwenhoek hospital/The Netherlands Cancer Institute, for 80 patients with non-gastric MALT lymphoma treated between January 1977 and December 2005 who had complete clinical records at presentation and during follow-up. All cases were reviewed according to the current WHO criteria and the diagnosis of MALT lymphoma was confirmed in 72 patients who were included in the present study.[14] The staging and follow-up data retrieved included findings of physical examination, hematologic and chemical surveys, chest radiograms, computed tomography of the chest and abdomen, ultrasonography of the abdomen, gastroduodenoscopy and bone marrow biopsy and aspirate. All patients with orbital and conjunctival disease had a complete ophthalmic examination and all patients with disease of the salivary glands or other localizations in the head and neck region had an otorhinolaryngological examination and the results were retrieved.

Patients were divided into nine groups according to the primary dominant location at presentation, i.e. orbital (lacrimal gland and conjunctiva), Waldeyer's ring, lung, thyroid, breast, intestinal tract (colon and small intestine), hepatic and urogenital (bladder, prostate and cervix). The median follow-up time was 84.1 months (range 1.7-198.1 months). All primary biopsy samples and biopsy samples at transformation were reviewed, including an assessment of complete immunohistochemical data, and the diagnoses confirmed (DdJ). Criteria for the diagnosis of diffuse large B-cell lymphoma (DLBCL) in the context of MALT lymphoma were the internationally most generally accepted criteria and included large sheets of blasts. A diffusely increased percentage of blasts on a background of indolent MALT lymphoma was not considered sufficient for the diagnosis of DLBCL. Patients with DLBCL were treated with CHOP or CHOP-like regimens. Data on first line treatment and therapy during follow-up were recorded.

Statistical analysis

Cox proportional hazard models were applied to investigate associations between clinical characteristics and death. Time was calculated from the date of diagnosis to the date of death or last follow-up. Patients were excluded from analysis if data for a factor involved in the analysis were missing. The following clinical variables were investigated: age, affected sites at diagnosis, number of affected sites at diagnosis, primary location at diagnosis and transformation. Transformation was analyzed as a time-dependent factor. Survival curves were calculated according to the method of Kaplan and Meier.

For the analysis of site-specific dissemination patterns and relapse patterns, additional data from patients (n=34) from the University of Vienna were used. The association between primary site of disease at presentation and site-specific dissemination (in 14 localizations) was analyzed with logistic regressions. Bonferroni's adjustment for multiple comparisons was made i.e. a critical p value of 0.00046. The level of statistical significance was set at 5%. All analyses were performed using SAS V9.1.

Results

Patients' characteristics

The clinical characteristics at diagnosis of the 72 patients

are summarized in Table 1. The median age of the 23 men and 49 women was 65 years (range 22-85 years). At diagnosis, the majority of the patients had localized disease, (53% stage IE, 21% stage IIE) and 19 patients (26%) had stage IV disease. Twenty-three patients (32%) presented with more than one extranodal MALT site of disease and 13 patients (18%) had regional nodal involvement. No disseminated nodal disease was seen. Seven patients (10%) had bone marrow involvement. In 30% of the patients, some form of immunological disorder was present, i.e. 19 patients (26%) had autoimmune disease, including Sjögren's syndrome, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's thyroiditis and M-protein was present in three patients. In 8% of the patients, *H. pylori* infection was diagnosed at presentation or during follow-up.

Transformation to DLBCL was diagnosed at presentation in four patients (6%) and during follow-up in five patients (7%) with a median time to transformation of 66.5 (range, 14-146) months. The management was varied and consisted of chemotherapy, i.e. single agent therapy with chlorambucil or fludarabine and multi-agent therapy with CVP or CHOP-like regimens, surgery (primarily in patients with disease in Waldeyer's ring, salivary glands or the urogenital system), radiotherapy (primarily in the group with orbital disease) or a watch-and-wait policy. Twenty-four percent of the patients received *H. pylori* eradication therapy at presentation or during follow-up. Six patients were treated for proven *H. pylori* gastritis, whereas the remaining patients received *H. pylori* eradication treatment in the context of treatment of MALT lymphoma without gastric localizations and irrespective of *H. pylori* status.

Dissemination patterns at presentation and during follow-up

In the group of patients with orbital and thyroid disease, no additional lymphoma localizations were observed at presentation. In the other groups secondary sites of lymphoma were primarily observed in regional lymph nodes (18%), bone marrow (10%), Waldeyer's ring (6%) and in the gastric mucosa (10%). Other secondary localizations at diagnosis were incidentally observed, i.e. one intestinal localization in the Waldeyer's ring group, one hepatic localization in the breast group and one splenic localization in the hepatic group of patients (Table 2). Fifty-five percent of the gastric localizations were associated with *H. pylori* infection.

During follow-up, relapsed disease was for the most part demonstrated in the initial dominant organ system (11%), in lymph nodes (14%), bone marrow (7%), stomach (10%) and lung (13%) (Table 3). Relapsed disease in other organ systems was infrequently observed with one case each of adrenal, kidney, central nervous system, skin, bladder and breast localization (Table 3). During follow-up 33 patients developed one relapse of non-Hodgkin's lymphoma, 18 patients had two relapses, 10 patients had three relapses, 5 patients had four relapses and in one patient five relapses were observed.

Analysis of site-specific dissemination patterns in non-gastric MALT lymphoma at presentation

In order to investigate site-specific dissemination patterns in primary MALT lymphoma, our data were analyzed

Table 1. Clinical characteristics of the 72 patients with non-gastric MALT lymphoma at diagnosis.

Characteristic:	*No. of patients (%)*
Age, years	
Median	65
Range	22-85
Male/Female	23 (31.9)/49 (68.1)
Ann Arbor Stage	
IE	38 (52.8)
IIE	15 (20.8)
IV	19 (26.4)
Number of extranodal sites	
One	49 (68.1)
More than one	23 (31.9)
Nodal involvement	
Absent	59 (81.9)
Present	13 (18.1)
Bone marrow involvement	
Absent	65 (90.3)
Present	7 (9.7)
M-protein	
Absent	69 (95.8)
Present	3 (4.2)
Autoimmune disease	
Absent	53 (73.6)
Present	19 (26.4)

Table 2. Additional lymphoma localizations at diagnosis in the 72 patients with non-gastric MALT lymphoma.

Group: (n)	*Lymph node*	*Bone marrow*	*Salivary*	*Waldeyer's ring*	*Stomach*	*Intestinal*	*Spleen*	*Liver*
Orbital (7)								
Waldeyer's ring (6)	2				1	1		
Salivary (21)	4	2	1	1				
Thyroid (4)								
Breast (4)	1	2						1
Lung (8)				1	3			
Intestinal (11)	2	1		2	2	1		
Hepatic (3)	2	1			1		1	
Urogenital (8)	2	1						

n: number of patients.

in combination with those from a similar series of 34 patients from the University of Vienna[13] to include 106 evaluable patients. These 34 patients were selected on the basis of occurrence of further MALT localizations at presentation in addition to the primary dominant non-gastric MALT localization. In both series of patients similar staging procedures were performed to allow combined analysis. As is shown in Table 4, bilateral involvement of paired organs (17%), lymph nodes (22%) and bone marrow (8%) and gastric (13%) lymphoma localizations were seen most frequently. Moreover, specific patterns were seen for primary pulmonary, orbital and intestinal MALT lymphoma. In seven of 13 patients with primary lung involvement, gastric localizations were diagnosed at staging gastroduodenoscopy and histologically confirmed [odds ratio for simultaneous gastric localization in the lung group was 14.3 [(95% confidence interval (CI) 3.8-54.4, $p<0.0001$)]. A pattern of multiple sites confined to the intestinal tract with exclusion of the stomach were seen [odds ratio 34.2 (95% CI 6.2-190.1, $p<0.0001$)] as well as simultaneous involvement of different orbital structures, both ipsi- and contralateral [odds ratio 6.4 (95% CI 1.6-25.1, $p<0.008$)].

Survival and prognostic factors

After a median follow-up of 84.1 months, 23 (32%) of the patients had died. In nine patients (39%) death was related to disease progression, whereas in the other 14 patients (61%) it was related to other causes. In three of the nine lymphoma-related deaths transformation to aggressive B-cell lymphoma had occurred. Other causes of death (n=14) were second primary malignancy (n=4), infectious diseases (n=3), thromboembolic events (n=1), gastric bleeding (n=1), respiratory failure (n=1) and unknown (n=4). The estimated overall survival at 2, 4 and 6 years was 90%, 88% and 71%, respectively, whereas the estimated overall survival in the patients with transformation into an aggressive NHL was 69%, 57%, 46%, respectively (Figure 1). The estimated 6-year survivals of patients in the orbital, salivary, Waldeyer's ring, thyroid, lung, liver, intestinal and urogenital groups were 100%, 72%, 67%, 100%, 86%, 67%, 59% and 75%, respectively. Cox regression analysis revealed that adverse prognostic factors for survival were transformation to aggressive non-Hodgkin's lymphoma (hazard ratio [HR] 6.6; $p<0.001$), bone marrow involvement at diagnosis (HR 4.4; $p=0.005$), age >60 years (HR 2.6; $p=0.041$) and more than one affected region at diagnosis (HR 3.4; $p=0.007$). The initial primary MALT lymphoma localization did not affect prognosis in this group of patients.

Discussion

In contrast to the current dogma that MALT lymphoma remains confined to its original site for long periods of time, in this series of MALT lymphoma patients with a primary

Table 3. New MALT lymphoma localizations detected during follow-up in the 72 patients with non-gastric MALT lymphoma.

Group: (n)	*Lymph node*	*Bone marrow*	*Orbital*	*Salivary*	*Waldeyer's ring*	*Lung*	*Stomach*	*Intestinal*	*Other*
Orbital (7)			1						
Waldeyer's ring (6)	1				1	1	1		1 ADR
Salivary (21)	4	2	1	4		3	1		1 kid, 1 CNS
Thyroid (4)									
Breast (4)									1 skin
Lung (8)						3	2		
Intestinal(11)	2					2	2	2	1 BL, 1 BR
Hepatic (3)	1	1	1				1		
Urogenital (8)	2	2							

n: number of patients; ADR: adrenal gland; kid: kidney; CNS: central nervous system; BL: bladder; BR: breast.

Table 4. Additional lymphoma localizations at diagnosis in the 72 patients with non-gastric MALT lymphoma treated in Amsterdam and in 34 patients with non-gastric MALT lymphoma with more than one localization at presentation treated in Vienna.

Group: (n)	*Lymph node*	*Bone marrow*	*Orbital*	*Salivary*	*Waldeyer's ring*	*Lung*	*Stomach*	*Intestinal*	*Other*
Orbital (18)	1		5		1	2	1	1	2 skin
Waldeyer's ring (6)	2						1	1	
Salivary (29)	8	2	3	5	1				1 th
Thyroid (4)									
Breast (7)	1	2	2						2 skin, 1 BR
Lung (13)	1	1		2	1	1	7		
Intestinal(16)	4	1			2	2	3	7	1 BL, 1 BR
Hepatic (3)	2	1					1		1 spl
Urogenital (10)	4	1							

adr: adrenal gland; kid: kidney; CNS: central nervous system; BL: bladder; BR: breast; spl: spleen; th: thymus.

localization outside the stomach, extensive staging procedures at presentation revealed disseminated disease in 47.2% with multiple mucosal localizations (19%), dissemination to bone marrow (7%) and lymph nodes (18%). Thus far, dissemination in non-gastric MALT lymphoma has been reported at presentation with very varying frequencies and is probably mostly related to the thoroughness of the staging procedures.[10,11,13] Moreover, as shown in our combined Dutch and Austrian series of 106 patients, specific patterns of dissemination seem to be present and characteristic to the primary site of presentation, supporting the notion that expression of special homing receptors and adhesion molecules are involved in the trafficking of MALT specific lymphocytes to MALT-containing organs.[2,6,8,9] Additionally, the driving force of antigen-dependent lymphoproliferation by chronic antigenic stimulation by either microbial pathogens (e.g. *H. pylori, C. psittaci, B. burgdorferi*) or auto-antigens (e.g. in Hashimoto's thyroiditis and Sjögren's syndrome) may play a role in determining the risk of lymphoma involvement of additional specific mucosal sites in the different primary non-gastric MALT lymphoma groups.[15] The observed contralateral organ involvement and involvement within the same tract in the orbital, salivary gland, lung and intestinal groups, as observed in this study, strongly support this hypothesis. Bilateral involvement in salivary gland and orbital MALT lymphoma after a long-standing history of Sjögren's syndrome and lupus erythematosus, as observed by Raderer, underscores the principle of chronic antigenic stimulation in MALT lymphoma.[13] However, apart from the preference for mucosal sites, bone marrow and lymph node involvement at presentation was seen in 10% and 18% of the patients, respectively. Thus, since non-gastric MALT lymphoma is often a multifocal disease, extensive staging at diagnosis remains important.[16]

During follow-up, specific characteristics were observed between the different primary MALT lymphoma localizations and patterns of dissemination were retained. No relapses were seen in the thyroid group. In the other groups, relapses were primarily confined to the original organ system and the regional lymph nodes and bone marrow. The pattern of dissemination of primary lung localizations to the gastric mucosa was retained in cases of relapsed disease. However, a high percentage of relapses in the gastric mucosa was also observed in the other groups (18% of all relapsed localizations outside the original tract). Our findings that MALT lymphoma at some specific primary sites remain confined are largely in line with previous observations i.e. one single MALT localization was observed in 57 of 103 patients with non-gastrointestinal MALT lymphoma in a series reported by Thieblemont *et al.* and in 115 of 180 patients with non-gastric MALT lymphoma in a series described by Zucca *et al.*[5,10]

Based on this retrospective analysis and supported by other published data, there are sufficient arguments to recommend complete staging with emphasis on all MALT sites at presentation, but limited to the primary dominantly involved MALT organ system (including the regional lymph nodes) as well as the lungs and stomach as sites at risk of relapse during follow-up. Additional clinical investigations during follow-up, including bone marrow analysis, should only be performed in a sign- or symptom-driven approach. Since no randomized studies have been performed to date on treatment in non-gastric MALT lymphoma, treatment strategies are mainly based on a *patient-tailored* approach, including information on the primary MALT localization and stage. Knowledge of the characteristic patterns of dissemination at diagnosis and follow-up is essential for this approach to have the most favorable clinical outcome and to be carried out in an optimally patient-friendly and cost-effective manner.

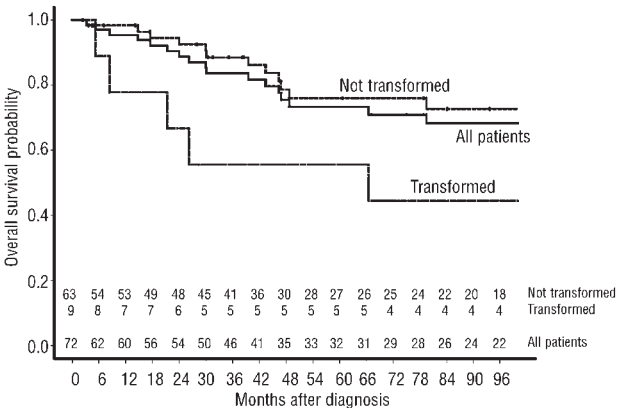

Figure 1. Overall survival of the 72 patients with non-gastric MALT lymphoma. The estimated 6-year survival for all patients was 71% and that for patients with transformation to aggressive lymphoma was 46%.

Current protocols for localized disease, e.g. localized orbital, salivary gland and thyroid lymphoma, most frequently include radiotherapy as first-line therapy, whereas chemotherapy is administered for localized pulmonary lymphoma.[5] In case of multiorgan involvement, which can be expected in almost 50% of the patients, according to this study and others,[10,12,13] systemic therapy with either chemotherapy or chemotherapy in combination with rituximab could be a good treatment approach. Alkylating agents, fludarabine, cladribine and platinum compounds as single agents or in combination have been active with good response rates (i.e. 93-100%) and acceptable toxicity in non-gastric MALT lymphoma.[17,18-20] Single agent therapy with rituximab has also been proven to be active with a median response rate of 73% and a median response duration of 10.5 months.[21] The value of combined therapy with rituximab and chlorambucil in patients with MALT lymphoma with no response to local therapy or with disseminated disease is currently under investigation by the IELSG in a multi-center, international, randomized study. In view of the high frequency of secondary localizations in the stomach, with 55% associated with *H. pylori*, special emphasis should be given to the diagnosis and treatment of *H. pylori* infection at presentation and during follow-up. It should be noted that non-gastric MALT lymphoma gener-

ally runs an indolent course in the majority of the patients; the estimated survival of 71% at 6 years in this analysis is fully in line with the results of other retrospective studies.[5,10-13] Moreover, only 40% of the deaths were lymphoma-related, and half of these were due to transformation into an aggressive B-cell lymphoma (DLBCL, n=3).

The prognosis of non-gastric MALT lymphoma is related to older age (>60 years), performance status, multiple MALT sites, nodal disease, International Prognastic Index score and bone marrow involvement.[5,11,13] As shown in this study, primary localization and several of these additional prognostic factors are not independent and, as expected, life expectancy in patients with primary orbital and thyroid localizations, the typically localized diseases without nodal disease or multi-organ involvement, is excellent.

In conclusion, the patterns of dissemination and relapse and the clinical course of patients with MALT lymphoma with primary localizations outside the stomach support a patient-tailored approach with primary site-directed protocols for follow-up focused on the primary involved tract/organ system including regional lymph nodes and additional emphasis on pulmonary and gastric relapses. In view of the high incidence of multifocal disease and the consequences, in terms of choosing systemic therapy, extensive staging at diagnosis remains essential.

Authorship and Disclosures

JPdB: designed the research, collected data, was involved in data analysis, wrote the manuscript, and approved the final manuscript; RH: collected data, was involved in data analysis, and approved the final manuscript; MR: collected data, was involved in data analysis, and approved the final manuscript; NA: performed the statistical analyses, and approved the final manuscript; BMPA: designed the research, was involved in data analysis, and approved the final manuscript; HB: designed the research, was involved in data analysis, and approved the final manuscript; DdJ: designed the research, revised all histological material, was involved in data analysis, wrote the manuscript, and approved the final manuscript. The authors reported no potential conflicts of interest.

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