

CHAPTER 17 GASTRIC LYMPHOMA

17.1 Introduction

The gastric lymphomas represent a wide spectrum of disease, ranging from indolent low-grade marginal-zone lymphoma to aggressive diffuse large B-cell lymphoma.

17.2 Summary of clinicopathological findings

These are described in Chapters 12 and 13.

17.3 Mucosal-associated lymphoid tissue (MALT) lymphoma

17.3.1 Aetiology and epidemiology

The aetiological link between *H.pylori* infection and the development of gastric lymphoma is discussed in Section 2.3.2.

17.3.2 Cytogenetic changes

In some 30–40% of cases, a cytogenetic anomaly reflecting a t(11;18) (q21;q21) translocation is detected. This t(11;18) translocation results in a chimeric transcript between the API2 and MLT genes.¹ Patients with such an abnormality tend to have aggressive, more advanced disease, suggesting prompt treatment and close follow up. However, it appears that t(11;18) positive lymphomas do not respond to *Helicobacter Pylori* (*H.pylori*) irradiation therapy.^{1–3} Therefore detection of the presence or absence of the translocation should assist in the clinical management of patients with gastric MALT lymphoma. By contrast, the t(11;18) negative MALT lymphomas show numerous allelic imbalances, some of them identical with aberrations seen in diffuse large B-cell lymphoma, suggesting that this group is the source of tumours eventually transforming into high-grade diffuse large B-cell lymphoma.⁴

17.3.3 Clinical presentation

There is generally an equal proportion of males and females at presentation, with median age in the mid-60s. Symptoms are usually non-specific indigestion and epigastric discomfort. The disease is multi-focal in about 30% of cases. The immunophenotyping and morphology is described above and in Chapter 5.

17.3.4 Diagnosis and staging

This should be carried out as recommended for lymphomas in general, as described in this and other chapters (e.g. see Chapter 8 and Section 9.7). The most appropriate staging systems are controversial and are described in Table 17.1.⁵ Patients require testing for *H.pylori* infection.

Table 17.1 Staging of gastric MALT lymphoma: comparison of different systems

TMN Stage	Lugano staging system for gastrointestinal lymphomas	TNM staging system adapted for gastric lymphoma	Ann Arbor stage	Tumour extension
I	Confined to gastrointestinal tract (single primary or multiple, non-contiguous)	T ₁ N ₀ M ₀	IE	Mucosa, submucosa
		T ₂ N ₀ M ₀	IE	Muscularis propria
		T ₃ N ₀ M ₀	IE	Serosa
II	Extending into abdomen			
	III = local nodal involvement	T ₁₋₃ N ₁ M ₀	IIE	Perigastric lymph nodes
	II2 = distant nodal involvement	T ₁₋₃ N ₂ M ₀	IIE	More distant regional lymph nodes
III E	Penetration of serosa to involve adjacent organs or tissues	T ₄ N ₀ M ₀	IE	Invasion of adjacent structures
IV	Disseminated extranodal involvement or concomitant metastases	T ₁₋₄ N ₃ M ₀	IIIE	Lymph nodes on both sides of the diaphragm/distant (e.g. bone marrow or additional extranodal sites)
	Supradiaphragmatic nodal involvement	T ₁₋₄ N ₀₋₃ M ₁	IVE	

Source: Yalhalom et al.⁵

17.3.5 Endoscopic ultrasound examination

Endoscopic ultrasound (EUS) may become a gold standard for accurately imaging and staging gastric lymphoma. EUS allows direct visualisation of the individual layers of the five-layered gastric wall and assessment of peri-gastric structures and lymph nodes. This accurate staging allows determination of the best therapy for individual patients.⁶

However, reports from several centres suggest that inter-observer agreement for staging by EUS is suboptimal. Others suggest that gastroscopy with biopsy seems sufficient for the routine follow up of patients with gastric lymphomas. Clearly, improvements in the accuracy of EUS need to be demonstrated before this can be recommended as a routine procedure. This may require operators to become more experienced in the technique.⁷⁻⁹

Guideline — Gastric MALT lymphoma staging and evaluation	Level of evidence	Refs
Patients should be staged as for lymphomas in general.	III	5
Endoscopic ultrasound should be included in the staging process if experienced operators are available.	III	6-9
Markers for the t(11;18) (q21; q21) translocation should be obtained on tumour biopsy samples.	III	1, 4

17.3.6 Role of antibiotics in *H.pylori* treatment

The concept for the use of antibiotics to eradicate *H.pylori* was based on the assumption that *H.pylori* was evoking an immunological response, that is, that the tumour is antigen driven. The original report is based on six patients in whom biopsy showed histological and molecular genetic evidence of MALT lymphoma with *H.pylori* infection, and who were treated with antibiotics. In all cases, *H.pylori* was eradicated. In five patients, repeat biopsy showed no evidence of lymphoma.¹⁰

Confirmation of this observation came from Roggero in a series of 26 patients with localised primary low-grade gastric MALT lymphoma. *H.pylori* was completely eradicated in 25 of 26 patients, but four patients needed second-line antibiotic therapy. Disappearance or almost total regression of lymphomatous tissue was observed in 15 of 25 evaluable patients.¹¹ Several other series have confirmed these results. Standard antibiotic combination regimes are recommended.^{12,13}

Similarly, Fischbach followed some 90 patients with stage I disease and *H.pylori* infection. The patients were treated with antibiotics. The *H.pylori* was eradicated in 88 patients. The long-term outcome was characterised by CR in 56 patients, minimal residual disease in 17 patients, and partial remission in 11 patients. There was no change in four patients, and progressive disease in two patients. Four patients with complete remission relapsed between six and 15 months, one revealing reinfection by *H.pylori*. The authors concluded that the majority of patients with low-grade MALT lymphoma treated by exclusive *H.pylori* eradication have a favourable long-term outcome offering a real chance of cure.¹⁴

17.3.7 Persistent evidence of disease after antibiotics

Despite complete remissions of low-grade gastric MALT lymphomas after cure of *H.pylori* infection, many patients display evidence of monoclonal B cells during follow up. Neubauer followed a series of 50 patients in which *H.pylori* was cured in all 50. Forty patients achieved complete remission of their lymphomas, but five subsequently relapsed. Among six patients whose lymphoma did not respond to *H.pylori* eradication, four revealed high-grade lymphomas. PCR indicated the presence of monoclonal B cells during follow up of 22 of 31 assessable patients in complete remission.¹²

Thiede's group in Germany followed 97 patients, of whom 77 achieved complete endoscopic and histological remission. Twenty of 24 patients with PCR monoclonality at diagnosis and with sufficient molecular follow up displayed monoclonal bands for a median time of 20 months after CR. The authors suggest that patients with monoclonal PCR should be observed closely, whereas long-term PCR negativity may indicate cure of the disease.¹⁵

Further evidence of the presence of molecular disease following complete clinical and pathological remission came from Bertoni's group. At an interim analysis in a large series, some 105 of 189 patients had achieved a complete histological remission after anti-*H.pylori* treatment. Gastric biopsies from a subset of the patients were analysed by PCR targeted to IgG heavy-chain genes as a molecular marker for minimal residual disease. Some 44 cases were monoclonal by PCR diagnosis. Of these, 42 achieved histological complete remission. Of 34 cases undergoing molecular follow up, some 15 (44%) were in molecular remission, with a median follow up of two years after antibiotic treatment. Therefore, less than half of the patients with MALT lymphoma can achieve sustained molecular remission after anti-*H.pylori* therapy. The authors concluded that the presence of molecular disease in the absence of histological disease does not appear to be associated with histological relapse, but given the indolent nature of MALT lymphomas, a longer follow up is needed.¹⁶

17.3.8 Prognostic factors

Cytogenetic markers

The t(11;18) translocation marker will predict resistance to antibiotic therapy. Liu et al. screened for the AP12/MLT fusion transcript as a marker for t(11;18) in ten antibiotic responsive and 12 non-responsive gastric MALT lymphomas. The AP12/MLT transcript was detected in nine of 12 patients non-responsive to antibiotic therapy, but none in responsive patients. Therefore, most *H.pylori*-associated gastric MALT lymphomas that do not respond to antibiotic therapy are associated with the t(11;18) translocation.¹

Similarly, Starostik has shown that the patients with the t(11;18) transcript do not transform to high-grade diffuse large B-cell lymphomas.⁴

Lui et al. have further investigated the relationship between t(11;18) as a marker for all stage gastric MALT lymphomas that will not respond to eradication of *H.pylori*. The t(11;18) translocation was detected in two of 48 complete regression cases and those positive cases showed relapse of lymphoma in the absence of *H.pylori* re-infection. In contrast, the translocation was present in 42 of the 63 non-responsive cases, including 26 of 43 at stage IE. They concluded that t(11;18) positive tumours, independent of early stage, do not respond to *H.pylori* eradication.²

Inagaki's group in Japan have taken this observation further in a molecular and clinicopathological study of 115 patients. All eradication responsive cases were devoid of the AP12/MLT fusion product. All tumours positive for the fusion product and as well negative *H.pylori* infection were non-responsive to eradication. They consider that gastric MALT lymphomas can be divided into three groups:

- Group A — eradication responsive and fusion negative,
- Group B — eradication non-responsive and fusion negative
- Group C — eradication non-responsive and fusion positive.

Group A tumours were characterised by low clinical stage and superficial gastric wall involvement, and Group C tumours by low *H.pylori* infection rates, advanced clinical stage and nuclear-10 expression. All group C tumours showed exclusively low-grade histology. Group B tumours, which have not been well recognised, frequently showed nodal involvement, deep gastric wall involvement, advanced clinical stage and sometimes an increased large-cell component. Multivariate discriminant analysis revealed that responsiveness to eradication could be predicted accurately by negative AP12/MLT fusion product, positive *H.pylori* infection, low clinical stage and superficial gastric wall invasion.¹⁷

Endoscopic ultrasound

EUS has predicted outcome of treatment of MALT lymphoma following simple eradication therapy of *H.pylori*. Thus patients with disease limited to the mucosa and/or submucosa at EUS will show complete remission rates up to 100%, whereas very few patients with a more extensive infiltration will show complete remission. The TNM classification appears to be more appropriate for staging lesions by EUS.⁶

Caletti's group in Bologna, Italy, evaluated 51 patients in stage T₁–T₂, N₀–N₁. Some 66% of T₁N₀ patients achieve CR, compared with only four of eight patients with T₁N₁, and one of four patients with T₂N₀ staged disease. None of the patients in stage T₂N₁ achieved complete response.⁶

This group concluded EUS is the most accurate imaging modality for staging infiltrating gastric lesions, allowing determination of the best modality of therapy for individual patients. The early-stage T₁ lesions are likely to regress after anti-*H.pylori* therapy, while more advanced lesions (T₂–T₄) may require more aggressive treatment protocols. They also note that patients who continue to have a thickened gastric wall on EUS after antibiotic therapy may be considered for other treatment modalities, even if endoscopic biopsies are negative. Many of these patients have persistent lymphoma.

17.3.9 Gastric MALT lymphoma treatment

Antibiotic therapy for *H.pylori* is regarded as standard primary treatment. There are many series documenting histological regression after successful eradication. A standard course of triple therapy should be used.^{1–5,18}

Given that more than 90% of cases are associated with *H.pylori*, it is reasonable to treat all patients with a course of eradication therapy at the outset. Patients who are truly *H.pylori* negative will not

respond to this approach, and occasional patients have false negative testing. As well, patients with more advanced-stage disease and the t(11;18) translocation are unlikely to respond to *H.pylori* eradication. It has been recommended that a trial of eradication therapy is worthwhile, as a minority of such patients will have lymphoma regression.¹⁸

It is suggested that endoscopy be repeated at two months after the completion of eradication assessment, and that patients with complete regression be monitored yearly with endoscopy and biopsy. Patients with no response are considered for alternate therapies, and patients with partial regression should undergo continued monitoring until regression is complete or it is clear that it will not occur.¹⁸

17.3.10 Management of patients unresponsive to *H.pylori* eradication

Radiation therapy

Schechter showed in a series of 17 patients without evidence of *H.pylori* infection or with persistent lymphoma after antibiotic therapy, that all patients achieved a biopsy-confirmed complete response following a total radiation dose of 30 Gy delivered in 1.5 Gy fractions. At a median follow-up time of 27 months, event-free survival was 100%.¹⁹

Similarly, the Princess Margaret Group in Toronto treated 70 patients between 1989 and 1998. Included in this group were 15 patients with gastric involvement. Complete response was seen in 66 of 69 patients. No relapses were observed in patients with stomach lymphoma. The group concluded that localised MALT lymphomas have an excellent prognosis following moderate-dose RT. Median radiotherapy dose of 30 Gy. They reported a further series of patients, including 17 with gastric MALToma treated from 1989 to 2000. Again, no relapses were observed in patients with stomach lymphoma.^{20,21}

Guideline — Treatment of gastric MALT lymphoma	Level of evidence	Refs
Standard triple therapy should be used in all patients (<i>H.pylori</i> positive and negative).	III	1–5, 18
Patients require endoscopic follow up with biopsy initially, at two months after eradication, and then yearly.	III	18
Patients failing to respond to eradication therapy may require radiation therapy.	III	19–21

Diminishing role for surgery in gastric lymphoma

Following excellent results achieved with radiotherapy, a surgical approach has been questioned in recent years. The German Multicentre Study Group compared the treatment of patients with gastric lymphoma with a combined surgical and conservative treatment versus conservative treatment alone. They were concerned that a truly randomised study would not be accepted by physicians, and the decision as to whether surgery or conservative management was carried out was left to the discretion of each participating centre.²²

For low-grade lymphomas, if patients had had gastric resection, patients with stage IE and IIE were treated by extended-field radiotherapy with total abdominal radiation of 30 Gy. Without resection, patients with stages IE and IIE received extended-field radiotherapy as above and, in addition, patients with stage IIE received six cycles of COP chemotherapy. Patients with high-grade lymphoma received, in addition, CHOP chemotherapy whether or not resection had been performed. Between 1992 and 1996, some 106 patients had conservative treatment only. The survival rate after five years was 84.4% ,and was influenced neither by patient characteristics nor stage of histological grade.

Seventy-nine patients had combined surgical and conservative treatment, and at five years, their survival was 82%. They concluded that a gastric conservative approach should be favoured.²²

Yoon and colleagues reviewed the changing role of surgery. In a review of a Medline search (1984 to 2003), they note that 40% of gastric lymphomas are low-grade and nearly all classified as MALT lymphoma. The remainder are high-grade lesions with or without a low-grade MALT component. They note that for the low-grade MALT lymphomas confined to the gastric wall without certain negative prognostic factors, *H.pylori* eradication was highly successful in causing lymphoma regression. The more advanced low-grade lymphomas, or those that did not regress with antibiotic therapy, could be treated with a combination of *H.pylori* eradication, radiation therapy and chemotherapy. By contrast, the high-grade lymphomas could be treated with chemotherapy and radiation therapy according to the extent of the disease. They note that surgery for gastric lymphoma was reserved for patients with localised residual disease after non-surgical therapy or for rare patients with complications.²³

Guideline — Lack of role for surgery	Level of evidence	Refs
In general, patients with gastric MALT lymphoma do not require surgery, because results of radiotherapy and/or chemotherapy are superior.	III	22, 23

17.4 Diffuse large B-cell lymphoma of the stomach

17.4.1 Aetiology

Molecular evidence now suggests that diffuse large-cell lymphoma (DLCL) may originate either by transformation of a gastric MALToma that is negative for the t(11,18) translocation, or as a *de novo* tumour with other genetic aberrations.⁴

17.4.2 Staging

It now appears to be well established that such lymphomas should be managed according to the principles established for the treatment of nodal DLBCL.²³ The patients are clinically staged as such, obviously including gastroscopy and endoscopic ultrasound where available.

17.4.3 Diminishing role for surgery

Over the last decade or so, the treatment has changed, with virtual elimination of the need for gastrectomy. This change is based not so much on randomised clinical trials, but on analysis of outcome in cohort studies.²³

The Princess Margaret Hospital (Toronto) saw 122 patients with DLCL lymphoma between 1967 and 1996. Previous treatment of partial gastrectomy followed by radiation therapy led to an overall ten-year survival of 66% and cause-specific survival of 88%. In the past decade, for combination chemotherapy (CHOP) followed by radiation therapy, the overall five year rate was 87% and cause specific survival 95%.²⁴

Similarly, in Taiwan, some 38 patients with DLCL were treated with anthracycline containing combination chemotherapy, or curative surgery followed by adjuvant chemotherapy. There were 38 patients in the first group and 21 in the second. The projected five-year relapse-free survival and overall survival were 86% and 73% respectively in the group receiving chemotherapy alone, while in the group with surgery and chemotherapy, the five year relapse-free survival and overall survival were 78% and 78% respectively, that is, not significantly different from group A.²⁵

A randomised trial has been done in terms of the role of surgery in primary gastric lymphoma. Avials in Mexico randomised 589 patients with primary gastric diffuse large-cell lymphoma in early-stages IE and II. One hundred and forty-eight patients were randomised to surgery, 138 to surgery plus radiotherapy, 153 to surgery plus chemotherapy, and 150 patients to chemotherapy alone. Radiotherapy was at a dose of 40 Gy, and chemotherapy was CHOP at standard doses. Actuarial overall survival at ten years was for surgery 54%, surgery plus radiotherapy 53%, surgery plus chemotherapy was 91%, and chemotherapy alone 96%. They therefore concluded that chemotherapy should be considered the treatment of choice in this patient setting. It was interest that there was not a chemotherapy plus radiotherapy arm.²⁶ Similarly studies in Japan demonstrated that patients who received non-surgical treatment showed a better overall survival than those treated by surgery.²⁷

17.4.4 Systemic chemotherapy

These data suggest that systemic chemotherapy alone is a reasonable alternative treatment for stage I and stage II DLCL (see Chapter 13). Resection of the primary tumour before systemic chemotherapy does not appear to improve the cure rate of this group of patients.

Guideline — Treatment of gastric and diffuse large-cell lymphoma (DLCL)	Level of evidence	Refs
Patients are managed as for DLCL as described elsewhere with CHOP chemotherapy.	I–III	23–27

17.5 References

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