REVIEW

Korean J Intern Med 2026;41:8-14
https://doi.org/10.3904/kjim.2024.143

Clinical management of gastric mucosa-associated lymphoid tissue lymphoma

Ji Yong Ahn

Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is often associated with chronic *Helicobacter pylori* infection. For an accurate diagnosis of gastric MALT lymphoma, clinical suspicion and careful endoscopic examination with multiple biopsies should be performed, and the final pathological confirmation should be provided. Gastric MALT lymphomas present with nonspecific symptoms and endoscopic findings. In most cases, *H. pylori* infection is the main cause of gastric MALT lymphoma. Therefore, *H. pylori* eradication should be considered the first-line treatment, even in cases of *H. pylori*-negative gastric MALT lymphoma. Radiotherapy or chemotherapy can be considered in patients in whom eradication therapy has failed. Because the clinical course of gastric MALT lymphoma is usually indolent, the "watch-and-wait" strategy is one of the choices for selected patients who can undergo scheduled regular follow-up examination.

Keywords: Stomach; Lymphoma; *Helicobacter pylori*

INTRODUCTION

Gastric mucosa-associated lymphoid tissue (MALT) lymphoma, a subtype of non-Hodgkin lymphoma, arises from the MALT of the stomach. This indolent lymphoma is often associated with chronic *Helicobacter pylori* infection, a bacterium implicated in several gastric diseases. The discovery of the association between *H. pylori* and gastric MALT lymphoma has improved the management of this disease, indicating the importance of microbial factors in its pathogenesis and therapy [1]. Gastric MALT lymphoma is typically indolent and may remain localized in the gastric mucosa for extended periods.

Diagnostic and treatment strategies mainly focus on the identification and eradication of *H. pylori*, which can lead to complete remission in a significant proportion of cases. However, for *H. pylori*-negative cases or those unresponsive to eradication therapy, alternative therapeutic strategies such as radiotherapy and chemotherapy can be considered. In general, the prognosis for gastric MALT lymphoma is favorable, particularly when diagnosed early and managed appropriately [2]. This study aimed to provide updated information regarding the pathogenesis, diagnosis, treatment, and prognosis of gastric MALT lymphoma.

PATHOGENESIS OF GASTRIC MALT LYMPHOMA

Gastric MALT lymphoma is closely associated with chronic *H. pylori* infection, although a subset of cases are independent of this bacterium. The pathogenesis of gastric MALT lymphoma is a multistep process involving both infectious and genetic factors, leading to the malignant transformation of lymphoid cells.

The pathogenesis of most gastric MALT lymphomas begins with *H. pylori* infection. Notably, *H. pylori* induces a local immune response in the gastric mucosa, leading to

pISSN 1226-3303
eISSN 2005-6648
http://www.kjim.org

the recruitment and proliferation of MALT. A chronic inflammatory environment facilitates genetic mutations and acquisition of autonomic growth properties by lymphoid cells, eventually leading to lymphoma. Therefore, *H. pylori* eradication often leads to lymphoma regression, indicating the pivotal role of this infection in the early stages of lymphoma [3,4].

Other pathogenic mechanisms have been implicated in cases where the disease persists or recurs despite successful *H. pylori* eradication. Genetic alterations, including trisomies and translocations, such as t(11;18)(q21;q21), play crucial roles in treatment failure. These genetic events can activate oncogenes or deactivate tumor suppressor genes, thereby promoting the survival and proliferation of malignant cells independent of *H. pylori* infection [5].

The immune response to *H. pylori* infection can also contribute to the pathogenesis of gastric MALT lymphoma. Chronic antigenic stimulation by bacteria or other stimuli can lead to the unchecked clonal expansion of B cells. In addition, the tumor microenvironment, which is enriched in T cells and other immune cells, may contribute to the survival and proliferation of malignant B cells [6]. The interaction between *H. pylori* and gastric epithelial cells triggers molecular pathways that contribute to lymphomagenesis. Therefore, the CagA protein injected by *H. pylori* into the host cells can disrupt normal cellular functions and promote oncogenic activity [7]. Furthermore, the ongoing inflammatory response creates a background rich in cytokines and other growth factors, further supporting the growth of malignant lymphoid cells.

DIAGNOSIS OF GASTRIC MALT LYMPHOMA

Patients may experience symptoms such as indigestion, nausea, heartburn, and gastrointestinal bleeding; however, some are asymptomatic and symptoms are often accidentally detected during endoscopy [8]. Endoscopic biopsy and immunochemical staining are the most important techniques for diagnosing gastric MALT lymphoma. Gastric MALT lymphoma mainly arises in the distal part of the stomach but can also occur in the proximal part or multiple areas; thus, it is important to perform biopsies in multiple locations [9].

Endoscopic findings of gastric MALT lymphoma

The endoscopic findings of gastric MALT lymphoma are extremely diverse, making it challenging to distinguish the lymphoma from early gastric cancer or benign gastric lesions such as atrophic gastritis or erosions. In previous studies, endoscopic findings were classified into four main types, of which large ulcer was the most common (42.9%), followed by small ulcer with gastritis (28.5%), polyps (14.3%), and other atypical forms (14.3%) [10]. Japanese studies have reported the ulcer form (33.3%), multiple erosions (23.4%), scar form (12.8%), and early gastric cancer IIc form (10.6%) [11]. In a Korean study, the findings were classified into raised, ulcer infiltration, early gastric cancer IIc, subepithelial tumor, and multiple-erosion types [12]. Consequently, careful observation and multiple biopsies of suspected lesions are necessary; repeated endoscopy and biopsy are also needed in some cases [12,13]. The various endoscopic findings of MALT lymphomas are shown in Figure 1.

Histological analysis of gastric MALT lymphoma

Histological examination of the biopsy specimens is essential for a definitive diagnosis. Lymphoepithelial lesions are characteristic features of gastric MALT lymphoma, and the scoring system proposed by Wotherspoon et al. was used for the pathological diagnosis of the latter (Table 1) [14]. Gastric MALT lymphoma can be diagnosed if the histopathological changes correspond to a score of 5. If the score is 3 or 4, the diagnosis is confirmed based on the monoclonality of B cells using polymerase chain reaction [15]. However, these findings can be observed with inflammatory changes in the gastric mucosa; for an accurate diagnosis, evaluation by an expert pathologist is necessary [16]. Therefore, if gastric MALT lymphoma is endoscopically suspected, repeated biopsy and discussion with a pathologist should be performed, even if the histological results do not indicate MALT lymphoma in the initial examination. In some cases, endoscopic mucosal resection can be performed for a definite diagnosis that cannot be diagnosed using repeated forceps biopsy [17].

Staging workup of gastric MALT lymphoma

Gastric MALT lymphoma is often unaccompanied by symptoms and is limited to the primary lesion for a long period even after diagnosis. Furthermore, a long time is required before an improvement can be observed after *H. pylori*

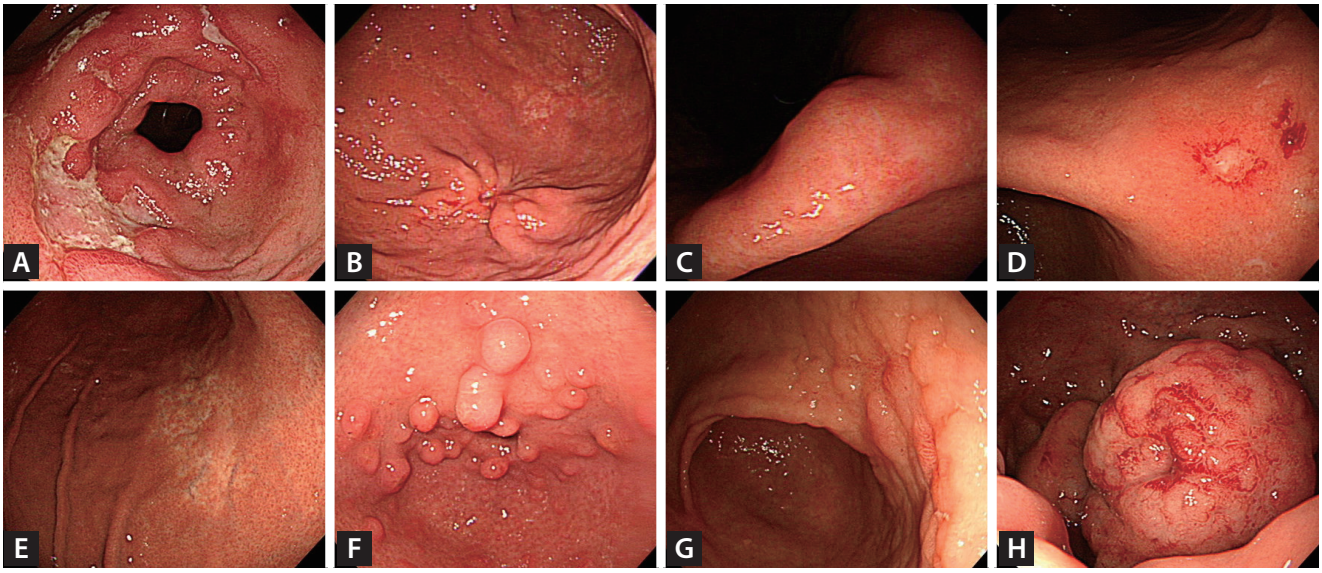

Figure 1. Various endoscopic findings of gastric mucosa-associated lymphoid tissue lymphoma. (A) Ulcer-infiltrative type. (B) Early gastric cancer IIc type. (C) Subepithelial tumor type. (D) Multiple erosion type. (E) Scar type. (F) Polyp type. (G) Cobble stone type. (H) Mass type.

Table 1. Wotherspoon histologic scoring system for gastric MALT lymphoma

Score	Diagnosis	Histological features
0	Normal	Scattered plasma cells in the lamina propria No lymphoid follicles
1	Chronic active gastritis	Small clusters of lymphocytes in the lamina propria No lymphoid follicle No lymphoepithelial lesions
2	Chronic active gastritis with florid lymphoid follicle formation	Prominent lymphoid follicles with surrounding mantle zone and plasma cells No lymphoepithelial lesions
3	Suspicious lymphoid infiltrate, probably reactive	Lymphoid follicles surrounded by small lymphocytes that diffusely infiltrate in the lamina propria and occasionally into the epithelium
4	Suspicious lymphoid infiltrate, probably lymphoma	Lymphoid follicles surrounded by marginal zone cells that diffusely infiltrate in the lamina propria and into the epithelium in small groups
5	Gastric MALT lymphoma	Presence of dense infiltrate of marginal zone cells in the lamina propria with prominent lymphoepithelial lesions

MALT, mucosa-associated lymphoid tissue.

eradication therapy; therefore, neglecting the test for staging is easy. However, approximately 10%–25% of MALT lymphomas are diagnosed at advanced stages [18,19]. Therefore, it is imperative to evaluate the extent of disease to determine the appropriate treatment method. For the staging workup of gastric MALT lymphoma, other diagnostic modalities such as abdominal and pelvic computed tomography (CT), chest CT, and endoscopic ultrasound (EUS) are recommended in addition to endoscopic examination, histological confirmation, and *H. pylori* evaluation [16,20]. EUS can be used to assess the depth of tumor infiltration into the gastric wall and evaluate regional lymph node involvement. This modality provides valuable information for accurate staging and can guide the development of appropriate treatment strategies. Among the various staging systems for gastric MALT lymphoma, the Lugano system is mainly used in clinical settings (Table 2) [16]. For further workup, positron emission tomography (PET), bone marrow biopsy, or t(11;18) translocation examination can be performed in selected cases. Gastric MALT lymphoma typically presents as a small, slowly progressing primary lesion, which limits the utility of PET. Therefore, routine PET scanning is

https://doi.org/10.3904/kjim.2024.143

Table 2. Various staging systems of gastric MALT lymphoma

Lugano staging system	Extent of lymphoma	Ann arbor system with musshoff modification
Stage I: Lymphoma confined to the gastrointestinal tract	Mucosa, submucosa Muscularis propria, subserosa/serosa penetration	Stage IE: Lymphoma restricted to the gastrointestinal tract IE1: Mucosa, submucosa IE2: Beyond the submucosa
Stage II: Lymphoma extending into the abdomen II1: Local nodal involvement II2: Distant nodal involvement	Regional lymph nodes Intraabdominal distant lymph node invasion of neighboring organ	Stage IIE: Lymphoma-infiltrating lymph nodes on the same side of the diaphragm IIE1: Regional lymph node involvement IIE2: Distant lymph node involvement
Stage IV: Disseminated extranodal involvement or a gastrointestinal tract lesion with supradiaphragmatic nodal	Extraabdominal lymph nodes Diffuse/disseminated spread; bone marrow involvement	Stage III: Lymphoma involving both sides of the diaphragm Stage IV: Disseminated disease

MALT, mucosa-associated lymphoid tissue.

not recommended for all patients with gastric MALT lymphoma and can be considered when assessing the extent of the disease, particularly when local treatments such as radiotherapy are planned [21]. The frequency of bone marrow involvement in gastric MALT lymphoma is relatively low. Although bone marrow involvement is classified as a stage IV disease according to the clinical staging system, its impact on the clinical course remains unclear. Therefore, there is an ongoing debate regarding the necessity of routine bone marrow examination in all patients, and can be considered in those with advanced-stage disease or those who do not respond to *H. pylori* eradication therapy [21]. Genetic alterations are observed in a subset of gastric MALT lymphomas, and the presence of the t(11;18)(q21;q21) translocation is associated with more advanced disease stages and poor response to *H. pylori* eradication. Although testing for genetic alterations can help predict treatment response and prognosis, its utility is limited; therefore, routine testing is not recommended for all patients [21].

TREATMENT AND PROGNOSIS OF GASTRIC MALT LYMPHOMA

The most important aspect of the treatment of gastric MALT lymphoma is the determination of the presence or absence of *H. pylori* infection. If the histological or rapid urease test results are negative, a urea breath test or serum antibody test should be conducted to identify false-negative infections [22]. In Lugano clinical stage I or II1 gastric MALT lymphoma, *H. pylori* eradication therapy is considered the first-line treatment, regardless of the presence of *H. pylori* infection.

In *H. pylori*-positive gastric MALT lymphoma, the complete remission rate is reported to be 60%–100% [23,24]. A recent Korean multicenter study reported that the 10-year survival rate of 1,163 patients with gastric MALT lymphoma was 99.1%, particularly in patients with low-stage and those with positive *H. pylori* infections [2]. In general, endoscopic and histological remission is achieved at an average of 3–6 months after eradication therapy; however, remission is often achieved even after 1 or 2 years; therefore, complete remission after treatment should be carefully decided [24,25]. In cases of failed *H. pylori* eradication therapy or even successful eradication but incomplete remission, additional treatments, such as radiotherapy or chemotherapy, can be considered.

In high-grade gastric MALT lymphoma, chemotherapy can be considered; however, the evidence for this remains unclear. Therefore, the "watch-and-wait" strategy or radiotherapy is mainly performed as additional treatments for gastric MALT lymphoma that does not respond to *H. pylori* eradication therapy [16,26]. The entire stomach and perigastric area are irradiated with a total of 30.6 Gy during 17 treatments, with a treatment success rate of 88%–100% and a 5-year progression-free survival rate of 90%–100% [27-29]. Acute side effects associated with radiotherapy include nausea, vomiting, and loss of appetite; however, most symptoms are mild and can be controlled with conservative treatment [28].

Although the mechanism of *H. pylori*-negative gastric MALT lymphoma remains unclear, some hypotheses such as the infection of *Helicobacter* strains, including *Helicobacter heilmannii*, the existence of t(11;18)(q21;q21) gene mutation, or autoimmune mechanism are being proposed [8,30]. The clinical symptoms of *H. pylori*-negative gastric MALT lymphoma are similar to those of *H. pylori*-positive MALT lymphoma, with indigestion and epigastric pain being the most common symptoms. Diagnostic evaluation and staging workup through endoscopic examination and biopsy should be performed similar to that in *H. pylori*-positive gastric MALT lymphoma; however, at least two diagnostic tests for *H. pylori* are recommended to exclude false-negative *H. pylori* infections [31].

The treatment success rate of *H. pylori* eradication therapy in *H. pylori*-negative gastric MALT lymphoma is 0%–83%; however, the treatment success rate is low when multiple lesions are found, tumor invasion is deeper than the submucosal layer, lymph node involvement is positive, and gene mutation of t(11;18)(q21;q21) is observed [31-33]. If there is no response to *H. pylori* eradication therapy, chemotherapy or radiotherapy can be considered as an additional treatment [34,35]. A Korean study reported that 57.1% of patients with *H. pylori*-negative gastric MALT lymphoma showed complete remission only after *H. pylori* eradication; this can be explained as the possibility of hidden *H. pylori* infection which was not properly diagnosed or other *Helicobacter* spp. that can induce gastric MALT lymphoma being removed by eradication therapy [25].

CONCLUSIONS

Gastric MALT lymphoma represents a unique model of malignancy in which chronic *H. pylori* infection plays a pivotal role in pathogenesis. Therefore, successful *H. pylori* eradication therapy alone can lead to a complete remission in many cases.

Endoscopic examination and biopsy are important for diagnosing gastric MALT lymphoma. However, the symptoms are nonspecific and the endoscopic findings are diverse; thus, careful endoscopic examination and sufficient biopsies are necessary for an accurate diagnosis. Gastric MALT lymphoma is closely associated with *H. pylori* infection in most cases, and remission can only be achieved with *H. pylori* eradication therapy. Radiotherapy for gastric invasion may be an effective treatment method for patients who fail to respond to *H. pylori* eradication therapy. Even after successful treatment, remission can take a long time; thus, follow-up examinations with endoscopy and biopsy should be considered.

REFERENCES

1. Zucca E, Bertoni F. The spectrum of MALT lymphoma at different sites: biological and therapeutic relevance. Blood 2016;127:2082-2092.
2. Kim JS, Park JC, Lee JY, et al. Long-term clinical outcomes of gastric MALT lymphoma: a nationwide multicenter study in Korea. Front Oncol 2021;11:681689.
3. Wotherspoon AC, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. Lancet 1991;338:1175-1176.
4. Parsonnet J, Hansen S, Rodriguez L, et al. *Helicobacter pylori* infection and gastric lymphoma. N Engl J Med 1994;330:1267-1271.
5. Liu H, Ruskon-Fourmestraux A, Lavergne-Slove A, et al. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to *Helicobacter pylori* eradication therapy. Lancet 2001;357:39-40.
6. Moyat M, Velin D. Immune responses to *Helicobacter pylori* infection. World J Gastroenterol 2014;20:5583-5593.
7. Denic M, Touati E, De Reuse H. Review: pathogenesis of *Helicobacter pylori* infection. Helicobacter 2020;25 Suppl 1:e12736.
8. Zullo A, Hassan C, Andriani A, et al. Primary low-grade and high-grade gastric MALT-lymphoma presentation. J Clin Gastroenterol 2010;44:340-344.
9. Taal BG, Boot H, van Heerde P, de Jong D, Hart AA, Burgers JM. Primary non-Hodgkin lymphoma of the stomach: endoscopic pattern and prognosis in low versus high grade malignancy in relation to the MALT concept. Gut 1996;39:556-561.
10. Aoun JP, Moukarbel N, Khoury S. Endoscopic patterns of primary gastric MALT lymphoma. J Med Liban 1998;46:131-135.
11. Urakami Y, Sano T, Begum S, Endo H, Kawamata H, Oki Y. Endoscopic characteristics of low-grade gastric mucosa-associated lymphoid tissue lymphoma after eradication of *Helicobacter pylori*. J Gastroenterol Hepatol 2000;15:1113-1119.
12. Park BS, Lee SH. Endoscopic features aiding the diagnosis of gastric mucosa-associated lymphoid tissue lymphoma. Yeun-

https://doi.org/10.3904/kjim.2024.143

gnam Univ J Med 2019;36:85-91.
13. Choi MK, Kim GH. [Diagnosis and treatment of gastric MALT lymphoma]. Korean J Gastroenterol 2011;57:272-280. Korean.
14. Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of *Helicobacter pylori*. Lancet 1993;342:575-577.
15. Hummel M, Oeschger S, Barth TF, et al. Wotherspoon criteria combined with B cell clonality analysis by advanced polymerase chain reaction technology discriminates covert gastric marginal zone lymphoma from chronic gastritis. Gut 2006;55:782-787.
16. Zucca E, Copie-Bergman C, Ricardi U, Thieblemont C, Raderer M, Ladetto M. Gastric marginal zone lymphoma of MALT type: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24 Suppl 6:vi144-vi148.
17. Suekane H, Iida M, Kuwano Y, et al. Diagnosis of primary early gastric lymphoma. Usefulness of endoscopic mucosal resection for histologic evaluation. Cancer 1993;71:1207-1213.
18. Raderer M, Wöhrer S, Streubel B, et al. Assessment of disease dissemination in gastric compared with extragastric mucosa-associated lymphoid tissue lymphoma using extensive staging: a single-center experience. J Clin Oncol 2006;24:3136-3141.
19. Thieblemont C, Berger F, Dumontet C, et al. Mucosa-associated lymphoid tissue lymphoma is a disseminated disease in one third of 158 patients analyzed. Blood 2000;95:802-806.
20. Ruskoné-Fourmestraux A, Fischbach W, Aleman BM, et al. EGILS consensus report. Gastric extranodal marginal zone B-cell lymphoma of MALT. Gut 2011;60:747-758.
21. Gong EJ, Choi KD. [Diagnosis and treatment of gastric mucosa-associated lymphoid tissue lymphoma]. Korean J Gastroenterol 2019;74:304-313.
22. Lehours P, Ruskone-Fourmestraux A, Lavergne A, Cantet F, Mégraud F. Which test to use to detect *Helicobacter pylori* infection in patients with low-grade gastric mucosa-associated lymphoid tissue lymphoma? Am J Gastroenterol 2003;98:291-295.
23. Hong SS, Jung HY, Choi KD, et al. A prospective analysis of low-grade gastric malt lymphoma after *Helicobacter pylori* eradication. Helicobacter 2006;11:569-573.
24. Sugizaki K, Tari A, Kitadai Y, et al. Anti-*Helicobacter pylori* therapy in localized gastric mucosa-associated lymphoid tissue lymphoma: a prospective, nationwide, multicenter study in Japan. Helicobacter 2018;23:e12474.
25. Gong EJ, Ahn JY, Jung HY, et al. *Helicobacter pylori* eradication therapy is effective as the initial treatment for patients with H. pylori-negative and disseminated gastric mucosa-associated lymphoid tissue lymphoma. Gut Liver 2016;10:706-713.
26. Aleman BM, Haas RL, van der Maazen RW. Role of radiotherapy in the treatment of lymphomas of the gastrointestinal tract. Best Pract Res Clin Gastroenterol 2010;24:27-34.
27. Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. Hematol Oncol 2005;23:10-17.
28. Akamatsu T, Mochizuki T, Okiyama Y, Matsumoto A, Miyabayashi H, Ota H. Comparison of localized gastric mucosa-associated lymphoid tissue (MALT) lymphoma with and without *Helicobacter pylori* infection. Helicobacter 2006;11:86-95.
29. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003;21:4157-4164.
30. Fox JG. The non-*H pylori* helicobacters: their expanding role in gastrointestinal and systemic diseases. Gut 2002;50:273-283.
31. Raderer M, Streubel B, Wöhrer S, Häfner M, Chott A. Successful antibiotic treatment of *Helicobacter pylori* negative gastric mucosa associated lymphoid tissue lymphomas. Gut 2006;55:616-618.
32. Ruskoné-Fourmestraux A, Lavergne A, Aegerter PH, et al. Predictive factors for regression of gastric MALT lymphoma after anti-*Helicobacter pylori* treatment. Gut 2001;48:297-303.
33. Choi YJ, Kim N, Paik JH, et al. Characteristics of *Helicobacter pylori*-positive and *Helicobacter pylori*-negative gastric mucosa-associated lymphoid tissue lymphoma and their influence on clinical outcome. Helicobacter 2013;18:197-205.
34. Zullo A, Hassan C, Andriani A, et al. Treatment of low-grade gastric MALT-lymphoma unresponsive to Helicobacter pylori therapy: a pooled-data analysis. Med Oncol 2010;27:291-295.
35. Zucca E, Conconi A, Laszlo D, et al. Addition of rituximab to chlorambucil produces superior event-free survival in the treatment of patients with extranodal marginal-zone B-cell lymphoma: 5-year analysis of the IELSG-19 Randomized Study. J Clin Oncol 2013;31:565-572.

Received : April 27, 2024
Revised : April 26, 2025
Accepted : October 18, 2025

Correspondence to
Ji Yong Ahn, M.D., Ph.D.
Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul

05505, Korea
Tel: +82-2-3010-5667, Fax: +82-2-476-0824
E-mail: ji110@hanmail.net
https://orcid.org/0000-0002-0030-3744

Conflicts of interest
The author discloses no conflicts.

Funding
None

https://doi.org/10.3904/kjim.2024.143