

Review of the molecular profile and modern prognostic markers for gastric lymphoma: How do they affect clinical practice?

Leonidas Alevizos, MD
 Ilias P. Gomas, MD, PhD
 Spyridon Smparounis, MD
 Manousos M. Konstadoulakis,
 MD, PhD
 Georgios Zografos, MD, PhD

From the 1st Department of Propaedeutic Surgery, Hippokraton Hospital of Athens, Athens Medical School, Vasilissis, Sofia Avenue 114, 11527, Athens, Greece

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Correspondence to:
 Dr. I. Gomas
 Kalvou 24, Old Psichiko
 15452 Athens, Attica
 Greece
 ealevi@otenet.gr

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Primary gastric lymphoma is a rare cancer of the stomach with an indeterminate prognosis. Recently, a series of molecular prognostic markers has been introduced to better describe this clinical entity. This review describes the clinical importance of several oncogenes, apoptotic genes and chromosomal mutations in the initiation and progress of primary non-Hodgkin gastric lymphoma and their effect on patient survival. We also outline the prognostic clinical importance of certain cellular adhesion molecules, such as ICAM and PECAM-1, in patients with gastric lymphoma, and we analyze the correlation of these molecules with apoptosis, angiogenesis, tumour growth and metastatic potential. We also focus on the host-immune response and the impact of *Helicobacter pylori* infection on gastric lymphoma development and progression. Finally, we explore the therapeutic methods currently available for gastric lymphoma, comparing the traditional invasive approach with more recent conservative options, and we stress the importance of the application of novel molecular markers in clinical practice.

Le lymphome gastrique primaire est une forme rare de cancer de l'estomac dont le pronostic est indéterminé. On a présenté récemment une série de marqueurs pronostiques moléculaires pour mieux décrire cette entité clinique. La présente analyse décrit l'importance clinique de plusieurs oncogènes, gènes apoptotiques et mutations chromosomiques en cause dans le déclenchement et la progression du lymphome gastrique non hodgkinien primaire et leur effet sur la survie des patients. Nous présentons aussi la portée pronostique clinique de certaines molécules de l'adhésion cellulaire, telles que l'ICAM et la PECAM-1, chez des patients atteints d'un lymphome gastrique, et nous analysons la corrélation entre ces molécules et l'apoptose, l'angiogenèse, la croissance tumorale et le potentiel métastatique. Nous nous penchons également sur la réponse immunitaire de l'hôte et l'impact de l'infection à *Helicobacter pylori* sur l'installation et la progression du lymphome gastrique. Finalement, nous explorons les méthodes thérapeutiques actuellement offertes pour le lymphome gastrique, en comparant l'ancienne approche effractive aux options conservatrices plus récentes, et nous rappelons l'importance d'appliquer les nouveaux marqueurs moléculaires dans la pratique clinique.

Gastric lymphoma (GL) is a member of the family of neoplasms derived from mucosa-associated lymphoid tissue and is the most common type of extranodal non-Hodgkin lymphoma (NHL).¹ Although its incidence is increasing, NHL is a rare disease, accounting for 2%–8% of all primary gastric cancers. It can present in any patient group, but it is most common in men (male:female ratio 2:1) aged 50 years or older.²

CLASSIC PROGNOSTIC MARKERS

Gastric lymphoma has a better prognosis than gastrointestinal lymphoma and gastric carcinoma, perhaps reflecting the tendency of GLs to remain localized in the stomach for a long time.³ The stage and histologic grade of the disease are the most clinically important independent prognostic factors.⁴ Stage I and II GLs have 5-year survival rates of 87% and 61%, respectively (Ann Arbor staging system, modified by Musshoff,⁵ Table 1), whereas high- and low-grade lymphomas account for 5-year survival rates of 56% and 91%, respectively.⁶ Younger patients have better survival rates than older patients with the

same tumour stage.⁷ Small lymphomatous lymphoma has a better prognosis than other histolytic types.^{7,8}

Until recently, the prognosis of GL has been based largely on clinical factors. These factors do not explain why patients at the same stage of disease and with similar clinical characteristics have different prognoses; they also cannot be used to safely determine which patients could benefit from adjuvant chemotherapy.¹

MUTATIONS AND ONCOGENES

Recent progress in molecular biology has contributed to the discovery of several oncogenes that contribute to carcinogenesis by disrupting the cellular cycle. For instance, oncogenes of the *ras* family underlie the development of several neoplasias. Specifically, *N-ras* has been associated with malignant transformation of blood cells, *Ki-ras* with tumours of epithelial tissues, and *Ha-ras* with cancer of the urinary bladder.⁹ Similarly, the *ERBB2* oncogene (formerly *HER2/neu*) plays a clinically important role in the pathogenesis of cancer of the cervix, endometrium, ovaries and breast, and has been linked to a worse prognosis in patients with these cancers.¹⁰

The *Ki-ras*, *c-Ha-ras* and *ERBB2* oncogenes are among those that initiate neoplasias of the gastrointestinal (GI) tract and are likely important to GL.^{9,11} Mutations to the *Ki-ras* proto-oncogene have been shown to occur early in colorectal tumorigenesis, with the resulting small GTPase protein driving the development of colorectal cancer.¹²⁻¹⁴ *Ki-ras* mutations are associated with significantly worse prognosis for the patient.¹⁴⁻¹⁶ Likewise, *c-Ha-ras* encodes the p21c-Ha-ras protein, which induces G₁ cell cycle phase arrest,¹⁷ and *c-Ha-ras* hypomethylation is detected in gastric carcinomas, though without affecting the histopathologic appearance of the cancers.¹⁸ Finally, increased serum levels of the *ERBB2* protein, which is involved in the signal transduction pathways leading to cell growth and differentiation, are common in patients with gastric carcinomas.¹⁹⁻²¹ The prognostic value of the oncogenes mentioned, however, has not been verified in patients with GL.²²

Ferreri and colleagues²³ have pointed out that cyclin E

and the p27 gene products are independent prognostic factors for GL and that the p27-/cyclin-E⁺ phenotype is associated with worse prognosis. Cyclin-E forms complexes with CDK2, stimulating progression from the G₁ to S phase of the cell cycle, whereas p27 inhibits the formation of the cyclin-E/CDK2 complex, thus regulating the cell cycle. The synergistic effect of low p27 and high cyclin-E expression accounts for the poor prognosis of the patients presenting this phenotype. The same research group has also reported a correlation between the lack of the expression of p16 and high-grade GLs.

The p16 tumour-suppressor gene may also play a clinically important role in GL. It encodes the cyclin-dependent kinase inhibitor 2A protein (CDKN2A), which plays an important role in regulating the cell cycle G1 progression by inhibiting the CDK4 kinase and, indirectly, p53. Min and colleagues²⁴ found that p16 methylation is more frequent in patients with higher-grade GLs. The role of p16 in the pathogenesis of other gastrointestinal neoplasias, as well as its prognostic value, has been the focus of rigorous investigation. Several researchers have reported that p16 can be used as a prognostic factor for GI stromal tumours, especially for those that range between benign and borderline.²⁵⁻²⁸ Li and colleagues²⁹ have reported that overexpression of p16 is correlated to endocrine (carcinoid) tumours of the GI tract. It has been noted that acid-induced hypermethylation of p16 is a common pattern in patients with upper GI adenocarcinomas (both esophageal and gastric).³⁰ More recently, Ajani and colleagues³¹ reported high p16 expression in patients with anal canal carcinoma; however, this observation had no impact on the disease-free survival of the patients.

The pathogenesis of GL is affected by various mutations, such as trisomy 3,³² t(11;18)(q21;q21) translocation,³³ (8)(q13q22) deletion¹¹ and t(1q14)(p22;q32) translocation. The latter has been associated with autonomous growth of the lymphoma and its expansion into adjacent gastric lymph nodes.³⁴ Moreover, patients with GL with aneuploid cells have worse survival rates and relapse more often than those with tumours composed of diploid cancer cells.³⁵ Finally, it has been shown with DNA flow cytometry that the median fraction of cells in the S phase (SPF) can be a clinically important prognostic index for GL.³⁶

APOPTOSIS

The balance between cancer cell proliferation and death determines the tumour cell population, thus the size of the tumour. Apoptosis (i.e., programmed cell death) is an active process that requires the contribution of many gene products, including p53, the members of the *bcl* family and cellular caspases.³⁷

Commonly, p53 mutations are found in many neoplasms and interfere with the natural oncosuppressor function of the protein, leading to accelerated tumour growth.

Table 1. Ann Arbor lymphoma staging, modified by Musshoff, for extranodal lymphomas⁵

Stage of disease	Traits of stage
Stage I	Single lymphatic organ or extranodal site
Stage II	Two or more lymphatic regions on the same side of the diaphragm, or a single extranodal organ plus lymph node involvement on the same side of the diaphragm
Stage II1	Regional lymph nodes involved
Stage II2	Distant lymph nodes involved
Stage III	Lymph node involvement detected on both sides of the diaphragm
Stage IV	Disseminated disease with involvement of other extranodal sites (i.e., liver, bone marrow, abdominal wall)

Immunohistochemical studies have shown that increased expression of p53 is present in high-malignancy GLs. Mutations in p53 appear during the last stages of carcinogenesis,³⁸ possibly playing a role in the transition from smaller to larger and more malignant lymphomas.³⁷ However, the expression of p53 presents no statistically significant effect on patients' survival and thus is used only as an index of cellular dedifferentiation.³⁸

The Bcl protein family plays a major role in the regulation of the apoptotic cascade, with individual members contributing either pro- or antiapoptotic signals. The Bcl-2-associated protein (Bax) promotes apoptosis and delays disease progression, whereas bcl-6 and bcl-10 are both proto-oncogenes; none of the 3 has any particular prognostic value in GL. Bax, however, has been associated with better patient prognosis and longer disease-free survival in patients with a number of gastrointestinal cancers, such as cancer of the esophagus, the stomach, the small intestine and the colon,³⁹⁻⁴⁴ and high bcl-6 expression is correlated with worse prognosis in patients with other tumours of the GI tract, such as esophageal adenocarcinoma.⁴⁵ Bcl-6 mutations have been detected in many patients with GL and may play an important role in disease pathogenesis,^{46,47} whereas irregular expression of bcl-10 is correlated with advanced stages of the disease as well as lymph node and remote metastases.⁴⁸ Bcl-2, a transmembrane member of the family with antiapoptotic qualities, has a significantly greater expression in highly differentiated GLs and GLs consisting of smaller lymphocytes.^{38,49}

Many members of the Bcl family interact with intracellular caspases, enzymes that are activated during the late phases of the apoptotic process, cleaving a number of structural and cellular proteins.^{50,51} Patients with GL exhibit increased caspase-3 activity in peripheral T lymphocytes.⁵² However, there is no bibliographic evidence for any prognostic value of caspases in patients with GL.

Individually, most of the genes described above have no prognostic significance in patients with GL; however, on multivariate analysis, several combinations of these genes can be useful as prognostic phenotypes. For example, *bcl-2*⁻/*bax*⁺ carriers with GL have better rates of survival than *bcl-2*⁻/*bax*⁻ carriers with GL. One interpretation is that the simultaneous loss of Bax and Bcl-2 proteins leads to loss of apoptotic control, resulting in aggressive tumour behaviour.³⁸ In addition, Go and Yang⁵³ have demonstrated that *p53*⁺/*p21*⁻ carriers are less likely to achieve complete remission.

CELLULAR ADHESION MOLECULES

Cellular adhesion molecules (CAMs) are glycoproteins of the cellular membrane that belong to the families of integrins, cadherins, selectins and immunoglobulins and control the relay of transcellular signals and the migration of cancer cells.^{54,55} The prognostic value of intracellular adhe-

sion molecules (ICAMs) and of PECAM-1 for several forms of cancer has been investigated recently.

Intracellular adhesion molecules are part of the immunoglobulin superfamily CAMs. They participate in the interaction between the endothelium and lymphocytes and mediate the transmigration and extravasation of the latter. They also participate in signal transduction and inflammatory pathways, in part by recruiting macrophages and other immune-competent cells. ICAM-1 in particular plays an important role in determining the host's response to malignant tumours and is related to the degree of differentiation and lymphoma stage in patients with NHL. ICAM-1 expression is known to increase in human gastric carcinoma cells as well, being a predictive factor for patients with gastric carcinoma.⁵⁶ Since non-neoplastic cells of the GI tract do not express ICAM-1, it presents an attractive target for therapeutic interventions.⁵⁷ The role of ICAM-1 in colonic neoplasms is still under research.⁵⁸ Terol and colleagues⁵⁹ reported that ICAM-1⁻ carriers with NHL were characterized by more severe clinical syndromes, numerous extranodal metastases, infiltration of bone marrow and worse prognosis. Although there is no concrete supporting evidence, there is speculation that the absence of ICAM-1 expression may be related to shorter life expectancy for patients with GL.

PECAM-1 is expressed on the surface of endothelial and blood cells and plays an important role in vascularization and cellular translocation. PECAM-1 is related to a worse prognosis in a large range of neoplasms, and previous studies have suggested that its prognostic value in patients with GL is limited to those with nodular infiltrations.^{60,61} However, we recently reported that PECAM-1-positive GL cells were an independent prognostic factor associated with unfavourable disease outcome in patients with GL.⁶² One possible explanation is that PECAM-1 leads to the extravasation of leukocytes via its involvement in the cellular adhesion process, thus facilitating the metastasis of lymphogenic neoplasms. We also found that the PECAM-1⁺/ICAM-3⁻ phenotype was associated with decreased 5-year survival compared with the PECAM-1⁻/ICAM-3⁺ phenotype.

Concerning the other CAMs, it is remarkable that low-malignancy GL cells generally have an $\alpha 4\beta 7$ integrin⁺/L-selectin⁺ phenotype, whereas high-malignancy GLs do not express these 2 molecules.⁶³ The percentage of ELAM-1⁺/VCAM-1⁺ venules in the tumour is increased in high-malignancy primary GLs compared with low-malignancy primary GLs or secondary GLs. The pattern of CAM expression may also be important. In most primary high-grade GLs, the stromal cells of the germinal centre are positive for ICAM-1, ELAM-1 and VCAM-1 (germinal centre pattern), whereas in low-grade and secondary high-grade GLs, the stromal cells of the marginal zone are positive only for ICAM-1 (marginal zone pattern).⁶⁴ The observation that low-grade and secondary high-grade GLs present the

marginal zone pattern, while most primary high-grade gastric GLs present the germinal centre pattern, is of exceptional significance, since it suggests that low-grade and secondary high-grade lymphomas are of marginal zone cell lineage, whereas most of the high-grade primary lymphomas are of germinal centre cell lineage.⁶⁴

NEOANGIOGENESIS

In addition to cellular adhesion, several of the CAMs, in particular ICAM-3 and PECAM-1, contribute to neoangiogenesis by participating in the transcellular relay of signals necessary for the recruitment and organization of endothelial cells into vascular canals. Neoangiogenesis is a prerequisite for tumour development beyond a critical size; it also allows the entrance of tumour cells into the bloodstream,⁶⁵ leading to metastasis. The link to the metastatic tumour potential helps to explain the correlation between the degree of neoangiogenesis (microvessel density [MVD]) and the aggressiveness and prognosis of many types of cancer.⁶⁶

Cyclooxygenase (COX), an intracellular enzyme belonging to the prostaglandin synthase family, participates in the process of neoangiogenesis in patients with GL. COX converts arachidonic acid to prostaglandin H₂, which is the rate-limiting step in the formation of prostaglandins. Recent evidence strongly implicates the COX-2 isoform in the tumorigenesis process, being influenced by mutation of genes such as *ras*, several cytokines and *Helicobacter pylori* infection. The latter observation explains the return of COX-2 expression to normal levels after treatment with amoxicillin.⁶⁷

The effect of COX-2 is exerted by the release of the PGE-2 prostaglandin and contributes to the development of GL by enhancing cancer cell division and neoangiogenesis and by suppressing the host's immune reaction. Tumour cells overexpressing COX-2 stave off apoptosis and exhibit irregular interaction with neighbouring cells. It has also been suggested that COX-2 promotes the production of angiogenic factors in perineoplastic cells.^{67,68} Both COX-1 and COX-2 inhibitors, which are expressed in tumour endothelial cells, inhibit angiogenesis and endothelial migration of cancer cells.⁶⁸

IMMUNE PROPERTIES OF GASTRIC LYMPHOMA

Gastric lymphoma — like all extranodal lymphomas — has immune-like properties. B-cell lymphomas have the common trait of proliferating under the influence of T cells.⁶⁹ Most of the T cells contributing to this process are of T helper (Th) type, possess HLA-DR antigens, and lack interleukin-2 (IL-2) receptors and the cytotoxic mechanisms necessary to control B cell growth. However, increased levels of activated Th lymphocytes in large cell B lymphomas are associated with better prognosis.⁷⁰ In

patients with high-malignancy GLs, the cytotoxic activity of cytotoxic T lymphocytes (CTLs) is more intense, which may in part account for the increased rate of apoptosis observed in patients with these tumours; the response of these CTLs is possibly related to better prognosis, since it is part of the host's immune reaction.⁷¹

Survival of patients with GL is substantially affected by changes in the expression of major histocompatibility complex (MHC) antigens as well. Reduced MHC I expression is often observed in patients with malignant tumours and lymphomas and is related to worse prognosis and aggressive tumour behaviour.⁷² Patients with NHL present elevated serum levels of sHLA, the soluble form of HLA secreted by B and T cells when activated.⁷³

The HLA-DR antigen is an MHC II-class glycoprotein located on the surface of cells of the immune system and certain tissues and is an index of the host's immune response to the tumour. Although this particular antigen is expressed in the healthy gastric epithelium, a small percentage of patients with gastric cancer express HLA-DR in cancer cells.⁷⁴ We have reported that HLA-DR expression in cancer cells of patients with GL is an independent factor associated with better prognosis, possibly because it induces the presentation of cancer cell antigens to Th lymphocytes, thereby improving the immune response against them.⁶² Patients with the HLA-DR⁻/ICAM-3⁻ phenotype have reduced 5-year survival odds compared with HLA-DR⁺/ICAM-3⁺ carriers, whereas all HLA-DR⁺/ICAM-3⁺/PECAM-1⁻ carriers have 100% 5-year survival compared with 54.2% for the rest of the population. It appears that ICAM-3, PECAM-1 and HLA-DR represent complementary molecular pathways that connect the host's immune reaction to nonspecific transcellular communication and cellular migration.⁶²

HELICOBACTER PYLORI

H. pylori has been detected in 86% of patients with low-malignancy GL and in 74% with high-malignancy GL, a percentage higher than that of the general population. The infection leads to chronic inflammation of the gastric epithelium and stimulation of the immune system via activation of Th lymphocytes. These in turn induce B lymphocyte proliferation in the gastric mucosa until a clone is mutated and eventually leads to lymphoma.⁷⁵

Recent research has focused on the effect of *H. pylori* on certain oncogenes. The activation of these genes is an important step in the initiation of neoplasia. Exposure of gastric mucosa to *H. pylori* activates the transcription factor activator protein 1 (TFA-1), ultimately leading to the activation of the proto-oncogenes *c-fos* and *c-jun*. *H. pylori* infection also activates the ERK/MAP kinase, which phosphorylates the transcription factor Elk-1 and increases the transcription of *c-fos*. Strains of *H. pylori* that do not express the CagA surface antigen (cytotoxin-associated antigen A)

or carry mutations of the *cag* family of genes do not activate TFA-1, *c-fos* and *c-jun*.⁷⁶

Radical antibiotic treatment of *H. pylori* is effective for localized low-malignancy GL, even though disease recurs quite often.⁷⁷ It has been recently reported that increased levels of paraprotein were inversely related to tumour response to radical treatment for *H. pylori*, whereas reduction of paraprotein levels were observed in patients who responded to radiation or chemotherapy. As a result, paraprotein levels could be used as a prognostic marker of response to *H. pylori* treatment and during patient follow-up.⁷⁸

SURGICAL TREATMENT AND MOLECULAR PROGNOSTIC MARKERS

The tumour–nodes–metastasis (TNM) system has not been widely used for staging of GI lymphomas. The most popular staging systems for such tumours are the Ann Arbor system, as modified by Musshoff for extranodal lymphomas in 1977⁵ (Table 1), the Lugano system established by Rohatiner and colleagues in 1994⁷⁹ (Table 2) and the more recent Paris staging system, suggested in 2003 by the European Gastro-Intestinal Lymphoma Study Group⁸⁰ (Table 3). Treatment decisions are made according to these staging systems.

Gastric lymphomas can be treated in a variety of ways: antimicrobial treatment seems to be the first-line therapy for patients with *H. pylori* infection, yielding high disease remission rates for all T1/stage I and most T2/stage I tumours (staging mentioned refers to both TMNB-Paris and Ann Arbor staging systems, respectively).⁸¹ Stage I tumours extending beyond the submucosa are better treated with chemotherapy, radiation or a combination of both, yielding remission rates of up to 90%.⁸² Stage II or higher GL tumours can be treated with subtotal gastrectomy (open or laparoscopic) combined with removal of any nodular metas-

tases.⁸³ Careful and periodic follow-up of patients is highly encouraged: endoscopic ultrasonography and gastric biopsies can detect any relapses early on, allowing these patients to switch to an alternative therapy.^{84,85} However, it has been suggested that organ-preserving treatments present the same survival rates as surgical treatment, indicating that primary stomach resection should be questioned.⁸³

To achieve the best therapeutic result, the surgeon must be aware of the factors that influence the effectiveness of therapeutic interventions. Thus, determining new prognostic markers is imperative; the analysis of these indices offers the surgeon the opportunity to predict the biological behaviour of the GL and choose an appropriate treating regimen according to tumour aggressiveness.² Molecular prognostic markers predict the aggressiveness and prognosis for each patient's particular disease better than the classic markers. The correlation of these modern markers with tumour relapse and overall survival makes possible the more specific and personalized choice of treatment for patients with GL. For example, the HLA-DR⁺/ICAM-3⁺/PECAM-1⁻ phenotype has been associated with a 100% 5-year survival rate compared with other phenotypes. Patients with this phenotype could be considered eligible for treatment with chemotherapy and radiation instead of more invasive methods, even when the tumour is not at stage I. The same strategy can be applied for patients with GL who have the *bcl2*⁻/*bax*⁺ and the $\alpha4\beta7$ integrin⁺/L-selectin⁺

Table 2. Lugano system for staging of lymphomas⁷⁹

Stage of disease	Traits of stage
Stage I	Tumour confined to the GI tract, single primary site or multiple noncontinuous lesions
Stage I ₁	Tumour does not exceed the mucosa and submucosa
Stage I ₂	Tumour infiltrates into muscularis propria and/or subserosa and/or serosa
Stage II	Tumour extends into abdomen from primary GI site
Stage II ₁	Local lymph node involvement*
Stage II ₂	Distant lymph node involvement†
Stage IIE	Penetration of serosa with involvement of adjacent organs/tissues‡
Stage IV	Disseminated disease with involvement of extranodal sites, or primary GI lesion plus supradiaphragmatic nodal involvement

GI = gastrointestinal.
 *Perigastric nodes are considered regional for gastric lymphoma.
 †Mesenteric nodes are considered distant for gastric lymphoma.
 ‡The actual site of involvement must be enumerated, e.g., IIE_{gastric}. In cases where there is both nodal and extranodal involvement beyond that of the primary site, this is denoted using both the final E and subscript, e.g., IIE1_{gastric}.

Table 3. Paris staging system (TNMB) for primary gastrointestinal tract lymphomas⁸⁰

Stage of disease	Traits of stage
Tx	Lymphoma extent unspecified
T0	No evidence of lymphoma
T1	Lymphoma confined to the mucosa/submucosa
T1m	Lymphoma confined to the mucosa
T1sm	Lymphoma confined to the submucosa
T2	Lymphoma infiltrates muscularis propria or subserosa
T3	Lymphoma penetrates serosa without invading adjacent structures
T4	Lymphoma infiltrates adjacent structures or organs
Nx	Nodal involvement not assessed
N0	No evidence of lymph node involvement
N1	Involvement of regional lymph nodes (for GL: perigastric nodes, as well as those located along the splenic, the common hepatic and the left gastric arteries)
N2	Involvement of intra-abdominal lymph nodes beyond the regional area
N3	Involvement of extra-abdominal nodes
Mx	Dissemination not assessed
M0	No evidence of extranodal dissemination
M1	Noncontinuous involvement of separate sites in the GI tract (i.e., stomach and rectum)
M2	Noncontinuous involvement of other tissues or organs
Bx	Involvement of bone marrow not assessed
B0	No evidence of bone marrow involvement
B1	Lymphomatous infiltration of the bone marrow

GI = gastrointestinal; GL = gastric lymphoma.

phenotypes. On the contrary, lower remission rates for these tumours have been reported in patients with the p53+/p21- phenotypes. These patients could be treated in a more radical and efficient manner to prevent disease recurrence; at the very least, the surgeon should consider these patients as high-risk individuals and pursue their follow-up meticulously.

CONCLUSION

Recent work in the molecular biology of GL offers a much better appreciation of an individual patient's prognosis. The p27-/cyclin E+ phenotype is associated with worse prognosis. The expression of p53 increases with the degree of malignancy and is indicative of cellular dedifferentiation. Bcl-2 expression is greater in patients with highly differentiated lymphoma, and irregular bcl-10 expression is related to advanced stages of disease. Moreover, bcl-2-/bax+ phenotypes are associated with better prognosis, whereas the p53+/p21- phenotypes are associated with lower rates of complete remission. On the CAM level, PECAM-1 is an independent prognostic factor associated with unfavourable disease outcome, whereas increased ELAM-1 and VCAM-1 expression are associated with high-malignancy lymphomas. Conversely, absence of ICAM-1 expression is predictive of advanced disease stage, worse survival prognosis and both extra-nodal and marrow infiltration; lack of the adhesion molecule could relate to aggressive dissemination of the disease. The PECAM-1+/ICAM-3- phenotype is associated with a reduced 5-year survival rate. The ICAM-3 and PECAM-1 molecules play a major role along with the COX enzyme in neoangiogenesis, whose increased rate leads to worse prognosis. Intense T cell reactions may

translate to longer life expectancy, whereas increased HLA-DR expression is an independent prognostic factor associated with increased survival. There is a correlation with the HLA-DR-/ICAM-3- phenotype and reduced 5-year survival rate in contrast to the HLA-DR+/ICAM+/PECAM- phenotype, which has been correlated with increased 5-year survival rates. Proliferation of gastric mucosa B cells and *H. pylori*-induced activation of *c-fos* and *c-jun* contributes to the pathogenesis of GL; serum para-protein levels may be used as an index of patient response to *H. pylori* eradication treatment.

The proper treatment for a patient with GL is influenced by the presence of *H. pylori* and by the size and the stage of the disease. Patients infected with *H. pylori* who exhibit T1/2 tumours (Paris staging system; Table 3) or stage I tumours (Lugano staging system; Table 2) are best treated with antibiotics, whereas patients with larger tumours can be subjected to radiation and chemotherapy. Disease at stage II or higher (Ann Arbor staging; Table 1) is a clear indication for surgical treatment, although recent research debates the necessity of invasive compared with conservative treatment.

The new generation of molecular markers summarized in Table 4 enables personalized prognosis and allows the surgeon to select the optimal therapeutic modality when treating primary GL. To maintain low recurrence rates and greater disease-free survival, patients with tumours of stage II or higher by Ann Arbor staging and/or phenotypes indicating more aggressive or more persistent disease behaviour (ELAM-1+/VCAM-1+, p53+/p21-, PECAM-1+/ICAM-3-) could be treated using more conventional and proven surgical methods. Conversely, patients with GLs whose genetic profile is indicative of favourable disease outcome and lower malignancy potential (HLA-DR+/ICAM-3+/PECAM-1-, bcl2-/bax+, α4β7 integrin+/L-selectin+) are candidates for less invasive treatment, such as chemotherapy and radiation. The specific guidelines for this modern concept of treating patients with GL merits further research before becoming mainstream clinical practice. Whatever the treatment modality, careful patient follow-up via ultrasonography and endoscopic biopsies is paramount in preventing GL relapses and ensuring maximum disease-free survival for the patient.

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Table 4. Molecular markers and their prognostic value for gastric lymphoma

Marker	Correlation with prognosis
Unfavourable	
ELAM-1+/VCAM-1+	Indicates high-malignancy GL
p16-	Indicates high-malignancy GL
p53+	Indicates high-malignancy GL; patient prognosis unaffected
cyclin-E-/p27+	Worse patient prognosis
p53+/p21-	Lower CR rates
ICAM-1-	Shorter life expectancy
PECAM-1+	Unfavourable disease outcome
PECAM-1+/ICAM-3-	Reduced 5-year SR v. PECAM-1-/ICAM-3+
HLA-DR-/ICAM-3-	Reduced 5-year SR v. HLA-DR+/ICAM-3+
Favourable	
HLA-DR+	Better patient prognosis
α4β7 integrin+/L-selectin+	Indicates low-malignancy GL
HLA-DR+/ICAM-3+/PECAM-1-	100% 5-year SR v. other phenotypes
bcl2-/bax+	Increased 5-year SR
CR = complete remission; GL = gastric lymphoma; SR = survival rate.	

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