

Limited Role of Bone Marrow Aspiration and Biopsy in the Initial Staging Work-up of Gastric Mucosa-Associated Lymphoid Tissue Lymphoma in Korea

Byung-Hoon Min, Jun Young Park, Eun Ran Kim, Yang Won Min, Jun Haeng Lee, Poong-Lyul Rhee, Jong Chul Rhee, and Jae J. Kim

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

See editorial on page 577.

Background/Aims: The aim of this study was to investigate the frequency of disseminated gastric mucosa-associated lymphoid tissue (MALT) lymphoma and the role of bone marrow study in the initial staging work-up. **Methods:** A total of 194 patients with gastric MALT lymphoma was enrolled. The incidence of disseminated disease was evaluated in the initial staging work-up. The demographic data and tumor characteristics were compared according to *Helicobacter pylori* infection status. **Results:** Localized disease of Lugano stage I accounted for 97.4% of the enrolled cases. Abdominal computed tomography revealed abdominal lymph node metastasis in five patients (2.6%). Bone marrow (BM) involvement was found in only one patient without *H. pylori* infection (0.5%). No patient showed positive findings on chest computed tomography or positron emission tomography. *H. pylori*-negative cases showed a significantly higher frequency of advanced-stage disease than *H. pylori*-positive cases (10.0% vs 0.6%). In patients achieving complete remission, no extragastric recurrence occurred during follow-up. **Conclusions:** The incidence of disseminated disease, including BM involvement, was very low in Korean gastric MALT lymphoma patients. It might be beneficial to perform BM aspiration and biopsy as a part of staging work-up only in patients with risk factors for advanced-stage disease such as *H. pylori* negativity. (**Gut Liver 2014;8:637-642**)

Key Words: Lymphoma, B-cell, marginal zone; Stomach; Bone marrow; Staging

INTRODUCTION

Mucosa-associated lymphoid tissue (MALT) lymphomas represent about 7% of all non-Hodgkin's lymphoma.¹ The stomach is by far the most common site of MALT lymphoma, accounting for 70% of total cases.²

Gastric MALT lymphoma behaves as an indolent disease and has a favorable long-term prognosis with a 10-year survival of over 90%.² Most cases remain localized within the stomach for many years. Despite the favorable prognosis, this disease has a limited tendency for distant spread to other organs, such as lung or bone marrow. To date, there have been few reports assessing the frequency of disseminated disease in gastric MALT lymphoma patients.³ In Austrian study that evaluated 61 cases of gastric MALT lymphoma, bone marrow involvement was found in 4.9% of cases.³ Interestingly, previous studies consistently reported that the survival of gastric MALT lymphoma patients was not adversely influenced by the dissemination of the disease, such as bone marrow involvement.^{3,4} Given the probably limited influence on survival and low incidence of bone marrow involvement, the clinical value of routine bone marrow aspiration and biopsy in initial staging work-up may be limited. Therefore, it remains controversial whether bone marrow aspiration and biopsy should be included in the staging work-up of gastric MALT lymphoma.^{1,5} The European Society for Medical Oncology guidelines recommend inclusion of bone marrow aspiration and biopsy as an initial staging work-up of gastric MALT lymphoma.¹ In the recent European Gastro-Intestinal Lymphoma Study (EGILS) consensus report, however, bone marrow aspiration and biopsy is not recommended as a routine procedure in initial staging work-up. Instead, bone marrow aspiration and biopsy is recommended only when no gastric MALT lymphoma regression is seen after an adequate interval

Correspondence to: Jae J. Kim

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3409, Fax: +82-2-3410-6983, E-mail: jikim@skku.edu

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Byung-Hoon Min and Jun Young Park contributed equally to this work.

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following *Helicobacter pylori* eradication.⁵ Since bone marrow biopsy is an invasive procedure and can cause complications, such as pain or bleeding, it might be beneficial to define the patient group at high risk for bone marrow dissemination and make a limited recommendation for selected patients with a high risk of involvement.

In Korea and Japan, the screening endoscopy for gastric cancer is actively performed and consequently gastric MALT lymphomas seem to be diagnosed in early stage in the majority of case. Therefore, the incidence of disseminated gastric MALT lymphoma in Korea and Japan may be lower than that reported in Western countries. To date, however, few efforts have been made to evaluate the frequency of disseminated gastric MALT lymphoma in Far Eastern countries including Korea and Japan.

The aim of this study was to evaluate the incidence of disseminated disease in Korean gastric MALT lymphoma patients and to investigate the role of bone marrow aspiration and biopsy in the initial staging work-up of gastric MALT lymphoma.

MATERIALS AND METHODS

1. Patients

Hospital database was searched for gastric MALT lymphoma diagnosed in Samsung Medical Center from January 2000 to December 2010. A total of 232 consecutive patients with gastric MALT lymphoma was identified. Histopathologic diagnosis of gastric MALT lymphoma was made according to World Health Organization classification.⁶ Patients were excluded from the study subjects if 1) they underwent treatment for gastric MALT lymphoma before visiting our hospital; 2) they had another malignancy at the time of diagnosis; or 3) the follow-up period was shorter than 12 months. After exclusion, a total of 194 patients was finally included in this study. Initial staging procedures included physical examination including Waldeyer ring, complete blood counts, basic biochemical studies, esophagogastroduodenoscopy (EGD), chest radiograph, computed tomography (CT) of abdomen and pelvis, and bilateral bone marrow aspirate and biopsy. In addition, 67 patients (34.5%) underwent chest CT and 54 (27.8%) underwent endoscopic ultrasonography (EUS). ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography (PET) was performed in 42 patients (21.6%). The diagnosis of abdominal or mediastinal lymph node (LN) involvement and distant metastasis was made based on imaging studies or histological confirmation, if necessary. The results of initial staging work-up and follow-up examinations were retrospectively reviewed. The *H. pylori* status was determined by histology, rapid urease test, ¹³C-urea breath test, and/or serology. *H. pylori* infection was judged to be positive if one or more of the tests showed a positive result and to be negative when all tests were negative. The clinical stage was determined based on the Lugano staging system, a modification of the Ann Arbor classification.⁷ The study protocol was approved by the Institutional

Review Board at Samsung Medical Center.

2. Treatment

Patients with localized gastric MALT lymphoma (Lugano stage I) associated with *H. pylori* infection underwent *H. pylori* eradication therapy using a combination of proton pump inhibitor and antibiotics for 1 to 2 weeks. *H. pylori* eradication therapy was performed for 153 patients with *H. pylori* infection and nine patients without *H. pylori* infection. Other treatment modalities, such as radiotherapy, chemotherapy, or surgery, were used for treatment if 1) the patient had advanced stage disease of Lugano stage II or IV; 2) the patient showed no evidence of *H. pylori* infection in initial work-up; 3) *H. pylori* eradication was not achieved even after third-line eradication treatment; or 4) complete remission (CR) was not achieved within 1 year after successful *H. pylori* eradication.

3. Follow-up after treatment

After *H. pylori* eradication or other nonsurgical treatments, biopsy specimens were assessed using the Groupe d'Etude des Lymphomes de l'Adult (GELA) histological grading system.^{5,8} In this study, CR was defined if two consecutive posttreatment biopsy specimens showed complete histological response or probable minimal residual disease by the GELA grading system. For patients with advanced stage disease (Lugano stage II or IV), no visible lesion on imaging studies was also required for a diagnosis of CR.

All patients undergoing *H. pylori* eradication or other nonsurgical treatments were followed up by EGD with multiple biopsies every 3 to 6 months until CR and every 6 to 12 months thereafter. For patients with advanced stage disease (Lugano stage II or IV), follow-up imaging studies including abdominal CT were also performed.

RESULTS

1. Patient characteristics and results of staging work-up

Table 1 summarizes the baseline characteristics of the 194 enrolled patients. Localized disease with Lugano stage I accounted for 97.4% of cases. Abdomen-pelvis CT revealed abdominal LN metastasis in five (2.6%) patients. There was no evidence of metastasis to abdominal organs, such as spleen. Table 2 shows details of work-up and follow-up results of the five patients with abdominal LN involvement. Four patients (80%, 4/5) with advanced stage disease were *H. pylori*-negative.

In bilateral bone marrow aspirate and biopsy, only one patient (0.5%, 1/194) showed tumor cell infiltration into the bone marrow. The tumor volume in bone marrow biopsy specimens was 5% and 10% in left- and right-side biopsies, respectively. This patient did not show cytopenia or evidence of *H. pylori* infection at the time of bone marrow biopsy. However, abdomen-pelvis CT demonstrated massive abdominal LN involvement

Table 1. Baseline Patient Characteristics (n=194)

Characteristic	Value
Age, yr	53.3±11.4
Median (range)	53 (30–78)
Gender	
Male	88 (45.4)
Female	106 (54.6)
<i>H. pylori</i> infection	
Absent	40 (20.6)
Present	154 (79.4)
Abdomen-pelvis CT	
Localized in stomach	189 (97.4)
Abdominal LN involvement	5 (2.6)
Metastasis to organ in abdomen	0
Bone marrow involvement	
Absent	193 (99.5)
Present	1 (0.5)
Chest CT (n=67)	
No involvement	67 (100.0)
Mediastinal LN involvement	0
Metastasis to lung	0
Tumor depth by EUS (n=54)	
Mucosa or submucosa	50 (92.6)
Proper muscle, subserosa, serosa	4 (7.4)
PET (n=42)	
No specific findings	42 (100.0)
Findings suggesting metastasis	0
Stage by Lugano system	
I	189 (97.4)
II	4 (2.1)
IV	1 (0.5)
Initial treatment	
<i>H. pylori</i> eradication	162 (83.5)
Radiotherapy	22 (11.3)
Chemotherapy	8 (4.1)
Resection	2 (1.0)

Data are presented as mean±SD or number (%).

H. pylori, *Helicobacter pylori*; CT, computed tomography; LN, lymph node; EUS, endoscopic ultrasonography; PET, positron emission tomography.

encasing major vascular structures (case 5 in Table 2 and Fig. 1).

None of the patients showed positive findings in either chest CT or PET scan. Among five patients with abdominal LN involvement, three patients underwent chest CT and one patient underwent PET (Table 2).

The majority of patients (83.5%) underwent *H. pylori* eradication. Radiotherapy and chemotherapy were performed in 11.3% and 4.1% of patients, respectively.

Fifty-four patients received EUS examination. Among them, only 7.4% of patients showed involvement of MALT lymphoma beyond the submucosa layer.

When compared with *H. pylori*-positive cases, *H. pylori*-negative gastric MALT lymphoma showed a significantly higher frequency of advanced stage disease and tumor invasion beyond the submucosa layer (Table 3).

2. Outcomes after treatment and pattern of recurrence

Fig. 2 shows the 1-year treatment outcomes according to the initial treatment modalities in 189 patients with Lugano stage I disease. Table 2 summarizes the 1-year treatment outcomes in 5 patients with Lugano stage II or IV disease.

Table 4 shows follow-up results of 153 *H. pylori*-positive patients who underwent *H. pylori* eradication therapy as the initial main treatment. All patients had localized disease with Lugano stage I. At the 12-month follow-up examination, CR was achieved in 88.2% (135/153) of cases. During a median 45 months of follow-up, recurrence after CR occurred in three cases (3/135, 2.2%), all of which showed intragastric recurrence. No extragastric recurrence was found during the follow-up period.

A total of 22 patients received radiotherapy as the initial main treatment. All of these patients were *H. pylori*-negative and had localized disease with Lugano stage I. At the 12-month follow-up examination, the CR rate was 95.5%. During a median 40 months of follow-up, no recurrence occurred after achieving CR.

Chemotherapy was initially administered in eight patients, including five with Lugano stage II or IV disease (Table 2). CR was achieved 12 months after treatment in 50.0% of cases. During a median 71 months of follow-up, no recurrence occurred after achieving CR.

DISCUSSION

The initial staging work-up of lymphoma usually includes the examination for the disseminated disease, such as bone marrow aspiration and biopsy, as patients' prognoses and the selection of treatment modality are affected by the presence of disseminated disease. However, previous studies consistently reported that the presence of disseminated disease had a limited influence on the survival of patients with gastric MALT lymphoma.^{3,4} In addition, the incidence of disseminated disease is low in gastric MALT lymphoma. In a Western study, the frequency of bone marrow involvement was 4.9%.³ In the same study, the incidence of lung metastasis and mediastinal LN involvement was 6.6%.^{3,9} The present study showed an even lower incidence; only one case of bone marrow involvement (0.5%) and no cases of lung or mediastinal LN metastasis (0%) were observed in initial staging work-up. After achieving CR, no extragastric recurrence occurred during follow-up. Considering these factors, Raderer *et al.*³ argued against the necessity for routine bone

Table 2. Details of Patients Whose Abdominal Computed Tomography Scans Showed Abdominal Lymph Node Enlargement Consistent with Metastasis

Case	Sex	Age, yr	Symptom	<i>H. pylori</i> infection	Abdomen-pelvis CT	BM involvement	Chest CT	Tumor depth by EUS	PET	Stage	Initial treatment	12-mo outcome
1	F	40	Weight loss	Negative	LN (+)	No	Not done	Not done	Not done	II	Chemotherapy	Non-CR
2	M	39	Vomiting	Positive	LN (+)	No	Not done	Not done	Not done	II	Chemotherapy	Non-CR
3	F	73	Nausea	Negative	LN (+)	No	Negative	Not done	Negative	II	Chemotherapy	CR
4	M	64	Epigastric pain	Negative	LN (+)	No	Negative	Proper muscle	Not done	II	Chemotherapy	CR
5	M	51	Distension	Negative	LN (+)	Yes	Negative	Not done	Not done	IV	Chemotherapy	Non-CR

H. pylori, *Helicobacter pylori*; CT, computed tomography; BM, bone marrow; EUS, endoscopic ultrasonography; PET, positron emission tomography; F, female; LN, lymph node; CR, complete response; M, male.

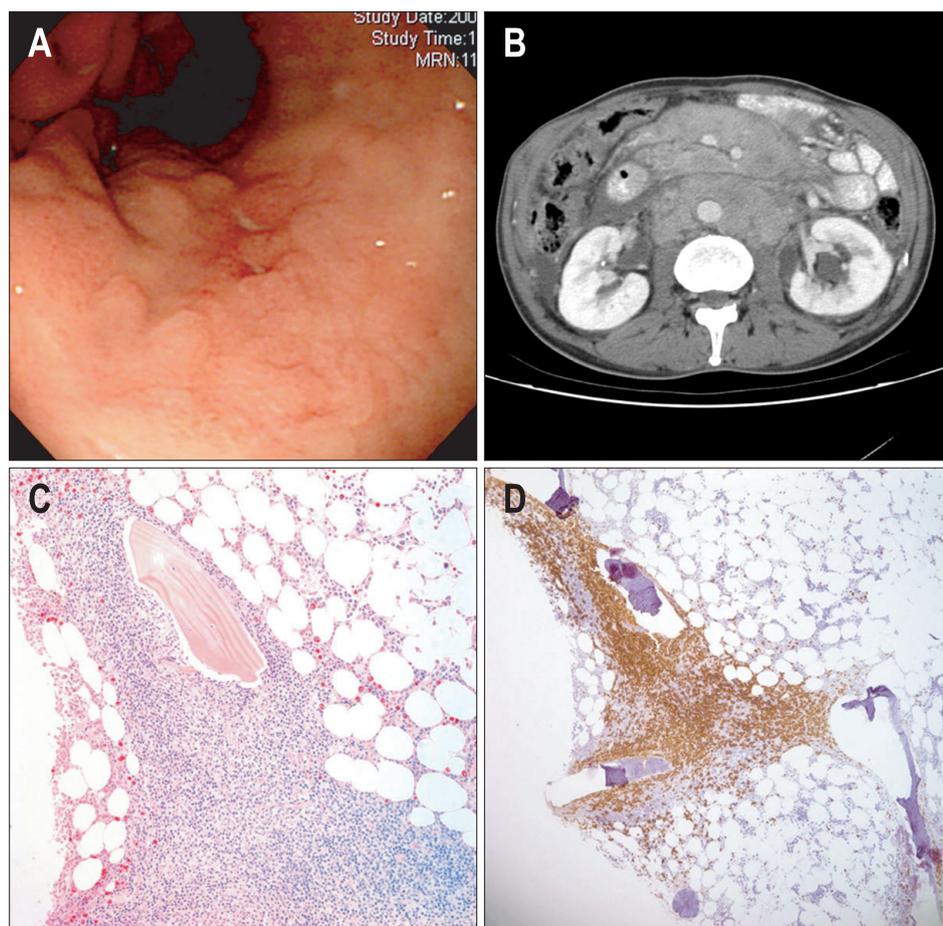


Fig. 1. Results of staging work-up in a patient with bone marrow involvement. (A) White light endoscopy image showing nodular mucosal changes and ulcers at the lesser curvature side of the gastric body. (B) Abdominal computed tomography image showing massive lymph node enlargement encasing the aorta, renal vessels, and mesenteric vessels. (C) Pathological findings showing paratrabecular infiltration of lymphoma cells into the bone marrow (H&E stain, $\times 200$). (D) Immunohistochemical staining of bone marrow with CD20.

marrow biopsy in patients with gastric MALT lymphoma and recommended the individually targeted staging. In the recent EGILS consensus report, bone marrow aspiration and biopsy are not recommended as routine procedures in initial staging work-up of gastric MALT lymphoma.⁵

In the present study, localized disease (Lugano stage I) accounted for 97.4% of total cases. Among 54 patients who underwent EUS, tumor depth was limited to the mucosa or submucosa layer in 92.6% of cases. This proportion of localized disease is higher than that reported in Western studies, which ranged from 70% to 75%.^{3,10} However, a recent large Japanese study by

Nakamura *et al.*¹¹ showed comparable results to ours. In their study, 90% of patients had stage I disease and 90% of patients undergoing EUS showed that tumor depth was confined to the mucosa or submucosa layer. This difference between studies from Far Eastern and Western countries might be largely due to the periodic screening endoscopy actively performed in Korea and Japan for the early detection of gastric cancer. Screening endoscopy may result in the detection of gastric MALT lymphoma in early stages and consequently a lower rate of disseminated disease in Far Eastern countries compared to Western countries. Therefore, the value of extensive staging work-up,

such as bone marrow biopsy and chest CT, may be more limited in Far Eastern countries than in Western countries.

In addition to above mentioned low incidence of disseminated disease, bone marrow aspiration and biopsy is an invasive procedure and chest CT has several disadvantages, such as cost, radiation exposure, and a high rate of indeterminate lesions. Therefore, it might be beneficial to define the patient group at high risk for disseminated disease and selectively perform bone marrow biopsy and chest CT only in patients with a high risk of involvement. There are few studies evaluating the risk factors for bone marrow and lung involvement that represents disseminated gastric MALT lymphoma. As the incidence of gastric MALT lymphoma itself is low and that of disseminated disease

with bone marrow or lung involvement is even lower, no studies have identified definite risk factors by multivariate analysis. Indeed, multivariate analysis to identify risk factors could not be done since the present study included only one case with disseminated disease. Several studies have reported that *H. pylori*-negative gastric MALT lymphoma presents as advanced disease more frequently than *H. pylori*-positive disease.^{12,13} The results of our study support this association (Table 3); 80% of cases with advanced stage disease (Lugano stage II or IV) were *H. pylori*-negative, including the one case with bone marrow involvement. This might be explained by the high frequency of t(11;18)(q21;q21) in *H. pylori*-negative gastric MALT lymphoma compared to its *H. pylori*-positive counterpart^{13,14} since the presence of t(11;18)(q21;q21) is known to be a significant risk factor for disease dissemination.³ Therefore, patients with *H. pylori*-negative gastric MALT lymphoma can be reasonable targets for an extensive staging work-up including bone marrow biopsy and chest CT.

There are some limitations in the present study. First, as this

Table 3. Patient Characteristics according to *Helicobacter pylori* Infection Status

Characteristic	<i>H. pylori</i> -positive (n=154)	<i>H. pylori</i> -negative (n=40)	p-value
Age, yr	53.2±11.3	53.8±11.7	0.760
Median (range)	53.0 (30–78)	52.5 (33–74)	
Gender			0.169
Male	66 (42.9)	22 (55.0)	
Female	88 (57.1)	18 (45.0)	
Abdomen-pelvis CT			0.007
Localized in stomach	153 (99.4)	36 (90.0)	
Abdominal LN involvement	1 (0.6)	4 (10.0)	
Bone marrow involvement			0.206
Absent	154 (100.0)	39 (97.5)	
Present	0	1 (2.5)	
Tumor depth by EUS (n=54)			<0.001
Mucosa or submucosa	46 (100.0)	4 (50.0)	
Proper muscle, subserosa, serosa	0	4 (50.0)	
Stage by Lugano system			0.007
I	153 (99.4)	36 (90.0)	
II or IV	1 (0.6)	4 (10.0)	

Data are presented as mean±SD or number (%). CT, computed tomography; LN, lymph node; EUS, endoscopic ultrasonography.

Table 4. Outcomes after *Helicobacter pylori* Eradication in *H. pylori*-Positive Cases (n=153)

Parameter	Value
Stage by Lugano system	
I	153 (100.0)
II or IV	0
Outcomes 12 mo after treatment	
CR	135 (88.2)
Non-CR	18 (11.8)
Duration of total follow-up, mo	45 (12–126)
Recurrence after CR during follow-up	3 (2.2)
Recurrence site	
Stomach	3 (100.0)
Abdominal LN	0
Abdominal organ	0
Bone marrow	0
Mediastinal LN	0
Lung	0

Data are presented as number (%) or median (range). CR, complete remission; LN, lymph node.

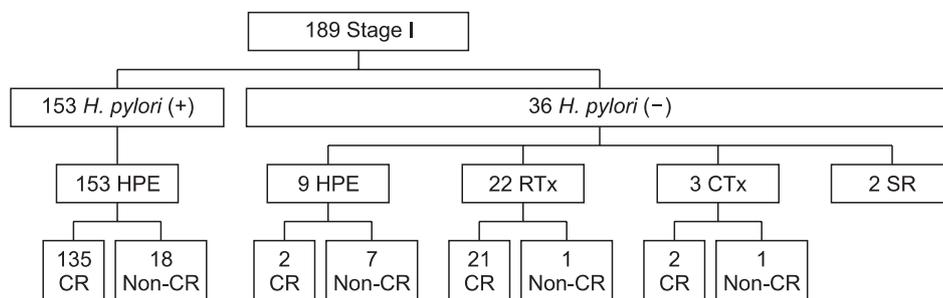


Fig. 2. Flowchart showing the 1-year treatment outcomes according to the initial treatment modality in 189 patients with Lugano stage I disease. HPE, *H. pylori* eradication; RTx, radiotherapy; CTx, chemotherapy; SR, surgical resection; CR, complete remission.

was a retrospective study, there could be a selection bias and treatment modalities were not decided under a standardized protocol. Secondly, the number of cases with advanced stage disease was too small to identify definite risk factors for disseminated disease by multivariate analysis. Thirdly, as chest CT and PET were performed only in 34.5% and 21.6% of enrolled cases, our ability to evaluate the role of these examinations in the initial work-up of gastric MALT lymphoma was limited.

In conclusion, our data indicate that the incidence of disseminated disease including bone marrow involvement was very low in Korean gastric MALT lymphoma patients. Given the probably limited influence on survival and low incidence of bone marrow involvement in Korea, the clinical value of routine bone marrow aspiration and biopsy in initial staging work-up of gastric MALT lymphoma may be limited. Therefore, it might be beneficial to define high-risk conditions for disseminated disease, such as *H. pylori*-negativity or t(11;18)(q21;q21), and selectively perform an extensive staging work-up, such as bone marrow aspiration and biopsy, only in patients with these risk factors. Further large prospective studies are required to identify definite risk factors for disease dissemination and to establish tailored guidelines for initial staging work-up of gastric MALT lymphoma.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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