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SURGICAL IMPLICATIONS OF HELICOBACTER PYLORI INFECTION

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1. ABSTRACT

Helicobacter pylori infection is the most common cause of peptic ulcer disease and is an etiologic factor in the development of gastric malignancies. Eradication of *H. pylori* heals most uncomplicated peptic ulcers, as well as preventing their relapse. In addition, *H. pylori* therapy has recently been used as a first line treatment for most low grade MALT lymphomas. Despite its efficacy, a small percentage of patients with peptic ulcer disease will require operative intervention and the indications for surgical intervention for the patient with peptic ulcer disease include; intractability, gastric outlet obstruction, acute perforation, and bleeding uncontrolled by endoscopic intervention. *H. pylori* has also been shown to be associated with an increased risk of gastric adenocarcinoma and surgical exploration may play a role in diagnosis, staging and treatment. Finally, the relationship between *H. pylori* infection and the development of gastric MALT lymphoma is well established. While treatment for *H. pylori* infection is indicated for low grade MALT lymphomas, surgical resection may be indicated for treatment failures, as well as for certain high grade lesions.

2. INTRODUCTION

The concept that peptic ulcer disease and gastric malignancy is, in part, an infectious disease was introduced nearly 20 years ago by Marshall and Warren (1). Since that time, the contribution of *Helicobacter pylori* (*H. pylori*) as an etiologic factor in the majority of patients with chronic gastritis, peptic ulcer disease, gastric adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach has been extensively studied (Figure 1). *H. pylori*, a motile flagellar bacillus that dwells in the mucous layer of the stomach, is found in more than 90% of patients with duodenal ulcers and up to 80% of patients with gastric malignancy (2,3). This translates into one in six persons infected with *H. pylori* will eventually develop peptic ulcer disease with a lifetime risk of gastric adenocarcinoma between 1% and 3%. Importantly, eradication of *H. pylori* leads to ulcer healing, regression of certain gastric lymphomas and may decrease the risk of gastric cancer. While the treatment of these conditions (with the exception of gastric adenocarcinoma) initially includes medical therapy, surgical intervention still may be indicated in specific cases. This chapter will review the current status of indications for surgery in *H. pylori*-induced peptic ulcer disease and gastric malignancies.

3. SURGERY FOR PEPTIC ULCER DISEASE

The indications for surgical intervention in patients with peptic ulcer disease (PUD) have not changed over the last fifty years. Specifically, these include: 1) failure of medical therapy (intractability), 2) gastric outlet

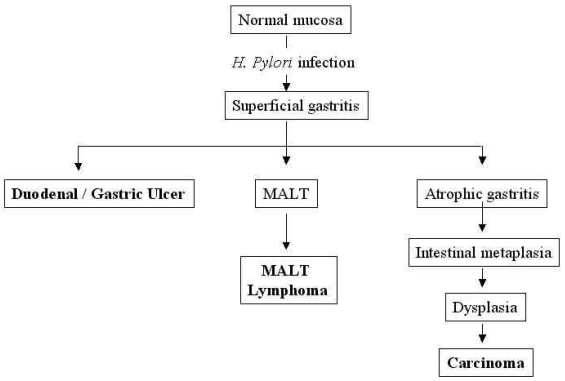

Figure 1. Potential clinical patterns of H. Pylori infection.

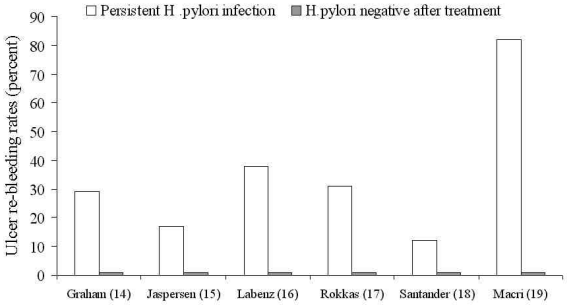

Figure 2. Summary of studies of re-bleeding after H. pylori treatment.

obstruction, 3) acute perforation, 4) bleeding uncontrolled by endoscopic intervention. While indications have not changed, the number of patients that fall into these categories has dramatically decreased. Medications that provide acid reduction and enhance the mucosal defenses, with the recognition that *H. pylori* infection is a key player in the pathogenesis of gastric and duodenal ulcer disease has dramatically changed the management of PUD. Today, medical and endoscopic therapies rarely fail to control peptic ulcer disease and the number of elective operative cases for PUD has all but disappeared. Intractability of PUD is often the result of the failure of *H. pylori* eradication, and can be explained by either the use of ineffective regimens, non-compliance or antibiotic resistance. While intractability by itself rarely leads to operation, complications of persistent or unrecognized PUD are observed in an estimated 10% of patients and this subset of patients often requires some form of surgical intervention (4).

3.1. Bleeding peptic ulcer disease

Upper gastrointestinal (GI) bleeding occurs at an annual incidence of about 100 per 100,000 people (5). The source of upper GI bleeding can originate from the duodenum, stomach or esophagus. Endoscopic control of acute GI bleeding is very effective and is considered the standard of care for these patients. In multiple meta-analyses, endoscopic therapy has been shown to reduce the rate of recurrent bleeds, the need for surgery and in-hospital mortality (6-8). Based on the data from these trials and clinical experience world wide, therapeutic endoscopy is considered the primary treatment for actively bleeding PUD. While more than 70% of patients who present with UGI bleeding from PUD will stop without surgical intervention, there are patients who are at high risk of having a life threatening re-bleed. Persistent or recurring bleeding occurs in as many as 20% to 30% of patients and this is associated with a 10-15% mortality rate. Patients who are at high risk for complications include patients who present with hypovolemic shock from hemorrhage, hospitalized patients with significant co morbid diseases, and patients with coagulopathy. In addition, those patients who fail initial endoscopic management are at a much higher risk for complications and death. In a series from Scandinavia, a 6.3% mortality rate was reported for patients with acute bleed from PUD. While only 5% of the patients required surgery, those patients requiring an operation for their bleeding ulcer suffered a mortality rate of 23.5% (9). While the prevalence of *H. pylori* infection in bleeding ulcer patients is not well defined, estimates range from 40-90% (10).

3.1.1. Choice of Operation

The procedure of choice for the patient with an acute bleed for PUD remains controversial. The armamentarium for the surgeon includes pyloroplasty and suture ligation, with or without vagotomy, partial gastrectomy, or wedge resection for gastric ulcer. In general, the more extensive the operative procedure, the lower the recurrence. However, the more definitive procedures are believed to be associated with increased operative morbidity and mortality. Some surgeons, rationalizing that *H. pylori* treatment and proton pump inhibitors are very effective, have promoted only suture ligation of the bleeding vessel in the ulcer bed in those patients that have not failed previous medical therapy. The argument for this approach is that suture ligation alone is a very simple procedure with little morbidity. Other groups advocate the addition of vagotomy with suture ligation, rationalizing that acid reduction is necessary for healing and reduction of recurrence. Finally, partial gastrectomy with vagotomy remains the gold standard for bleeding PUD in terms of recurrence, but in some series, operative mortality can be as a high as 25% (11-13). The actual choice of procedure should be tailored to each patient, taking into account age, co-morbid conditions, failure of previous therapies and hemodynamic stability.

In patients with peptic ulcer bleeding associated with *H. pylori* infection, after the successful endoscopic control of the index bleeding episode, *H. pylori* eradication has been unequivocally proven to not only heal the ulcer, but also to prevent further bleeding episodes (14-19) (Figure 2). For example, to evaluate whether eradication of *H. pylori* results in a reduction of ulcer recurrence and rebleeding in patients with *H. pylori*-associated duodenal ulcer hemorrhage, Jaspersen and colleagues randomized patients with upper GI hemorrhage from duodenal ulcer with documented *H. pylori* infection to receive either omeprazole and amoxicillin or omeprazole alone for 2 weeks. Patients underwent a second endoscopy 4 weeks after completion of therapy and were followed for 1 year. All patients showed ulcer healing 4 weeks after completion of therapy. *H. pylori* eradication rates were significantly increased in the *H. pylori* treatment group (83% vs 5%).

Despite, what may be considered inadequate treatment for *H. pylori infection*, ulcer recurrences were also significantly lower in *H. pylori* treated patients (10%) than in the omeprazole alone group (41%). Importantly, rebleeding occurred significantly less often in the *H. pylori* therapy group than in the omeprazole group (0% versus 27%) (15).

3.2. Perforated Duodenal ulcers

The rate of *H. pylori* infection in patients with perforated duodenal ulcers ranges from 50%-80% and *H. pylori* infection, as a risk factor for perforated duodenal ulcer (DU), appears to be more relevant in younger patients. This is in contrast to elderly patients, where NSAIDs may play a more significant etiologic role (20-22). The mortality rate for perforated DU is approximately 5%, but similar to upper GI bleeding, this figure can increase significantly with a delay in diagnosis or in patients with associated co-morbid conditions (23).

3.2.1. Choice of Therapy

Similar to acute bleeding, controversy surrounds the appropriate treatment for perforated DU. Therapeutic options for perforated DU range from non-operative treatment to simple omental patch closure to definitive surgery. Arguments for each of these approaches have raged on for many years. Non surgical therapy for perforated DU had been purported in the 1950s by Taylor (24). Forty years later, in a randomized trial comparing non-operative therapy, Crofts and colleague demonstrated that this approach was a viable therapy in select patients. In this study, 83 patients with a clinical suspicion of a perforated DU were randomly assigned to non-operative treatment versus emergency exploration. Non-operative therapy included intravenous resuscitation, intravenous antibiotic and nasogastric decompression. Eleven patients in the non-operative group (28%) had no improvement in symptoms and required surgical exploration. Morbidity and mortality were similar in both groups although the hospital stay for the non-operative group was longer and failures in the non-operative group were significantly higher in patients > 70 years of age (25). Non-operative treatment, although not widely practiced in the United States, is a very good option for patients who present with localized pain and tenderness, and are hemodynamically stable. While approximately thirty percent of patients may eventually fail non-operative therapy, there is no increased morbidity from an initial non-operative trial. In addition, over two-thirds of patients will recover and will avoid an emergency exploration. Therefore, in the appropriately selected patient, non-operative therapy with nasogastric decompression and intravenous antibiotics may provide the best and least invasive manner of treating this complication of PUD, thus allowing elective medical therapy.

For perforated DU patients with generalized peritonitis, hemodynamic instability or co-morbid conditions that may preclude non-operative therapy, surgical exploration is absolutely indicated. However, controversy also exists as to the extent of surgery for perforated DU. Simple closure has been compared with definitive surgery for perforated DU in three randomized trials. These studies report that in appropriately selected patients, acid reducing operations utilizing either truncal or selective vagotomy have been shown to reduce recurrence rates from about 50% with simple closure alone to less than 10% without a significant increase in operative morbidity and mortality (26-28). Despite this data, definitive surgery has not been widely practiced, most likely to secondary to patient factors (hemodynamic instability at the time of exploration) and/or surgeon factors (inexperience with gastric surgery).

In an attempt to resolve this controversy of extent of surgery, Ng *et al* performed a prospective randomized trial to determine whether eradication of *H. pylori* could reduce the recurrence of ulcers after simple closure of a perforated duodenal ulcer. They studied 104 patients who underwent simple patch closure for their acute duodenal perforation and were *H. pylori* positive. One group received anti-*H. pylori* therapy (bismuth, tetracycline and metronidazole) while the second group received only single agent acid reduction medication (omeprazole) treatment. Patients were followed up with endoscopy at 8 weeks, 16 weeks and 1 year after hospital discharge. Of the patients who had follow-up endoscopy, 43 of 44 patients in the anti-*H. pylori* therapy group and 8 of 46 in the proton pump inhibitor group had *H. pylori* eradication. While initial ulcer healing rates were similar between both groups, ulcer relapsed was significantly decreased in the anti-*H. pylori* group (4.8%) as compared to the omeprazole treated group (38.1%) (20). Some have argued that if the recurrence rate after simple patch closure with postoperative *H.pylori* eradication approach those recurrence rates after definitive surgery, then a laparoscopic closure should improve patient outcome. Although enticing, to date, neither randomized or non randomized studies have demonstrated any advantage over conventional open techniques (29-31). While the study by Ng and colleagues certainly adds evidence that simple closure with post-operative anti-*H. pylori* therapy should provide adequate therapy for perforated DU, some caveats must be discussed. Not all patients are *H. pylori* positive and the knowledge of *H pylori* status at the time of perforation is most often unknown. In addition, the etiology of perforated DU is often associated with NSAID use, independent of *H. pylori* status which adds an another factor to be considered.

In summary, the treatment of the acute perforated DU should be individualized. For younger, hemodynamically stable patients without peritoneal signs, non-operative therapy is appropriate. In terms of surgical strategy, either omental patch with or without vagotomy is indicated, depending on patient status, as well as surgeon's experience. Importantly, in those patients who are *H. pylori* positive, post-operative therapy should be considered.

3.3. Gastric outlet obstruction

Gastric outlet obstruction complicates PUD in approximately 5%-8% of patients (32). The incidence of H. pylori infection in patients with gastric outlet obstruction (GOO) has not been well documented, but small studies report incidence ranging from 30%-60%

(30,33). Obstruction of the pylorus becomes clinically evident as result of a combination of two processes: acute inflammation and edema and/or pyloric spasm from an acute ulcer can lead to obstruction of the lumen in addition to chronic scarring and fibrosis associated with long term PUD. The reversal of GOO has been reported after treatment for H. pylori infection (34-36). While the acute inflammation and edema is often reversible with medical therapy, more often than not, reversal of GOO requires either endoscopic pneumatic dilatation of surgical resection or bypass. Pneumatic dilatation should probably be reserved for those patients who are unfit for surgical exploration, since up to 50% of patients will have re-obstruction within 3 years of follow-up (37). The surgical approach for GOO should include both acid reduction, as well as a drainage procedure. In a prospective trial of surgical treatment for GOO, Csendes *et al* randomized patients with pyloric obstruction form PUD to either highly selective vagotomy (HSV) + gastrojejunostomy, HSV + gastroduodenostomy, or selective vagotomy + antrectomy. There was no observed difference in the postoperative complications, while the functional results of patients undergoing gastroduodenostomy were worse compared to resection or gastrojejunostomy (38).

3.4. Significance of H. pylori infection of the gastric remnant

As discussed above, over 95% of patients with duodenal ulcers and approximately 85% of patients with gastric ulcers are infected with *H. pylori* and treatment provides excellent resolution of both infection and ulceration. However, for patients requiring surgery for PUD, persistence of *H. pylori* infection has unknown clinical significance. There have been several studies on the prevalence of *H. pylori* infection in patients who have undergone surgery for complications of PUD. In a meta-analysis, Danesh *et al* reviewed 36 published studies that assessed *H. pylori* infection after gastric surgery. They reported that the prevalence of *H. pylori* in patients undergoing vagotomy alone was 83%, which dropped to 50% after partial gastrectomy. They postulated that the decrease in *H. pylori* infection were due partly to the resection of the distal gastric tissue, the usual site of infection and partly due the bactericidal effects of prolonged bile acid reflux (39).

In an attempt to explore the issue of bile reflux as a protective factor for subsequent *H. pylori* infection, Rino and colleagues studied 70 patients who underwent partial gastrectomy for gastric cancer and found 26 (37%) were *H. pylori* positive in the gastric remnant and 44 (63%) showed no signs of *H. pylori* infection. Of note, while no patients undergoing a Billroth II reconstruction (gastrojejunostomy) were *H. pylori* positive, nearly 40% of patients undergoing a Billroth I reconstruction (gastroduodenostomy) had *H. pylori* infection (40). Similar results have also been reported by Tomtitchong *et al* (41). In a study of post-gastrectomy patients for either cancer or PUD, they noted that 17/37 (46%) of patients were *H. pylori* positive in the gastric remnant after Billroth II reconstruction, while 71% of patients (51/72) were *H. pylori* positive after a Billroth I anastomosis. This decrease in post-gastrectomy infection of the gastric remnant after a Billroth II reconstruction provides indirect evidence that bile reflux, which is more common after a gastrojejunostomy reconstruction than gastroduodenostomy, may interfere with *H. pylori* colonization. The clinical impact of *H. pylori* infection in the gastric remnant is unknown. Some authors suggest that post-gastrectomy gastritis may be the result of persistent *H. pylori* infection (42,43), while author groups show no correlation (44). The issue of *H. pylori* infection in the gastric remnant after gastric resection as a risk factor for gastric stump cancer has also been raised. Mucosal cell proliferation rates in the gastric remnant have been shown to be increased with *H. pylori* infection, which is significantly increased in the presence of bile reflux (45,46). On the other hand, there is no clinical data to suggest that *H. pylori* infection is associated with gastric stump cancer. In fact, in one study, *H. pylori* infection was lower in gastric stump carcinoma patients as compared to patients with gastric cancer with intact stomachs (47).

4. SURGERY FOR GASTRIC MALIGNANCY

H. pylori was designated as a Class I carcinogen by the World Health Organization in 1994 and has been shown to be involved in the pathogenesis in two distinct gastric cancers; gastric adenocarcinoma and gastric MALT lymphomas. Based on this data, it has been suggested that eradication of *H. pylori* infection in high-risk populations may prevent gastric adenocarcinoma, while *H. pylori* treatment for certain MALT lymphomas may be curative. The following section reviews the surgical implications of *H. pylori* as it pertains to gastric malignancies.

4.1. Gastric adenocarcinoma

Once the leading cause of cancer death, the incidence of gastric adenocarcinoma in the United States has dramatically decreased since the 1930s. While the overall incidence of gastric cancer has decreased, there is a well documented shift from distal to proximal lesions. The clinical relevance of this shift is that the overall prognosis for patients with proximal gastric cancer is worse than those with distal tumors (48). Despite this decline in the incidence in the West, gastric carcinoma remains an important international health problem. In many countries, such as Japan, Costa Rica, Chile and Hungary, gastric cancer ranks high as a site of cancer-related mortality. In addition, in low risk countries, there are ethnic groups including African-Americans, Asians and Latinos, who are at a high risk for developing gastric adenocarcinoma (49,50). A variety of studies have indicated a strong association between chronic *H. pylori* infection and gastric adenocarcinoma (51-53) and this risk is further enhanced with cytotoxin-associated gene A (cagA) *H. pylori* strains (54). The central hypothesis generated from these observations is that *H. pylori* infection results in chronic inflammation, which may progress to atrophic gastritis, intestinal metaplasia, dysplasia and then to gastric cancer and this transformation may take several decades (55). Supporting this hypothesis, Blaser *et al* reported that early age of establishment of *H. pylori* infection increases the risk of developing gastric cancer (56). Additional support of the early infection risk factor stems from migrant studies

of people who move from regions of high gastric cancer risk to low risk. For first generation migrants, the risk of gastric cancer is minimally changed from that of the high risk region. It is not until second generation when the risk of gastric cancer approaches that of the low risk region (57,58). The exact mechanism by which *H. pylori* of this increased risk is unknown. Many investigators have demonstrated *H. pylori* induces apoptosis in gastric epithelium with an increase in cell proliferation and an expansion in the proliferative zone (59). In addition, infection with *H. pylori* is characterized by infiltration of lymphocytes, polymorphonuclear leukocytes and macrophages in the gastric mucosa and the role of oxygen free radicals originating from these white blood cells as well as the contribution of other immunologic pathways as inducers of mutations of the gastric epithelium are currently under study (60, 61).

4.1.1. Surgery for Staging

Once the diagnosis of gastric adenocarcinoma is established, the next step is the determination of extent of disease. For patients with metastatic disease in the absence of GOO or major bleeding, palliative chemotherapy, radiation or best supportive care should be offered. In this instance, gastric resection offers no chance of cure and palliation of minor symptoms can usually be adequately achieved medically. Patients with GOO or bleeding requiring multiple transfusions may require palliative surgery and this is addressed below. Patients with resectable tumors by CT scan with minimal symptoms should next be evaluated by laparoscopy. Preoperative staging using laparoscopy may enable many patients to avoid an unnecessary non-curative operation. Laparoscopy is a very useful modality for evaluating local, regional and distant extent of disease. Laparoscopy has been shown to be more sensitive in detecting peritoneal and omental metastases compared to a quality CT scan examination of the abdomen and pelvis (62). In addition, laparoscopic evaluation allows patients with minimal symptoms and advanced T stage or extensive nodal disease to be considered for preoperative chemotherapy regimens without having to undergo the morbidity of an exploratory laparotomy (63). Laparoscopic evidence of peritoneal or liver metastases in patients with minimal or no symptoms should be a contraindication for resection. These patients have a median survival of 6-8 months and almost uniformly die prior to developing symptoms severe enough to require surgical intervention from their primary tumor (64).

4.1.2. Surgery for Palliation

For gastric outlet obstruction or major bleeding from the primary tumor, most patients should proceed directly to an exploratory laparotomy despite evidence of distant disease. Intraoperative evaluation will dictate the procedure of choice. For gastric outlet obstruction, a gastric resection should be performed, as it will provide the best palliation. In the presence of widely metastatic disease or in the rare case of a locally unresectable tumor, a gastrojejunostomy will offer palliation for the obstruction. A third option for those patients with end stage metastatic disease is placement of a gastrostomy tube to relieve symptoms, which may be placed at the time of exploration or later, endoscopically. For those patients who present with an UGI bleed requiring blood transfusion, a gastric resection is the procedure of choice. For those patients with a technically unresectable tumor, external beam radiation may be an alternative to control bleeding. Endoscopic control of bleeding is often ineffective due to the presence of friable tissue, which is diffuse rather than focal.

4.1.3. Surgery for Cure

In the absence of metastases by laparoscopy, patients should proceed to gastric resection with curative intent. This includes surgical resection of the tumor with adjacent lymph nodes. The extent of gastric resection depends on the location and size of the primary tumor. For distal tumors in the antrum and body, a distal subtotal gastrectomy, removing 80%-85% of the stomach along with the greater and lesser omentum is the operation of choice. Reconstruction with either a Billroth I gastroduodenostomy or Billroth II gastrojejunostomy can be performed, as there is little difference in outcome or function. The issue of performing a more extend resection (total gastrectomy) for these lesions has been addressed by prospective studies and offers no improvement in survival (65,66). For proximal lesions in the cardia and gastroesophageal junction or large mid body tumors, a total gastrectomy or proximal gastrectomy with omentectomy can be performed with equal survival results (67).

The extent of lymphadenectomy for gastric cancer has long been debated. Reports of excellent long-term survival have been reported from the East, where extended lymphadenectomy (D2 dissection) is performed routinely. Unfortunately, Western results have not been as promising, with high morbidity and mortality without obvious survival benefits (68, 69). While extended lymphadenectomy improves the accuracy of staging, whether it adds to long-term survival is still a matter of ongoing debate (70). Related to the issue of lymphadenectomy is the question of performing a routine splenectomy with or without distal pancreatectomy in order to accomplish a more complete nodal dissection. Multiple studies demonstrate that routine pancreaticosplenectomy is not indicated, as it is associated with a higher incidence of postoperative complications without contributing a survival advantage (68,71). However, a select subset of patients whose primary tumors directly invade adjacent organs in the absence of significant nodal or metastatic disease (T4 N0-1 M0) may benefit from adjacent organ resection in order to attain a curative resection.

Based on the concept that *H. pylori* infections leads to carcinogenesis through a long process of chronic infection with subsequent dysplasia has lead some researchers to investigate whether early treatment of *H. pylori* infection would prevent gastric adenocarcinoma. Studies have shown that eradication of *H. pylori* causes resolution of the inflammatory changes, reduction of cellular proliferation in gastric mucosa and even reversal of intestinal metaplasia (72,73). However, the data on its effect on lowering the incidence of gastric adenocarcinoma are less convincing. In addition to antibiotic therapy, some have advocated the use of anti-*H.pylori* vaccines, but no data from clinical trial are available (74,75).

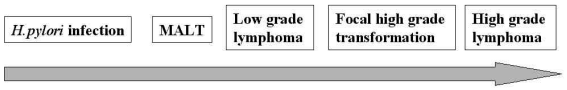

Figure 3. Spectrum of pathologic changes leading to MALT Lymphoma after H. pylori infection.

4.2. Gastric MALT lymphoma

The concept of B cell lymphomas arising from mucosa-associated lymphoid tissue (MALT) was introduced by Issaacson and Wright in 1983 and the initial evidence for a causal relationship between *H. pylori* infection and the development of gastric MALT lymphoma was provided a decade later by Wotherspoon and colleagues who demonstrated the presence of *H. pylori* infection in 92% of patients with primary low grade gastric MALT lymphoma (76,77). Since then, several other studies have confirmed this relationship and have provided evidence that the development and proliferation of MALT lymphoma depends on the immunologic stimulus of *H. pylori*. Supporting this immunologic model and similar to gastric adenocarcinoma, expression of the CagA appears to play an important role in pathogenesis of gastric MALT lymphomas (78). The revised European-American Lymphoma (REAL) lymphoma classification designates MALT lymphomas as marginal zone B-cell lymphomas of the MALT type, since these malignancies arise from B cells in the marginal zone of organized lymphoid tissue (79). MALT lymphomas are histologically classified as either low grade or high grade. Low grade lymphomas are composed of small cells with dense nuclear chromatin and low proliferation fraction, while high-grade tumors consist of large, transformed lymphoid blasts. The simultaneous presence of low-grade and high grade components is a well-known finding. The generally accepted concept for most primary gastric MALT lymphomas follows the sequence of gastric *H. pylori* infection followed by the acquisition of MALT, leading to low grade lymphoma, focal high grade transformation, and finally high grade lymphoma (Figure 3). Importantly, some gastric MALT lymphomas are *H. pylori* independent and high grade lymphomas can also arise de novo. The staging of gastric lymphoma is important since treatment is dependent on the extent of disease. Tumors are staged according to the modified Ann Arbor gastric lymphoma staging scheme. Tumors limited to the stomach are designated as Stage IE. The presence of perigastric and regional lymph node involvement is Stage IIE-1 and IIE-2, respectively. Disease on both sides of the diaphragm is Stage III disease and disseminated disease is categorized as Stage IV (Table 1). In addition, the tumor grade and cellular type are also predictive factors for outcome.

4.2.1. Evaluation

The information required for treatment of patients with MALT lymphomas includes the extent of involvement, including proximal extent of the primary lesion, regional adenopathy, bone marrow involvement, or non-nodal extra gastric involvement (liver or supradiaphragmatic nodal involvement). In addition, the grade of the lymphoma and the presence of *H. pylori* infection will also impact on the treatment algorithm. A complete history and physical examination and a CT scan of the chest, abdomen and pelvis are standard approaches for all patients. Some institutions have used EUS to evaluate depth of penetration of the primary, as well as evaluation of regional lymphadenopathy. In addition, some have advocated the use of EUS to predict regression after eradication of *H pylori* (80). Nakamura and colleagues evaluated 41 patients with MALT lymphomas with EUS before and after treatment for *H. pylori*. They found that 26 of 28 (93%) of patients with their tumors confined to mucosa had a complete response to *H pylori* therapy. Conversely, only 3 of 13 (23%) of patients had a complete response in which the tumor invaded into the submucosa or deeper. Interestingly, neither the presence of high-grade component, perigastric lymphadenopathy nor clinical stage prior to *H. pylori* therapy correlated with the probability of a complete response to *H. pylori* treatment (81). In contrast, others have reported that EUS-documented perigastric lymphadenopathy was the only significant predictor of response by multivariate analysis (82).

Laparoscopy has recently been introduced as a minimally invasive way of diagnosing and staging gastric lymphomas. In addition to staging information, laparoscopy can safely provide tissue samples of suspected lymphoma for full diagnostic analysis and should be considered when percutaneous biopsy is not technically possible or are inadequate to make therapeutic decisions (83). Laparoscopy can also be used as a method of resection of the tumor, either as a wedge resection (84) or as a formal gastrectomy.

4.2.2. Treatment

Early experience with primary chemotherapy and/or radiation in the 1980s revealed numerous reports of life-threatening complications related to gastric perforation and bleeding (85,86). As a result surgery was then considered the gold standard of therapy for gastric lymphomas. More recent reports have not confirmed this high morbidity and mortality after non-operative approach and some institutions have demonstrated equivalent survival rates after non-operative therapy for gastric lymphoma with similar complication rates and have advocated this non-operative approach (72,87). Presently, the selection of therapy for gastric lymphomas should be based on accurate histopathologic diagnosis, grading and clinical staging (Table 1).

The treatment of non MALT lymphomas has been reviewed extensively (73) and for the sake of brevity, this section will only address the treatment of *H. pylori* related MALT lymphomas. Based on the relationship between *H. pylori* and MALT tumors, the treatment and eradication of *H. pylori* in low-grade gastric MALT lymphomas has dramatically changed the therapeutic approach to this tumor and *H. pylori* therapy has been added to the treatment armamentarium for patients with gastric MALT lymphomas.

The perception that growth of low grade MALT lymphoma can be modulated by *H. pylori* -related factors and that eradication of *H. pylori* infection may influence tumor regression has lead to trials evaluating *H. pylori* eradication as primary therapy for this group of patients. Multiple published reports suggest that antibiotic treatment

Table 1. Staging and intial treatment of MALT lymphoma

Stage	T	N	Low Grade	High Grade
EI_1	Limited to mucosa and submucosa	Negative	H. Pylori treatment [1]	Surgery [2]
EI_2	Beyond submucosa	Negative	H. Pylori treatment [1]	Surgery [2]
EII_1		Perigastric	Surgery	Surgery [2]
EII_2		Regional	Chemotherapy	Chemotherapy[1]
EIII	Disease both sides of the diaphragm		Chemotherapy/XRT	Chemotherapy/XRT
EIV	Disseminated		Chemotherapy/XRT	Chemotherapy/XRT

[1] If partial or no response, then surgical resection +/- XRT, [2] Consider postoperative chemotherapy, XRT: Radiation treatment

of *H. pylori* -associated low grade MALT lymphomas provide a complete response of nearly 80% in all patients (88). After small studies of anti- *H. pylori* therapy for patients with low grade MALT lymphomas, the German MALT Lymphoma Study Group studied in a multicenter fashion 50 patients with stage E1 low grade gastric MALT lymphoma patients. All patients were treated with amoxycillin and omeprazole for two weeks. All patients had eradication of *H. pylori* infection. With a median follow-up of 24 months, forty patients achieved a complete response to *H. pylori* therapy (80%), four achieved a partial response and six demonstrated no response. Of the 40 patients with a complete response, 5 subsequently relapsed. Among the six patients that did not respond to *H pylori* therapy, four revealed high grade tumors after surgical resection (83). While most treat high grade MALT lymphoma patients with either surgery or chemotherapy, some have attempted to treat with anti-*H. pylori* therapy. In a study of eight patients with *H. pylori* infection and high grade lymphoma, all were treated with anti-*H. pylori* therapy and reevaluated. *H. pylori* eradication was successful in all patients and 7/8 patients achieved a complete response (89).

In general, for stage IE and IIE *H. pylori* positive low-grade gastric MALT lymphomas should initially be treated with anti-*H. pylori* therapy. Treatment evaluation should include serial CT scanning, upper endoscopy and EUS, when available. For those patients with a complete response, follow-up is indicated. Patients with partial or no response should be treated with surgical resection. EI and EII1 high-grade lesions should be considered for surgery and EIII and EIV patients should be treated with chemotherapy (Table 1).

5. PERSPECTIVE

H. pylori infection has recently declined in developed countries, probably contributing to the observed decrease in the incidence of complicated ulcer disease and gastric cancer. Increasing standards of hygiene and socioeconomic status have paralleled this reduction in the rate of peptic ulcer disease and gastric carcinoma, which may support an oral-oral and oral-fecal route mode of transmission. Despite this decrease, surgery plays a critical role for the complications of *H. pylori* -induced PUD, as well as for gastric adenocarcinoma and MALT lymphoma. Future studies are needed to define the mechanisms of *H. pylori*-induced disease, which will lead to better long term treatment and prevention.

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Abbreviations: PUD, peptic ulcer disease, GOO, gastric outlet obstruction

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