

GASTRIC LYMPHOMAS: 25+ Years of Revolution/Evolution

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The gastrointestinal tract is the most common location of extranodal lymphomas and the stomach in particular serves as an excellent model to illustrate many of the general issues concerning extranodal lymphomas. The stomach is the most frequent site of involvement of extranodal gastrointestinal lymphomas with small intestine second in frequency. Large intestinal and rectal lymphomas are less common, but are found in patients with AIDS and occasionally as a complication of ulcerative colitis and Crohn disease. In a study of 371 patients with primary gastrointestinal lymphomas registered in a German Multicenter Study, stomach accounted for 277 of cases ((74.8%). Curiously, the incidence of primary gastric lymphomas in the United States is increasing, specifically in patients over 60 years of age; this increase appears independent of the AIDS epidemic and the now common diagnosis of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type.

The concept of extranodal marginal zone lymphoma of MALT type has revolutionized the criteria for the morphologic diagnosis of an extranodal lymphoma, specifically those lymphomas dominated by small lymphocytes. Moreover, since the initial descriptions of lymphomas of MALT in 1983 and 1984 by Drs. Peter Isaacson and Dennis Wright, the criteria have evolved and expanded to encompass not only morphologic standards, specifically a more precise definition of various cell types in MALT lymphoma, the proposals for “lymphoepithelial lesions” and “follicular colonization,” the relationship between MALT lymphomas and marginal zone B cells, and a scoring system for diagnosis of gastric MALT lymphoma, but also to embrace immunophenotypic, biologic, molecular genetic and clinical discoveries. Such developments include refinement of the immunophenotype, the association of gastric MALT lymphoma and *Helicobacter pylori* infection, the notion of acquired MALT, the biology of auto-antigen activation and continuous somatic mutations, genetic aberrations, as for example the discovery of the t(11;18)(q21;q21) chromosomal translocation in lymphomas of MALT, and the clinical implications of specific cytogenetic alterations.

Revolution – Florid Gastric Lymphoid Hyperplasia (“Pseudolymphoma”) is Likely Malignant Lymphoma!

In establishing a histologic diagnosis of an extranodal lymphoma, pathologists are aware that various reactive lymphoid hyperplasias exist that mimic extranodal lymphomas clinically and pathologically, such as gastric lymphoid hyperplasia and chronic lymphocytic gastritis. To complicate matters, malignant lymphoma of extranodal marginal zone (MALT) type may develop in association with these reactive lymphoid infiltrates in the stomach.

In the 1960's and 1970's, the morphologic criteria to distinguish extranodal lymphoma from extranodal lymphoid hyperplasia were extrapolated from those used traditionally to distinguish malignant lymphoma from lymphoid hyperplasia in lymph nodes. The major criteria for this distinction included monomorphic lymphocytic infiltrates, cellular atypia, germinal centers and architectural disruption (Table 1).

Table 1
Traditional Histologic Criteria for Distinguishing Extranodal Lymphomas from Lymphoid Hyperplasias

Extranodal Lymphomas	Lymphoid Hyperplasias
Infiltrate monomorphous	Infiltrate polymorphous (lymphocytes in stages of transformation)
Cytologic atypia	Cytologic maturity (lymphocytes, plasma cells, and immunoblasts)
Germinal centers uncommon	Germinal centers common (usually in center of infiltrate)
Massive infiltration with architectural destruction	Random infiltration with architectural retention

Because more than 50% of gastric lymphomas are large B cell lymphomas with associated monomorphism, cellular atypia, and architectural destruction (e.g., obliteration of glands), these traditional criteria generally have proven to be reliable and applicable. Reactive lymphoid conditions that are at the opposite end of the spectrum equally do not pose diagnostic problems. Lymphocytic infiltrates that exhibit polymorphism, that display a range of mature lymphocytes (including plasma cells and immunoblasts), that are associated with well-defined germinal centers and that do not destroy completely the architectural landmarks of the stomach usually can be diagnosed confidently as benign and reactive.

The main difficulty in the separation of gastric extranodal lymphomas from

lymphoid hyperplasias concerns MALT lymphomas that are composed of small lymphocytes and that frequently are associated with germinal center formation. For these cases, the traditional histological criteria are not applicable. Multiparameter studies have revealed that many histologically ambiguous extranodal small lymphocytic proliferations in stomach are, in fact, monoclonal and, therefore, are presumed to be malignant lymphomas especially of MALT type. The application of immunologic and molecular genetic analyses to gastric small lymphocytic proliferations has served to vividly alter the traditional histologic criteria and has revealed myriad inconsistencies in these criteria (Table 2). For example, in a review of 97 cases originally diagnosed as gastric pseudolymphoma between 1970 and 1985 at the AFIP, 79% were reclassified as malignant lymphoma, with fully two-thirds of the newly classified lymphomatous cases interpreted as lymphomas of MALT type. The remaining cases were regarded as examples of lymphoid hyperplasia or atypical lymphocytic infiltrates. Consequently, the term "pseudolymphoma" is regarded as imprecise and anachronistic and no longer is acceptable as a diagnostic category.

Table 2
Modifications of the Traditional Histologic Criteria for Distinguishing Extranodal Lymphomas From Lymphoid Hyperplasia

- Extranodal lymphomas may be polymorphous (e.g., peripheral T cell lymphomas)
- Extranodal lymphomas may be composed of cytologically mature-appearing lymphocytes (marginal zone lymphoma of MALT type and other low-grade lymphomas with or without plasma cell differentiation)
- Germinal centers may be observed at the periphery of extranodal lymphomas and in the centers of many low-grade extranodal lymphomas, especially those of MALT type
- Degree of infiltration, architectural and epithelial destruction is highly variable in benign and malignant extranodal lymphocytic infiltrates

The conventional view was that extranodal lymphomas are characterized by nuclear membrane irregularities or atypia. Marginal zone lymphomas of MALT type, however, are cytologically mutable. Although MALT lymphomas typically are composed of marginal zone or centrocyte-like cells in the marginal zones, they also may have a monocytoid appearance, or they be composed of plasma cells, or they may have no, or only subtle, nuclear membrane irregularities similar to the cells of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL); the latter variant often is readily confused with extranodal lymphoid hyperplasia. A small lymphocytic proliferation that appears mature is the histologic norm of most cases of gastric lymphoid hyperplasia, yet cytologic maturity or minimal atypia is equally the histologic hallmark of most low-grade malignant lymphomas including those of MALT. How then

can these two groups be distinguished in a small biopsy specimen? In many cases, it is impossible to do when applying only histological criteria. This histologic dilemma prompted the use of the noncommittal term “extranodal small lymphocytic proliferation” to describe histologically ambiguous or indeterminate extranodal lymphocytic infiltrates. Current morphologic criteria used to separate a benign small lymphocytic infiltrate from a malignant small lymphocytic infiltrate includes the designations of whether the infiltrate is monomorphous, dense, or exhibits cytologic atypia or Dutcher bodies and whether this results in destruction of glands, follicles, or other structures indigenous to the stomach. If these morphologic features are unequivocally present, then the lymphocytic infiltrate likely is malignant lymphoma (see Table 3).

Our perspective of the small extranodal lymphocytic proliferations that appear mature has revised dramatically with the application of immunologic markers to analyze the clonality of these lesions. Correlative immunopathologic studies have now reduced the number of cases regarded as atypical or indeterminate. Naturally, cases remain, especially small biopsy specimens, in which the histologic features or immunologic findings remain equivocal; these cases should receive not only a descriptive diagnosis but also a request for a repeat biopsy with reservation of fresh tissues to determine clonality, whether by immunohistochemistry, flow cytometry, molecular techniques, or a combination thereof. When only fixed, paraffin-embedded tissues are available, a consistent determination of clonality in a biopsy specimen dominated by small lymphocytes usually is not possible in most laboratories. In some cases, however, immunologic studies of paraffin-embedded tissues can reveal an aberrant phenotype in the suspicious small lymphocytic population, such as the coexpression of B cell antigen CD20 and T cell antigen CD43. In most instances, the aberrant immunophenotype supports the diagnosis of an extranodal gastric B cell lymphoma. Prudence is necessary in the evaluation of immunoglobulin gene rearrangement studies employing polymerase chain reaction (PCR) techniques in fixed paraffin-embedded tissues; small monoclonal bands may occur in extranodal reactive lymphoid hyperplasias, as for example in chronic active gastritis associated with *Helicobacter pylori*.

As well as diagnostic problems encountered with the gastric lesions dominated by small lymphocytes, benign reactive germinal centers (lymphoid follicles) pose another risk in diagnosis. The presence of germinal centers is a commonly accepted histologic attribute of extranodal lymphoid hyperplasias. Germinal centers, however, are regular constituents of most gastric lymphomas of MALT. The essential morphologic characteristic of MALT lymphomas is their emulation of normal MALT as typified by Peyer patches found in the terminal ileum. The neoplastic B cells of MALT lymphomas are found in marginal-type zones surrounding reactive follicles and frequently attenuated rims of mantle zone lymphocytes. The germinal centers vary in appearance but commonly appear atrophic as a result of impingement by the

surrounding small lymphocytes. In MALT lymphomas of the stomach associated with peptic ulceration, germinal centers occur at the base of the ulcer and in the adjacent mucosa where they seem encroached upon and entrapped by the monotonous marginal zone lymphocytes. In some cases, the neoplastic B cells in the marginal zone invade the germinal centers in a process referred to as “follicular colonization.” Follicular colonization may simulate follicular lymphoma in cases where there are numerous follicles. At times, the lymphomatous proliferation may be so extensive as to result in architectural obliteration with masking of any residual germinal centers; however, the presence of former germinal centers can be highlighted by the immunohistochemical demonstration of follicular dendritic cells employing an antibody against CD21 or CD23.

Evolution – Refinement of Morphologic Criteria, Immunophenotype, Biology, Molecular Genetics and Clinical Therapy of Gastric MALT Lymphomas

The morphologic features of extranodal marginal zone lymphoma of MALT type have witnessed gradual changes since the initial descriptions by Isaacson and Wright. Although originally thought to be of follicular center cell origin, the lymphoma cells of MALT were later designated as “centrocyte-like” and currently are termed as “marginal zone cells.” Gastric lymphomas of MALT type typically are characterized by an expansion of the marginal-like zones surrounding benign germinal centers. As described, marginal zone cells constitute a variety of cell types ranging from small, to intermediate-sized lymphocytes, to large cells resembling immunoblasts. The marginal zone or centrocyte-like cells are small to medium-sized lymphocytes with variable nuclear membrane irregularities resembling a centrocyte or small cleaved cell. The most common form has abundant pale-staining cytoplasm and is referred to as monocytoid. Others forms of gastric MALT exhibit plasmacytoid features or resemble small lymphocytes. Occasionally, signet ring-type cells are observed in gastric MALT lymphomas and appear to represent a peculiar type of lymphoepithelial lesion in which the foveolar cells, disaggregated by the lymphomatous infiltrate, acquire a globoid, signet ring-type appearance. Regardless of cytologic composition, the marginal zone cells of MALT cells share immunophenotypic characteristics. Gastric MALT lymphomas are B cell derived with CD20 expression and frequently containing numerous admixed CD3-positive reactive T cells. Up to 50% of cases exhibit aberrant coexpression of CD43 which can prove helpful in diagnosis. Unlike CLL/SLL and mantle cell lymphomas, the lymphomas of MALT origin lack CD5 and are without *bcl-1* gene rearrangements. MALT lymphomas differ from follicular lymphomas in that they are CD10 negative and do not exhibit rearrangements of the *bcl-2* proto-oncogene. The absence of CD10 and *bcl-2* positivity in gastric lymphoma with an apparent follicular architecture has been rationalized by the concept of “follicular colonization”. As discussed above, follicular colonization refers to the simulation of a follicular lymphoma as a result of invasion by the marginal zone cells of MALT into pre-existing reactive follicles.

The marginal zone cells of MALT not only are thought to invade residual reactive follicles, but also epithelium. As mentioned previously, epithelial invasion by the centrocyte-like cells of MALT has been referred to as a “lymphoepithelial lesion” and is an important morphologic feature in the diagnosis of gastric MALT-derived lymphomas. Such lesions may be accentuated by an immunohistochemical stain for cytokeratin. Lymphoepithelial lesions are most significant as a diagnostic characteristic in the stomach, but are less relevant in other extranodal sites since they may be observed in non-lymphomatous extranodal lymphocytic infiltrates. In stomach, lymphoepithelial lesions usually are defined as invasion of gastric epithelium by three or more lymphomatous cells. A decade following the primary proposal for a lymphoma of MALT, a histologic scoring system for gastric MALT lymphoma was proposed in which invasion of epithelial structures or lymphoepithelial lesions is considered paramount to the diagnosis (Table 3).

Table 3
Gastric Marginal Zone (MALT) Lymphomas: Histologic Scoring*

Grade	Description	Histologic Features
0	Normal	Plasma cells in lamina propria No lymphoid follicles
1	Chronic active gastritis	Lymphocyte clusters in lamina propria No follicles, lymphoepithelial lesions
2	Chronic active gastritis with florid lymphoid follicle formation	Prominent follicles with surrounding mantle zone & plasma cells No LELs
3	Suspicious lymphoid infiltrate in LP, probably reactive	Follicles surrounded by lymphocytes that infiltrate diffusely in LP and +/- epithelium
4	Suspicious lymphoid infiltrate in LP, probably lymphoma	Follicles surrounded by CCL cells (MZO) that infiltrate diffusely in LP & epithelium
5	MZ (MALT) lymphoma	Dense diffuse infiltrate of CCL cells in LP with prominent LELs

**Lancet 1993;342:575-577*

Employing the scoring system, a definite diagnosis of low-grade B cell lymphoma of MALT is based on the presence of a dense diffuse infiltrate of centrocyte-like cells/marginal zone cells in the lamina propria with prominent lymphoepithelial lesions. Cases regarded as suspicious lymphocytic infiltrates are those in which reactive follicles are surrounded by marginal zone cells that diffusely infiltrate into the lamina propria and into epithelium in small groups. However, caution is required as there may

be dense infiltrates, slight cytologic atypia, and also lymphoepithelial-like lesions in cases of lymphoid hyperplasia in the stomach. As well, the criteria may be difficult to apply. In an interobserver study, 41 H&E sections of stomach that ranged from simple gastritis to lymphoma were reviewed by 17 pathologists, including hematopathologists, gi pathologists and general pathologists. Interobserver reproducibility was suboptimal and the degree of disagreement was directly related to the pathologist's experience in evaluating gastric biopsies for MALT lesions. The study recommended that diagnostic accuracy would be enhanced by clinical information, extensive sampling, recognition of lymphoepithelial lesions, immunophenotypic information and cytogenetic results. This recommendation was supported by another report stating that a combination of the morphologic scoring system and B cell clonality analysis by an advanced PCR method accurately discriminated chronic gastritis from covert gastric marginal zone lymphoma. PCR was particularly valuable in the interpretation of cases that exhibited an ambiguous score of grade 3 or 4.

Paradoxically, most MALT-type lymphomas arise in extranodal sites without normal MALT, such as the stomach, while non-MALT lymphomas, for example Burkitt lymphoma, arise in MALT sites. In order to resolve this apparent paradox, it was proposed that lymphomas in non-MALT sites arise in a setting of "acquired" MALT. This non-indigenous extranodal lymphoid tissue is thought to be acquired secondary to an infection, such as *Helicobacter pylori* in the stomach, or an autoimmune disease. The lymphoid infiltrates in stomach associated with *Helicobacter pylori* seemingly predispose patients to malignant lymphoma. There currently is sufficient histological, clinical, and epidemiologic evidence for the virtually fixed association of gastric MALT lymphomas with *Helicobacter pylori* infection, particularly the CagA strain. For example, in a collaborative study of more than 230,000 patients whose serum had been stored, 33 cases of gastric lymphoma developed a median of 14 years after serum collection. The patients with gastric lymphoma were significantly more likely than matched controls to have evidence of previous *Helicobacter pylori* infection. In contrast, no association was discovered among 31 patients who had developed nongastric non-Hodgkin lymphoma and previous *Helicobacter pylori* infection. In addition, molecular analysis by PCR has documented the clonal progression from *Helicobacter pylori*-associated chronic gastritis to MALT lymphoma of the stomach and *Helicobacter pylori* provides the antigenic stimulus for prolonging the clonal expansion of gastric MALT lymphomas. This view has been supported by Isaacson's group who have exhibited evidence of ongoing Ig gene mutations in most case of MALT-type lymphoma. The discovery of ongoing mutations reinforces the perception that direct antigen stimulation is paramount in the clonal expansion of gastric MALT lymphomas.

Clinically, gastric MALT lymphomas arise in adults with a peak in the seventh decade and with a male:female ratio of approximately 1.5:1. Patients commonly present with nonspecific gastritis and/or a peptic ulcer and at endoscopy, there often are reddened and slightly thickened rugae with superficial spreading of lesions without

formation of a tumor mass. The gastric lesions commonly are multifocal and most patients have stage IE disease. The linkage of *Helicobacter pylori* with gastric MALT lymphoma led to antibiotic therapy for treatment of low-grade gastric lymphomas of MALT and this therapy may induce sustained remissions in about 75% of patients. There are no apparent differences in survival and relapse-free survival between patients treated with antibiotics and with other modalities, such as local treatment, combined treatment, or chemotherapy; in fact, no consensus exists for the optimal treatment of primary gastric lymphoma. In one study of gastric MALT lymphomas treated by various modalities, the five year projected overall survival was 82%. One significant issue for pathologists is the interpretation of stomach biopsy specimens following antibiotic therapy for gastric MALT lymphoma. Clearly, no diagnostic problem exists if the biopsy reveals regression of the lymphoma with loss of lymphocytic aggregates in the lamina propria or if the biopsy exhibits a total absence of histological regression with persistence of lymphoma. Parallel to the histological scoring system employed for the initial diagnosis of gastric marginal zone lymphoma, a histological grading system has been proposed for treated patients. (Table 4).

Table 4
Gastric MZ (MALT) Lymphoma: Post-Therapy Grading*

Score	Lymphoid Infiltrate	LEL	Stromal Changes
CR	Absent or scattered plasma cells & small lymphoid cells in the LP	–	Normal or empty LP &/or fibrosis
pMRD	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM &/or SM	–	Empty LP &/or fibrosis
rRD	Dense, diffuse, or nodular extending around glands in the LP	+/-	Focal empty LP &/or fibrosis
NC	Dense, diffuse, or nodular	+/-	No changes

CR, complete histologic remission; pMRD, probable minimal residual disease; rRD, responding residual disease; NC, no change; LEL, lymphoepithelial lesions; LP, lamina propria; MM, muscularis mucosa; SM, submucosa
**Gut* 2003;52:1656

The probable minimal disease category (pMRD) does not signify a requirement for further therapy and patients are managed with followup as though they were in remission. Of interest, approximately 50% of patients with histologically negative post-antibiotic therapy gastric biopsies (CR/pMRD) exhibit persistent monoclonality, although in some patients the clone disappears with prolonged followup. In other patients, continued monoclonality may result in a delay in realizing remission.

However, following antibiotic therapy for gastric MALT lymphoma, the association between ongoing monoclonality and risk of relapse is tenuous. One bone of contention is that that serial gastric biopsy specimens frequently exhibit an oscillating clonal status, due perhaps to sampling or recurrent *Helicobacter pylori* infection. Therefore, except for clinical investigations, the determination of clonality employing PCR currently is not considered pragmatic or recommended in the evaluation of post-therapy gastric MALT lymphoma biopsy specimens.

The establishment of extranodal gastric marginal zone lymphoma of MALT type as a recognized clinicopathologic entity has progressed to incorporate molecular genetics and specific chromosomal translocations. For MALT lymphomas in general, the genetic abnormalities encompass trisomies 3, 12 and 18, as well as balanced translocations, specifically t(11;18)(q21;q21), t(14;18)(q32;q21), t(1;14)(p22;q32) and t(3;14)(p14;q32). The most common translocation in gastric MALT lymphoma arising in approximately 20-30% of cases (although lower in North America) is t(11;18)(q21;q21) in which the t(11;18) fuses with amino terminal of the inhibitor of apoptosis *API2* at 11q21 to the carboxyl terminal of *MALT1* at 18q21 leading to a chimeric fusion product. *MALT1* is involved in antigen receptor-mediated NF κ B activation. The *API2-MALT1* fusion product is detectable by FISH. The t(11;18)(q21;q21) is restricted to extranodal MALT lymphomas and has not been reported in other forms of marginal zone lymphoma, such as splenic or nodal, or in chronic gastritis associated with *Helicobacter pylori*. Gastric MALT lymphomas without a t(11;18)(q21;q21) often exhibit aneuploidy, as for example trisomy 3 or 18.

In this decade, the discovery of t(11;18)(q21;q21) in some patients with gastric MALT lymphoma has led to exciting clinical prognostic correlations. Specifically, patients with gastric MALT lymphoma who prove positive for t(11;18)(q21;q21) often fail to respond to *Helicobacter pylori* therapy and this translocation frequently arises in patients who are *Helicobacter pylori* negative. Employing endosonographic staging, such t(11;18)(q21;q21) positive patients who do not respond to *Helicobacter pylori* eradication with antibiotics are found to have disease that has spread beyond the gastric submucosa into muscularis and/or serosa in contrast to patients with lymphoma limited to the mucosa and submucosa who generally are t(11;18)(q21;q21) negative. Moreover, t(11;18)(q21;q21) is uncommon in extranodal diffuse large B cell lymphoma and patients with this translocation rarely metamorphose to diffuse large B cell lymphoma. In contrast, aneuploid t(11;18)(q21;q21) negative patients who are unresponsive to *Helicobacter pylori* treatment are at risk to evolve to diffuse large B cell lymphoma. For example, microsatellite screening of gastric MALT and large B cell lymphomas display allelic imbalances limited to t(11;18)(q21;q21) negative patients that are shared by both MALT and diffuse large B cell lymphomas; this observation indicates that t(11;18)(q21;q21) negative patients are the genesis of MALT lymphomas than convert to one of large B cell type. It is therefore paramount to ascertain as to whether or not the gastric marginal zone lymphoma of MALT type is t(11;18)(q21;q21) positive since this information has prognostic and therapeutic repercussions.

In the 1990's, many diffuse large B cell lymphoma cases of stomach were designated as "high-grade MALT lymphoma" based on the belief that these cases had transformed from "low-grade MALT lymphoma" especially when both components were present in a single specimen. Despite the likelihood that such transformations occur, the term "high-grade MALT lymphoma" presently is discouraged and all such cases are interpreted as large B cell lymphoma. By current definition, marginal zone lymphoma of MALT type is strictly an indolent or low-grade extranodal lymphoma. Despite the considerable recent emphasis on MALT-type lymphomas, in fact, greater than 50% of gastric lymphomas are high-grade, diffuse large B cell lymphomas. Except in small gastroscopic biopsy specimens, differentiation of large cell lymphoma from carcinoma usually is not a problem in view of the tendency of the lymphomas to be diffuse, massive, and lacking in cohesive cell aggregates. Nonetheless, immunohistochemical verification of diagnosis is recommended and is particularly valuable in delineating cases of large cell lymphoma from gastric adenocarcinoma. The infiltration by lymphoma around, or into, partially intact gastric glands, negative mucin and keratin stains, positive reactivity for CD20, and the lack of syncytial cell aggregates or malignant acinar formation aid in the distinction of large cell lymphoma from poorly differentiated adenocarcinoma, even in small biopsy specimens. Small gastric biopsy specimens, however, are subject to sampling errors and artifactual distortion, and on occasion it may be necessary to request a second biopsy, in order to render a more complete pathologic examination.

One consequential diagnostic issue is the observation of large cells in a background of a marginal zone lymphoma of MALT type in a gastric biopsy specimen. No current consensus exists as to how many large cells are required to establish the evolution from MALT lymphoma to one of diffuse large B cell type. Clearly, the presence of large cells in discrete nodular aggregates or sheets is likely an indication of transformation; however, diagnostic difficulties remain for cases in which the large cells are numerous and diffusely admixed with small marginal zone lymphocytes. In one study of 106 patients with gastric MALT lymphomas, the prognostic impact of a large cell component was assessed by semiquantitative analysis of clusters and diffusely intermingled malignant large cells; in MALT lymphomas, the observation of a diffuse large cell component in the range of 1-10%, with and without non-confluent clusters of large cells, predicted a significantly worse prognosis. In a report from Italy, the presence of scattered large cells that comprised 5-10% of the MALT lymphoma cell population was regarded as prognostically irrelevant, whereas compact clustered large cells that represented more than 10% of the MALT lymphoma proved significant, as they were associated with a worse survival.

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