Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed

Catherine Thieblemont, Françoise Berger, Charles Dumontet, Isabelle Moullet, Fadhela Bouafia, Pascale Felman, Gilles Salles, and Bertrand Coiffier

Mucosa-associated lymphoid tissue–derived lymphoma (MALT lymphoma) is usually a very indolent lymphoma, described as localized at diagnosis and remaining localized for a prolonged period; dissemination occurs only after a long course of evolution. In our database, out of 158 patients with MALT lymphoma, 54 patients presented with a disseminated disease at diagnosis. Of these 54 patients, 17 patients (30%) presented with multiple involved mucosal sites; 37 patients (70%) presented with 1 involved mucosal site, but in 23 of these patients (44%), dissemination of the disease was due to bone marrow involvement; 12 patients (22%) had multiple lymph node involvement; and 2 patients (4%) had nonmucosal site involvement. No significant difference in clinical characteristics (sex, age, performance status, B symptoms) and biological parameters (hemoglobin [Hb] and lactate dehydrogenase levels) was observed between localized or disseminated MALT-lymphoma patients. Only β2-microglobulin level was significantly more elevated in disseminated disease patients than in localized disease patients. Complete response after the first treatment was achieved in 74% of the patients, and there was no difference between the 2 groups. With a median follow-up of 4 years, the estimated 5- and 10-year overall survival rates were similar in the 2 groups, 86% and 80%, respectively. The median freedom-from-progression survival was 5.6 years for all patients, surprisingly without any difference between localized and disseminated MALT-lymphoma patients. In conclusion, MALT lymphoma is an indolent disease but presents as a disseminated disease in one-third of the cases at diagnosis. The dissemination does not change the outcome of the patients. (Blood. 2000;95:802-806)

Introduction

Mucosa-associated lymphoid tissue–derived lymphoma (MALT lymphoma), first described in 1983 by Isaacson and Wright,[1] was recognized only in 1994 as a distinct entity of lymphoma in the revised European–American lymphoma (REAL) classification among the marginal zone B-lymphomas[2] as well as in the more recent classification proposed by the World Health Organization (WHO).[3]

Histologically, MALT lymphomas are characterized by a proliferation of neoplastic marginal zone–related cells that invade epithelial structures and form characteristic lymphoepithelial lesions. MALT lymphomas are the most common subset of the extranodal lymphomas. They arise not only from the stomach but also from various nongastrointestinal sites, such as salivary gland, conjunctiva, thyroid, orbit, lung, breast, kidney, skin, liver, and prostate.[4] The origin of MALT lymphoma is an accumulation of autoreactive lymphoid tissue generated by either chronic inflammatory disorders or autoimmune disease such as *Helicobacter pylori* infection of the stomach,[5] Hashimoto's thyroiditis,[6] or myoepithelial sialoadenitis (Sjögren's syndrome) of the salivary gland.[7] This lymphoid tissue becomes genetically unstable with the acquisition of abnormalities such as translocations t11;18 and t1;14 trisomy 3, c-myc (8q24), and p53 (17p13) mutations leading to transformation into MALT lymphoma. MALT lymphomas are low-grade lymphomas, and histologic progression from a low-grade MALT lymphoma to a high-grade lymphoma is rare, occurring in $<10\%$ of the cases,[4] and is associated with other genetic events such as $p16^{Ink}$ or p53 inactivation.

Clinically, MALT lymphomas behave as an indolent disease with a prolonged clinical course. Patients have a good outcome with a long disease-free survival and long overall survival, and as a result, MALT lymphomas are known as ''pseudolymphomas.'' Several explanations for this indolence have been given, and the most frequently cited reasons are that these lymphomas are believed not to disseminate as often as their nodal equivalents, and then they often remain localized for long periods.[8]

Among the patients with MALT lymphoma treated in our department, we found a significant number presenting with a disseminated disease at diagnosis. This observation prompted us to review all our patients with MALT lymphoma and to analyze the behavior of 2 groups of patients: those with localized disease at diagnosis and those with disseminated disease at diagnosis. We analyzed 158 patients, and we confirmed that one third of the patients presented at diagnosis with disseminated disease.

Patients and methods

Patient selection

Between October 1987 and January 1999, 159 patients with low-grade MALT lymphoma were seen in our department; this represents approximately 5% of all lymphoma patients in our database. To be included in this study, patients were required to fulfill all histologic criteria defined

From the Service d'hématologie and laboratoire d'hématologie, Centre Hospitalier Lyon Sud, Pierre-Bénite, France, and the Service d'Anatomie pathologique, Hôpital Edouard Herriot, Lyon, France.

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Reprints: Bertrand Coiffier, Service d'hématologie, Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Université Claude Bernard, 69495 Pierre-Bénite, France; e-mail: bertrand.coiffier@chu-lyon.fr.

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previously.[1,9] Histologic transformation to high-grade MALT lymphoma was diagnosed by the presence of 50% blast cells or by the presence of sheets of large cells associated with a high mitotic activity.

All cases were retrospectively studied to collect complete information about disease history. One patient diagnosed simultaneously with localized gastric MALT lymphoma and colon carcinoma was excluded from the analysis.

Staging procedure

Initial staging procedures included complete physical examination; computed tomography of the thorax, abdomen, and pelvis; gastrointestinal (GI) tract endoscopic examination with or without echography for the patients with GI symptoms; bone marrow biopsy; and biological parameters with serum lactic dehydrogenase (LDH), β2-microglobulin, and blood count. Performance status (PS) was evaluated according to the Eastern Cooperative Oncology Group (ECOG) scale. Patients were staged according to an adapted classification of extranodal lymphoma.[10] Localized disease was defined as a stage I or IIE disease, and disseminated disease was defined as a stage III or IV disease. Abdominal computed tomography or echo-endoscopic exploration was used to stage GI tract patients. Stage IE corresponded to disease confined to the stomach, and stage IIE corresponded to disease with gastric or intestinal wall involvement associated with regional nodes. No biopsy of the nodes was required to classify the disease in stage IIE. Stage IV corresponded to disseminated extranodal involvement or a GI tract lesion with supradiaphragmatic nodal involvement. Non-GI tract involvement was classified as nongastric-involved disease. Localized disease corresponded to a disease confined to the involved organ with or without regional node involvement. Disseminated disease corresponded to a disease with involvement outside the initially involved organ and the regional nodes.

Treatment modalities

Patients were treated according to the disease stage and disease location. Treatments are listed in Table 1. Patients with localized lymphoma were treated with surgery, local radiation therapy (RT), or single-agent chemotherapy (chlorambucil, cyclophosphamide, or fludarabine). Some patients received adjuvant treatment (chemotherapy or RT) after surgery. Patients with localized gastric MALT lymphoma with *H. pylori* (HP) infection were treated with antibiotics (amoxicillin and clarithromycin) and an antiacid (omeprazole). Most of the patients with disseminated lymphoma were treated with chemotherapy using single agents (chlorambucil, cyclophosphamide, or fludarabine). If adverse prognostic factors, such as PS ≥ 2, a high LDH level, or an extranodal location > 2, were present, one of two multidrug regimens were used: CHOP (cyclophosphamide, doxorubicin, vincristine (Oncovin), and prednisone) or CHOP-like (ACVB; adriamycin, cyclophosphamide, vincristine, and bleomycin).[11]

Treatment

Surgery or RT was used to treat 64 patients (62%) with localized lymphoma; 15 of these patients required additional adjuvant chemotherapy and/or RT treatment (Table 1). Chemotherapy was used to treat 32 patients (31%) with localized disease: chlorambucil (n = 22), cyclophosphamide (n = 1), fludarabine (n = 5), or polychemotherapy regimens with CHOP (n = 3) or an association of vepeside (VP) 16 and ifosfamide (n = 1). Of the 8 patients with localized GI tract involvement, 7 patients (6%) were treated with an anti-HP treatment, and 1 patient was not given any treatment. We treated 95% (n = 50) of the disseminated lymphoma patients with chemotherapy: 35 patients (70%) were treated with single agents chlorambucil (n = 24) or fludarabine (n = 11), and 15 patients (30%) were treated with multidrug regimens CHOP (n = 11) or ACVB (n = 4). Of the disseminated lymphoma patients, 23% underwent surgery before chemotherapy.

Table 1. Treatment of MALT lymphoma patients according to the stage of the disease

	All Patients		Stage I-II		Stage III-IV	
	n	(%)	n	(%)	n	(%)
Total	158	(100)	104	(67)	54	(33)
No initial treatment	1	(0.006)	1	(1)	0	—
Anti-HP treatment	7	(4)	7	(6)	0	—
RT	14	(9)	11	(11)	3	(3)
RT and chemotherapy	1	(0.006)	1	(1)	0	—
Surgery						
Surgery alone	39	(25)	38	(37)	1	(2)
Surgery and RT	4	(3)	4	(3)	0	—
Surgery and chemotherapy	21	(14)	9	(9)	12	(23)
Surgery and chemotherapy and RT	1	(0.006)	1	(1)	0	—
Chemotherapy	70	(45)	32	(31)	38	(72)

Statistical analysis

Overall survival was defined as the time from diagnosis (first biopsy) to death or last follow-up. Freedom-from-progression (FFP) survival was defined from onset of treatment to the date of the first progression or last follow-up. Complete remission (CR) was defined as the disappearance of all clinical evidences of the lymphoma. In one patient with GI involvement that was not treated surgically, CR was proven when a biopsy examination revealed the disappearance of histologically active neoplastic disease. Relapse was defined as the appearance of a new lesion for patients in CR or an increase in the volume of preexisting lesions for patients in partial remission. The following parameters were recorded: sex, age, stage, PS, B symptoms, anemia, LDH and β2-microglobulin levels, treatment, response to treatment, and histology at relapse. Actuarial survival curves were calculated using the Kaplan-Meier method, and differences between these parameters were tested for significance with the log-rank test.[12,13] The chi-square (χ^2) test was used in univariate analysis to determine significant difference between percentage, which was defined as $P < .05$. All of the factors found to be significant in univariate analysis were included in a multivariate analysis using a Cox proportional hazards model to determine independent prognostic factors for survival.[14] All statistical analyses were performed on the same software (Statistica version 5, 97 edition, Statsoft, Tulsa, OK).

Results

Patient characteristics

Patient characteristics are listed in Table 2. Median age at diagnosis was 57 years (range, 21-89 years). The female-to-male ratio was 1.06:1. Of the patients retrospectively assessable for PS, 64 patients (97%) had good PS, and 23 patients (14%) had B symptoms. Only 24 patients (15%) had anemia, 9 had increased LDH, and 20 had high levels of β2-microglobulin.

Initial lymphoma locations at diagnosis are detailed in Table 3. The majority of patients, 140 (89%), presented with only 1 location in MALT, and 18 patients (11%) presented with multiple locations. At diagnosis, 78 patients (49.5%) presented with GI tract involvement. Among these patients, 7 patients presented with multiple locations inside the GI tract, and 7 presented with multiple locations inside and outside the GI tract. Half of the total patients (n = 80, 50.5%) had involvement outside of the GI tract, 22 with lung involvement, 6 with breast involvement, 19 with orbit involvement, 22 with head and neck involvement, 6 with thyroid involvement, and 17 with skin involvement; 4 patients had multiple MALT locations outside the GI tract.

Among the 158 patients with MALT lymphoma, 2 groups were distinguished by the dissemination of the disease at diagnosis: 104 patients (66%) had stage I or stage IIE disease, and 54 patients (34%) had stage III or stage IV disease (Table 4). Dissemination

Table 2. Clinical and biological characteristics of MALT lymphoma patients according to the stage of the disease

	All Patients		Stage I-II		Stage III-IV	
	n	(%)	n	(%)	n	(%)
Total	158	(100)	104	(66)	54	(34)
Sex						
Male	76	(48)	54	(52)	22	(41)
Female	82	(52)	51	(48)	31	(59)
Age (years)						
Less than 65	111	(70)	78	(75)	33	(61)
At least 65	47	(30)	26	(35)	21	(39)
Performance status (ECOG)						
0-1	63	(97)	33	(97)	30	(97)
> 2	2	(3)	1	(3)	1	(3)
B symptoms						
Absent	135	(85)	92	(88)	43	(80)
Present	23	(14)	12	(12)	11	(20)
Bone marrow involvement	31	(20)	0	—	31	(58)
Spleen involvement	13	(8)	1*	(1)	12	(22)
Liver involvement	7	(4)	0	—	7	(13)
Extra nodal involvement						
1	116	(75)	103	(99)	12	(23)
At least 2	42	(25)	1†	(1)	42	(77)
Hb less than 12 g/dL	24	(21)	10	(10)	14	(26)
LDH greater than normal	9	(6.5)	5	(5)	4	(7)
β2-microglobuline greater than 3 mg/L	20	(22)	4	(4)	16	(30)

*This patient presented with gastric MALT lymphoma with histologically involved mesenteric lymph nodes and splenomegaly without histologically proven involvement. This patient was considered as having a stage II disease.

†This patient presented with gastric localized MALT lymphoma, but the histologic analysis of systematic hepatic biopsy made during the gastrectomy reported a suspicious infiltration of small lymphocytes with cellular atypia. This patient did not present any sign of clinical or biological liver disease during the evolution and then was considered as having a localized disease with 2 involved extranodal sites: stomach and suspected liver.

Table 3. MALT lymphoma localizations according to the stage of the disease

	All Patients		Stage I-II E		Stage III-IV	
	n	(%)	n	(%)	n	(%)
Total	158	(100)	104	(100)	54	(100)
One MALT-organ localization	140	(89)	103	(99)	37	(70)
GI tract						
Stomach	52	(33)	46	(44)	6	(13)
Intestinal tract	12	(8.5)	8	(8)	4	(7)
Non-GI tract						
Lung	15	(9.5)	8	(8)	7	(13)
Breast	5	(3)	3	(3)	2	(4)
Orbit	16	(10)	12	(11)	4	(7)
Head and neck	18	(11)	13	(12)	5	(9)
Thyroid	6	(4)	6	(6)	0	—
Skin	16	(10)	7	(7)	9	(17)
Multiple MALT-organ localizations	18	(11)	1	(1)	17	(30)
GI tract						
Stomach + intestinal tract	7	(3.5)	1	(1)	6	(10)
Non-GI tract						
Lung + orbit	1	(0.75)	0	—	1	(2)
Lung + skin	1	(0.75)	0	—	1	(2)
Orbit + head/neck	1	(0.75)	0	—	1	(2)
Orbit + head/neck + breast	1	(0.75)	0	—	1	(2)
GI tract + non-GI tract						
GI tract + lung	5	(3)	0	—	5	(10)
Stomach + head/neck	2	(1.5)	0	—	2	(04)

was explained by multiple locations of the disease in mucosal sites in 17 (30%) of the patients. The number of involved sites varied between 2 and 4 different locations. Among these 17 patients, 8 patients (47%) also had bone marrow involvement. Of the 54 patients with disseminated disease, 37 patients (70%) presented with only 1 MALT-organ involved. In these 37 cases, dissemination was observed because of bone marrow involvement in 23 patients, multiple lymph node involvement in 12 patients, or non-MALT organ involvement such as the liver or pleura. Considering all patients, bone marrow involvement was detected in 31 patients (20%) at diagnosis (Table 5).

The comparison between localized and disseminated MALT-lymphoma patients did not demonstrate any differences in either clinical characteristics (sex, age, performance status, B symptoms) or in biological parameters (Hb and LDH levels). Only β2-microglobulin was significantly more elevated in the disseminated disease patients than in the localized disease patients. Presentation with localized disease was significantly more frequent in patients with GI tract involvement (55/71 patients [77%]) compared with patients who had no GI tract involvement (49/80 patients [61%]) (χ^2, $P = .036$).

Response to treatment

Response to treatment was assessable in 144 patients, and 14 patients were still under treatment at the time of the analysis. Complete response after the first treatment was achieved in 74% (106/144 patients). A significant difference was observed between the percentage of complete response after the first treatment for localized lymphoma patients (80/97 patients, 82%) and for the disseminated lymphoma patients (27/47 patients, 57%) (χ^2, $P = .0017$). CR was obtained in more than 75% of patients, except in the group of patients treated with chemotherapy, which had a CR rate of 63%. Retrospectively, patients treated with chemotherapy had the worst prognosis. Sixty-three patients progressed with a median time of 3 years without statistical difference between localized disease (3.2 years) and disseminated disease (2 years). The same relapse rate was observed in the localized lymphoma patient group (27/80 patients, 33%) and in the disseminated lymphoma patient group (10/27 patients, 37%) (χ^2, $P = .84$). Histologic transformation, defined as an infiltration of 50% or more of large B cells, occurred in 8% of the patients during the course of the disease, without statistical difference between the localized lymphoma group (9 patients) and the disseminated lymphoma group (3 patients).

Table 4. Different locations making the lymphoma a stage III-IV disease

	Stage III-IV	
	n	(%)
Total of disseminated disease	54	(100)
One MALT location	37	(70)
Bone marrow involvement	23	(44)
No bone marrow involvement	14	(26)
With multiple lymph node involvement	12	(22)
With liver involvement	1	(2)
With spleen and pleural (without lung) involvement	1	(2)
Multiple MALT locations	17	(30)
With bone marrow involvement	8	(14)
Without bone marrow involvement	8	(14)
Bone marrow status unknown	1	(2)

Table 5. Bone marrow status in patients with stage III-IV disease

	Stage III-IV	
	n	(%)
Total	54	(100)
BM +	31	(58)
With multiple MALT locations	8	(15)
With one MALT location	23	(43)
BM −	22	(41)
With multiple MALT locations	8	(15)
With one MALT location		
With multiple lymph node locations	12	(22)
With non-MALT liver location	1	(2)
With non-MALT pleura and spleen location	1	(2)
BM status unknown		
With multiple MALT locations (lung + GI tract)	1	(1)

BM+ indicates bone marrow involvement; BM− indicates no bone marrow involvement.

Survival

The median follow-up was 4 years, 4.5 years for the localized lymphoma patient group and 4 years for the disseminated lymphoma patient group. The estimated 5- and 10-year overall survival rates were similar in the 2 groups, at 86% and 80%, respectively ($P = .28$), as given in Figure 1. The median FFP survival was 5.56 years for all patients, and surprisingly, there was little difference in the FFP survival times of localized and disseminated MALT-lymphoma patients ($P = .70$). Patients with localized disease had an average FFP survival of 3.23 years (range, 30 days to 23.6 years), and patients with disseminated disease averaged 1.95 years (range, 56 days to 8 years), as given in Figure 2. Death occurred in 17 patients. In 10 patients (60%), death was related to a progression of the disease with multiple localizations. The other 7 patients had various causes of death: sepsis, 2 patients; stroke, 2 patients; lung and gastric carcinoma (with the MALT lymphoma still in CR), 2 patients; and unknown reason, 1 patient.

Prognostic factors

Adverse prognostic factors for survival were age greater than 60 years, a high serum β2-microglobulin level, and a CR not reached after the first treatment. A shortened FFP survival was associated with localizations other than GI tract involvement at diagnosis, anemia, high β2-microglobulin level, and a CR not reached after the first treatment.

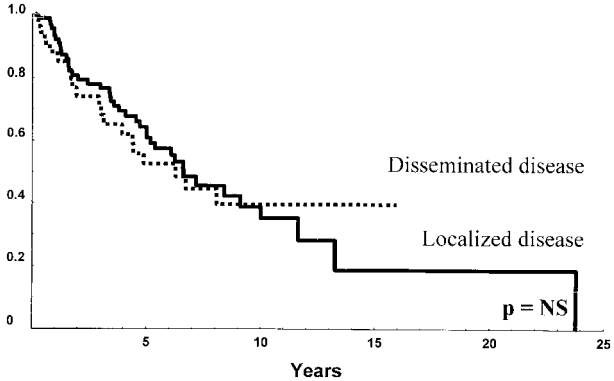

Figure 1. Overall survival of 158 MALT lymphoma patients according to the stage of the disease. Predicted overall survival of patients with localized and disseminated disease was similar: 86% at 5 years and 80% at 10 years, with a median follow-up time of 4 years.

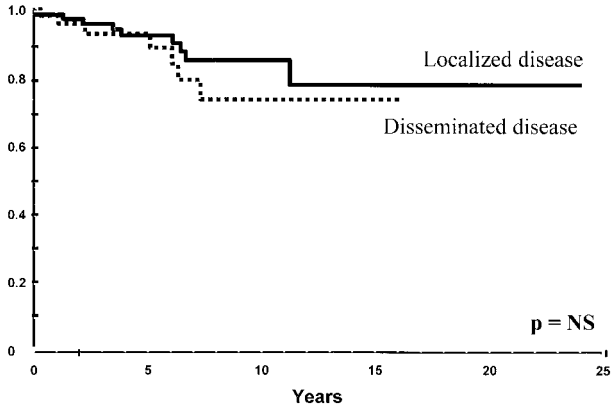

Figure 2. FFP survival of 158 MALT lymphoma patients according to the stage of the disease. No significant difference was observed between patients with either localized disease or disseminated disease. Median FFP survival was 5.56 years for all patients.

In a multivariate analysis, shorter overall survival was associated with high β2-microglobulin level only. Shorter FFP survival was associated with the absence of complete response after the first treatment.

Discussion

In our series concerning 158 cases with MALT lymphoma, one-third of patients presented at diagnosis with a disseminated disease. This observation stands in contrast with what is usually reported in the literature,[15] where MALT lymphoma presents as a localized disease in approximately 90% of the patients and remains confined to the site of origin for a prolonged period after diagnosis. However, Zinzani et al.[16] found that in a series of 75 patients with nongastric MALT lymphoma, 37% had disseminated disease. When dissemination occurred, described as usually late in the course of the disease after many relapses,[17] its tendency was to metastasize to another site within the organ of origin or to another MALT-containing organ. This particular behavior, unique among lymphomas, has been described by Isaacson[8,18] as the MALT concept. Biologically, dissemination both inside the same organ of origin and inside MALT-containing organs may be linked to the expression of special homing receptors or adhesion molecules at the surface of MALT normal cells and MALT lymphoma cells.[19,20]

Our analysis shows that dissemination of MALT lymphoma can be observed at diagnosis. This dissemination can be explained by an involvement of multiple mucosal sites (in 11% of the cases) and/or an involvement of nonmucosal sites such as bone marrow (in 20% of the cases). In our series, multiple mucosal site involvement concerned not only the GI tract, with dissemination to the stomach or intestines, but also the GI tract and non–GI tract organs, with dissemination to other mucosal organs. This is in keeping with the theory of homing of the neoplastic lymphocytes. The second type of dissemination was observed in non-MALT sites such as in the spleen or bone marrow. Explanation for spleen involvement in MALT lymphoma has been controversial, and the debate continues as to whether or not the dissemination is related to a preferential homing.[21,22] Bone marrow involvement, usually reported as a late occurrence in the course of the disease,[17] was not uncommon at diagnosis in our series; 20% of our cases had bone marrow involvement. No data are reported in the literature

concerning biological aspects of bone marrow involvement in MALT lymphoma.

Our observation of early dissemination of the disease led us to believe that at diagnosis, MALT lymphoma should be considered a multifocal disease, with involvement in MALT-containing organs or non–MALT-containing organs. This has already been reported in patients with apparently localized gastric MALT lymphomas who presented with colonic dissemination diagnosed with colonic biopsies.[23] What is the possible impact of this observation for patients presenting with MALT lymphoma? Should the staging procedure be changed and include systematic complete endoscopy of GI tract and bronchoscopy, even in the absence of clinical symptoms? Should the treatment be changed to include more frequent use of chemotherapy rather than local treatments such as surgery or radiotherapy?

It is important to know the exact extension of the disease at diagnosis. Indeed, we concluded that the diagnosis of dissemination did not change the outcome of the disease, particularly given the same FFP survival in patients with disseminated and localized disease. Given this, then aggressive staging procedures may have to be evaluated for each patient according to the clinical symptoms. Even with the development of a probable multifocal disease, we did not demonstrate better results with one treatment compared with another. As a result, we support the recently published treatment recommendations.[24,25] Patients with localized MALT lymphoma may be treated with surgery, local radiotherapy, or single chemotherapy using chlorambucil, with a preference for the last treatment proposed. Considering a particular *H Pylori*–related localized gastric MALT lymphoma, anti–*H Pylori* treatment has to be proposed as first-line therapy. Patients with disseminated forms of the disease should be treated with chemotherapy using chlorambucil, and patients with a large tumoral mass or an important large-cell component should be treated with the CHOP regimen.

Our curious observation of the same outcome in both groups, particularly with similar FFP survivals, may be the result of our failure to make the diagnosis of multifocal involvement in some patients and our resultant classification of these patients as having localized disease. It is true that the number of patients in the 2 groups is small, and we need to extend our follow-up to confirm any difference in terms of relapse between localized and disseminated MALT patients.

We confirmed, in spite of the high percentage of dissemination, that MALT lymphoma is an indolent disease. Our results of survival and response rates to treatment are in agreement with previous reports.[15,16] Heterogeneous treatments were given to the patients because of the different disease stages and the status of the patients at diagnosis. The impact of these different therapies was not analyzed, considering the small number of patients in each treatment group, as detailed in Table 1. Transformation to high-grade lymphoma was observed in the late course of the disease in 8% of the patients. This histologic progression appears to be independent of dissemination.

In conclusion, our analysis indicated that at diagnosis, MALT lymphoma can be a disseminated disease in mucosal or nonmucosal sites, and patient outcome is not altered because of this dissemination. In addition, patient outcome was not affected by various current treatment strategies, although this may change, depending on the outcome of prospective trials of new therapeutics, such as rituximab.

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