

## Endoscopic features and prognoses of mantle cell lymphoma with gastrointestinal involvement

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### Abstract

**AIM:** To evaluate the endoscopic manifestations and prognoses of gastrointestinal (GI) mantle cell lymphoma (MCL).

**METHODS:** A database search at the Department of Pathology of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences revealed 57 MCL patients with GI involvement. Clinical records were available for 35 of the 57 patients from 21 institutions, and those 35 patients were enrolled in this study. We summarized the gross types of endoscopic features, event-free survival (EFS), and overall survival (OS) of those patients.

**RESULTS:** Of the 35 patients, GI involvement in the esophagus, stomach, and duodenum was found in 2 (5.7%), 26 (74.3%), and 12 (34.3%) patients, respectively. Twenty-one of the 35 patients underwent colonoscopy; among them, GI involvement in the ileum, cecum, colon, and rectum was found in 10 (47.6%), 3 (14.3%), 12 (57.1%), and 10 (47.6%), respectively. Various lesions, such as superficial, protruded, fold thickening, or ulcerative, were found in the stomach, whereas multiple lymphomatous polyposis (MLP) was dominant from the duodenum to the rectum. Twelve patients were treated with a hyper-CVAD/MA regimen, and they had better OS (3-year rate, 88.3% vs 46.4%,  $P < 0.01$ ) and better EFS (3-year rate, 66.7% vs 33.8%,  $P < 0.05$ ) than the remaining 23 patients who were not treated with this regimen.

**CONCLUSION:** MLP was a representative form of intestinal involvement, whereas a variety of lesions were found in the stomach. The hyper-CVAD/MA regimen may improve survival in these patients.

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**Key words:** Chemotherapy; Gastrointestinal lymphoma; Mantle cell lymphoma; Multiple lymphomatous polyposis; Non-Hodgkin's lymphoma

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## INTRODUCTION

Mantle cell lymphoma (MCL) is a small B-cell neoplasm that may affect the gastrointestinal (GI) tract<sup>[1]</sup>. In 1961, Cornes<sup>[2]</sup> reviewed 22 case reports of multiple lymphomatous polyposis (MLP), and introduced that term as a unique form of malignant GI lymphoma. Two decades later, studies revealed that the neoplastic cells of MLP originate from the mantle zone of the lymphoid follicle in most cases, hence these days MLP is a representative intestinal manifestation of MCL<sup>[3]</sup>. On the other hand, the gastric lesions of MCL vary from pale folds<sup>[2,4]</sup> to nodules and inflammation<sup>[5,6]</sup>. Previously, the frequency of GI involvement was reported to be up to 30%<sup>[7,8]</sup>. However, recent reports based on endoscopic examinations have revealed that 46%-49% of MCL patients had esophagogastrroduodenal involvement, and that 38%-62% had colorectal involvement<sup>[5,6]</sup>. As these previous reports were conducted by hematologists, the endoscopic findings and data on frequency, particularly of the gastric lesions, have not yet been investigated thoroughly.

Importantly, MCL is clinically more aggressive and has a shorter median survival, only 3-5 years, compared with other types of small B-cell neoplasms, such as extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) and follicular lymphoma. However, due to the rarity of MCL (it represents only about 3%-10% of non-Hodgkin lymphomas)<sup>[1]</sup>, the prognoses of cases with GI MCL have not been discussed sufficiently.

In this report, we identified 35 MCL patients with GI involvement from 21 institutions and summarized their endoscopic manifestations, chemotherapy regimens, and prognoses.

## MATERIALS AND METHODS

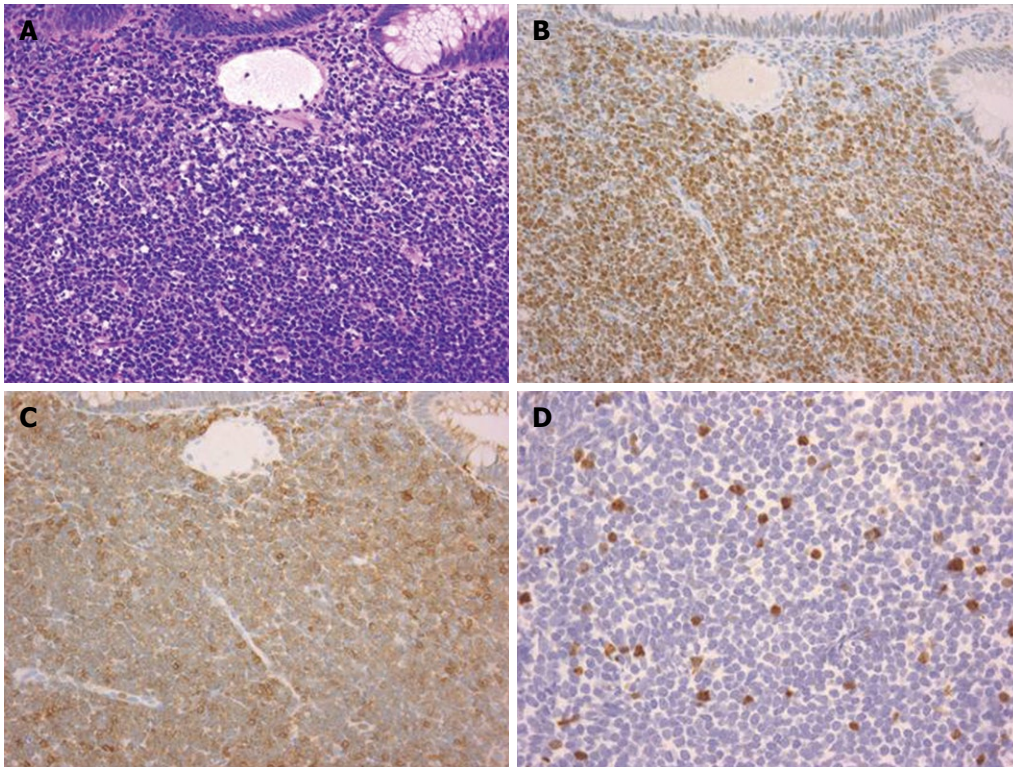
A database search at the Department of Pathology of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences found 57 patients who were histologically diagnosed as MCL with GI involvement from August 1999 to July 2009. The diagnosis of MCL was made according to the World Health Organization classification<sup>[9]</sup>. Briefly, histological diagnosis was made by morphologic and immunophenotypic analyses on surgically resected specimens or on endoscopically biopsied specimens<sup>[1]</sup>. All cases were blindly reviewed and the diagnosis was confirmed by a single pathologist (Morito T). The typical features of MCL were monomorphic proliferation of small to medium-sized lymphoid cells with a vaguely nodular, diffuse, or mantle zone growth pattern accompanying architectural destruction and the expression of cyclin D1 on immunohistochemical study (Figure 1). CD5 staining was also performed, and its positivity supported the diagnosis of MCL. All samples were also positive for BCL2 protein. Clinical records were available for 35 of the 57 patients from 21 institutions, and those 35 patients were enrolled in this study. Nine of the 35 patients were examined as subjects of our previous study<sup>[10]</sup>. For all patients, the results of endoscopic, radiological, and bio-

logical examinations, as well as clinical information including treatment regimens and prognoses, were retrospectively reviewed from clinical records.

Invaded GI organs were evaluated by esophagogastroduodenoscopy and colonoscopy. Neither capsule endoscopy nor double-balloon/single-balloon enteroscopy was performed to evaluate the jejunum and ileum. The GI tract was subdivided into three parts: the esophagus, the stomach, and the intestines (including the duodenum, ileum, cecum, colon, and rectum). GI lesions in each part were classified into the following six subtypes by gross findings: (1) the protruded type (solitary or fewer than 10 elevated lesions forming tumorous nodules; these lesions often resemble submucosal tumors and sometimes accompany ulcers on their tops); (2) the fold thickening type (thickened mucosal folds like large cerebriform folds; typically seen only in the stomach); (3) the MLP type (multiple micropolyps with or without some large polyps; the number of polyps is 10 or more); (4) the ulcerative type (solitary or multiple lowered lesions due to ulcers); (5) the superficial type (changes in the mucosal color and/or changes in mucosal morphology); and (6) the mixed type (combinations of these five subtypes). All cases were reviewed and their subtypes were classified by at least two board certified endoscopists (Iwamuro M and Okada H).

The Lugano staging system for the classification of GI tract lymphoma<sup>[11,12]</sup> was used to determine the patients' clinical stages. Patients were diagnosed with primary GI MCL based on a set of criteria established by Dawson *et al.*<sup>[13]</sup>. The response evaluation included a physical examination, a complete blood count, serum biochemistry profile, endoscopic examination, bone marrow aspirate and biopsy, chest X-ray, abdominal ultrasound, and computed tomography scans of the neck, chest, and abdomen. A complete response (CR), partial remission, stable disease, and progressive disease were defined according to the International Lymphoma Workshop response criteria<sup>[14]</sup>. Overall survival (OS) was measured from diagnosis until death from any cause, and event-free survival (EFS) was measured from diagnosis until documented progression/relapse, death from any cause, or off-protocol treatment for any reason.

Therapeutic regimens, international prognostic index (IPI)<sup>[15]</sup>, a recently introduced prognostic index for advanced-stage MCL (MCL IPI score: MIPI score)<sup>[16]</sup>, and mitotic rates in the histological specimens were investigated as predictive prognostic factors<sup>[17,18]</sup>. The MIPI score was calculated as follows:  $[0.03535 \times \text{age (years)}] + 0.6978$  (if the Eastern Cooperative Oncology Group performance status<sup>[19]</sup>  $> 1$ )  $+ [1.367 \times \log_{10} (\text{LDH}/\text{upper limits of normal LDH})] + [0.9393 \times \log_{10} (\text{white blood cell count per } 10^6 \text{ L})]$ . Patients were classified as low risk (score  $< 5.7$ ), intermediate risk ( $5.7 \leq \text{score} < 6.2$ ), or high risk (score  $\geq 6.2$ ) according to their MIPI scores, as previously reported<sup>[16]</sup>. To estimate the mitotic rate, Ki-67 staining was performed. Positivity of 0%-10% was classified as a low mitotic rate, while more than 10% positivity was classified as high. Cox proportional hazards regression analysis was used to ana-



**Figure 1** Histological features of mantle cell lymphoma. A: Rectal biopsied specimen demonstrated monomorphic proliferation of medium-sized lymphoid cells (Hematoxylin and eosin staining). This case illustrated typical immunohistochemical features of mantle cell lymphoma, showing positivity for cyclin D1 and CD5 staining; B: Immunohistochemical staining for cyclin D1; C: Immunohistochemical staining for CD5; D: Approximately 5% of neoplastic cells were positive for Ki-67 staining; consequently, this case was classified as a low mitotic rate. A-C: Original magnification,  $\times 200$ ; D:  $\times 400$ .

lyze the prognostic factors. Factors exhibiting significant values in the univariate analysis were further analyzed by multivariate analysis. Kaplan-Meier curves were generated for OS and EFS. We compared the curves for the two groups with the log-rank test. Statistical analyses were performed by JMP 8.0.1 software (SAS Institute, Cary, NC, USA), and  $P < 0.05$  was considered significant.

## RESULTS

### Clinical features

Thirty-five patients (32 male, 3 female) were enrolled; their characteristics are summarized in Table 1. The median age at diagnosis was 67 years (range: 47-86 years). Twenty-nine of 35 patients (82.9%) were Lugano stage IV, whereas only one patient was stage I with gastric involvement. Only this case fulfilled Dawson's criteria for primary GI MCL<sup>[13]</sup>. Essentially all the patients in this study had GI lesions. Other extranodal sites involved were bone marrow ( $n = 12$ ), spleen ( $n = 5$ ), liver ( $n = 3$ ), kidney ( $n = 3$ ), Waldeyer's ring ( $n = 3$ ), peripheral blood ( $n = 3$ ), skin ( $n = 2$ ), tongue ( $n = 1$ ), and ureter ( $n = 1$ ).

### Endoscopic features

All patients underwent esophagogastroduodenoscopy, and 21 of the 35 patients underwent colonoscopy. Of the 35 patients, GI involvement in the esophagus, stomach, and duodenum was found in 2 (5.7%), 26 (74.3%), and 12 (34.3%) patients, respectively. Among the 21 patients

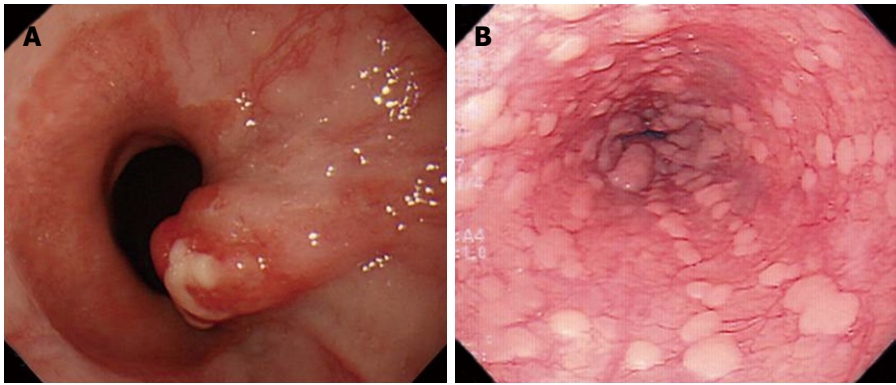
**Table 1** Characteristics of the 35 patients

	<i>n</i> (%)
Male sex	32 (91.4)
Median age (range, yr)	67 (47-86)
Lugano staging system	
Stage I	1
Stage II-1	1
Stage II-2	4
Stage IV	29
Involved site of gastrointestinal tract	
Esophagus	2/35 (5.7)
Stomach	26/35 (74.3)
Duodenum	12/35 (34.3)
Ileum	10/21 (47.6)
Cecum	3/21 (14.3)
Colon	12/21 (57.1)
Rectum	10/21 (47.6)
Mitotic rate (Ki-67 index) ( $n = 19$ )	
Low mitotic rate	9
High mitotic rate	10
MIPI score ( $n = 31$ )	
Average score (range)	6.01 (5.31-6.85)
Low risk	6
Intermediate risk	15
High risk	10

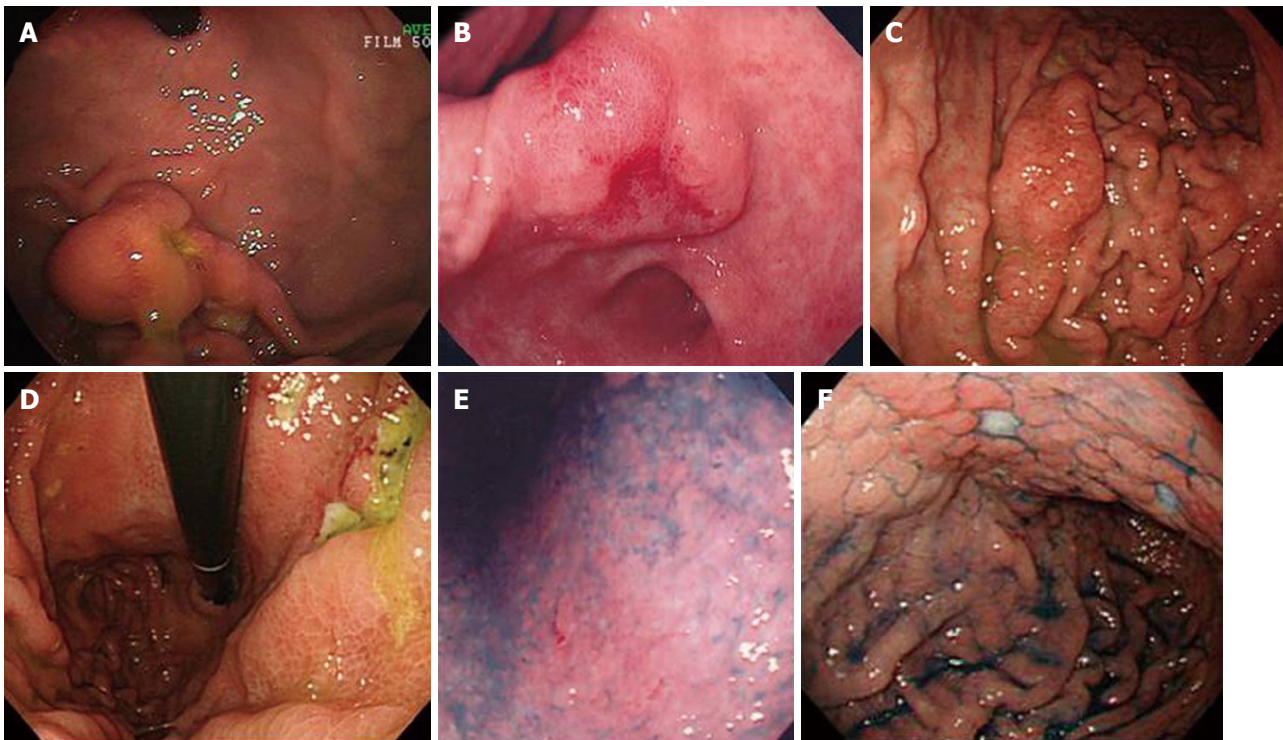
MIPI: Mantle cell lymphoma international prognostic index.

who also received colonoscopy, 10 (47.6%), 3 (14.3%), 12 (57.1%), and 10 (47.6%) patients showed GI involvement in the ileum, cecum, colon, and rectum, respectively





**Figure 2** Esophageal lesions of mantle cell lymphoma. A: A protruded tumor was seen in the esophagogastric junction; B: In another patient, multiple whitish plaques were seen throughout the whole esophagus.



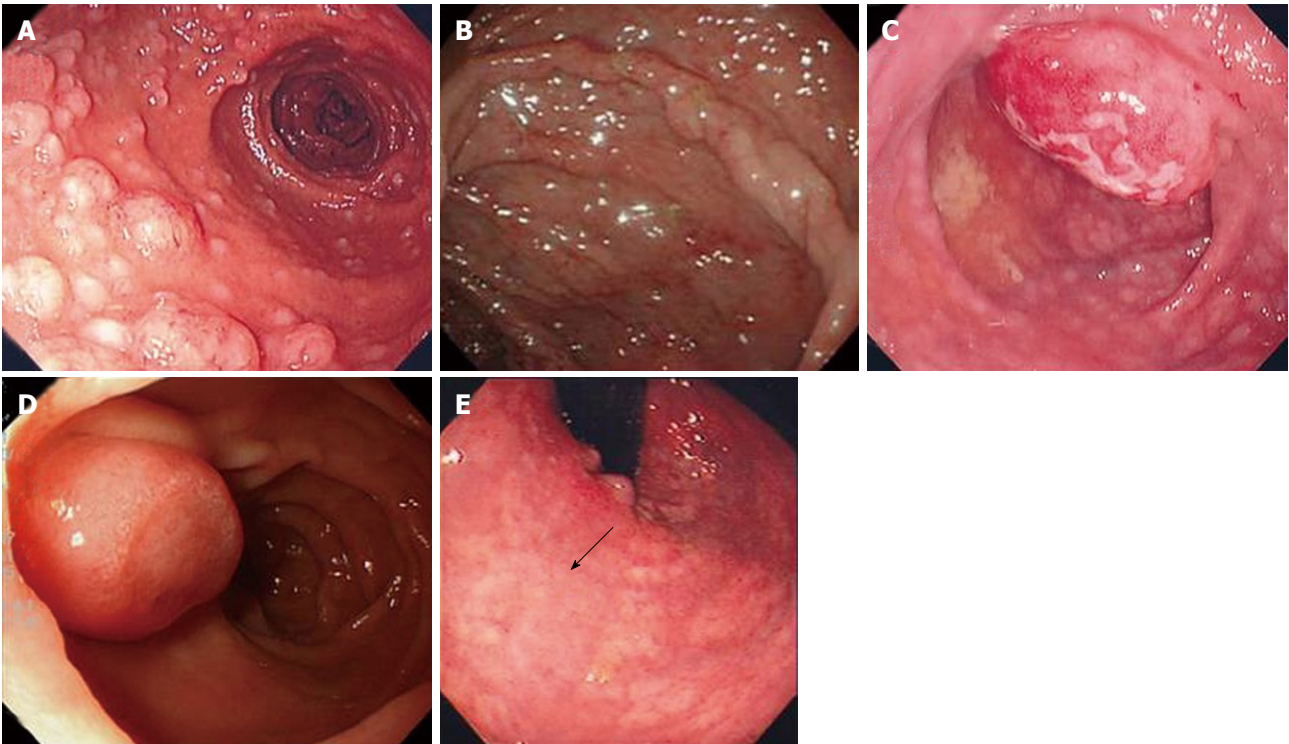
**Figure 3** Gastric lesions of mantle cell lymphoma. A: Protruded type ( $n = 6$ ) often resembled submucosal tumor; B: One patient with a protruded type lesion was diagnosed with stage I primary gastrointestinal mantle cell lymphoma; C: Fold thickening type ( $n = 6$ ); D: Ulcerative type ( $n = 6$ ); E: In one patient, only a change in mucosal color with redness was seen. This case was classified as the superficial type ( $n = 7$ ); F: Among superficial type lesions, cobblestone-like mucosa with a few shallow ulcers was also seen.

Table 2 Gross findings of the gastrointestinal tract			
	Esophagus ( $n = 2$ )	Stomach ( $n = 26$ )	Intestines ( $n = 22$ )
Protruded	1	6	4
Fold thickening	-	6	-
MLP	-	-	17
Ulcerative	-	6	-
Superficial	1	7	1
Mixed	-	1	-

The intestines include the duodenum, ileum, cecum, colon, and rectum. MLP: Multiple lymphomatous polyposis.

(Table 1). Twenty-two patients had at least one site of involvement in the intestines (from duodenum to rectum).

Endoscopic features are summarized in Table 2. Gross findings of the esophageal lesions were the protruded type in one patient and the superficial type in another. The former lesion was a solitary nodule in the esophago-gastric junction, and measured about 7 mm in diameter (Figure 2A). The latter lesion had a unique form showing slightly elevated multiple white plaques resembling glycogenic acanthosis (Figure 2B). The number of these plaques increased 13 mo after the initial endoscopy, and a biopsied specimen revealed infiltration by MCL cells. Gastric lesions varied morphologically: the superficial type was found in 7 cases (26.9%), the protruded type in 6 (23.1%), the fold thickening type in 6 (23.1%), the ulcerative type in 6 (23.1%), and the combined (protruded and ulcerative) type in 1 (3.8%) (Figure 3). In stark contrast to



**Figure 4** Intestinal lesions of mantle cell lymphoma. From the duodenum to the rectum, multiple lymphomatous polyposis (MLP) was dominant ( $n = 17$ ). A, B: Typical features of MLP were diffuse multiple micropolyps; C: Some large tumorous polyps were sometimes found together with micropolyps; D: Protruded type ( $n = 4$ ); E: Superficial type ( $n = 1$ , arrow).

the morphological variety of the gastric lesions, MLP was dominant in the intestines; it was identified in 17 of the 22 cases (77.3%). The remaining patients showed protruded type lesions in 4 (18.2%) and the superficial type in 1 (4.5%) (Figure 4).

### Prognosis and therapeutic regimens

Various regimens were employed for treatment of the 35 patients, because they were treated at 21 different institutions. CHOP-like regimens, which included CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and THP-COP (pirarubicin, cyclophosphamide, vincristine, and prednisone), were used for 16 patients, and rituximab was also administered to 10 of those 16 patients. The hyper-CVAD/MA regimen (fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high doses of methotrexate and cytarabine) was used for 12 patients, and rituximab was added to this regimen in 7 of the 12 patients. In the hyper-CVAD/MA regimen, cycles 1, 3, 5, 7 (Hyper-CVAD) consisted of cyclophosphamide ( $300 \text{ mg/m}^2$ , iv every 12 h for 6 doses) on Days 1-3, doxorubicin ( $16.6 \text{ mg/m}^2$  per day, iv continuous infusion for 72 h) on Days 4-6, vincristine ( $1.4 \text{ mg/m}^2$  iv, maximum 2 mg) on Days 4 and 11, and dexamethasone ( $40 \text{ mg/d}$ , iv or orally) on Days 1-4 and Days 11-14. Cycles 2, 4, 6, 8 (MA) consisted of methotrexate ( $200 \text{ mg/m}^2$ , iv) on Day 1, methotrexate ( $800 \text{ mg/m}^2$ , iv continuous infusion for 22 h) on Day 1, and cytarabine ( $3000 \text{ mg/m}^2$ , reduced to only  $1000 \text{ mg/m}^2$  if age  $> 60$  years or creatinine  $> 1.5 \text{ mg/dL}$ , iv every 12 h for 4 doses) on Days

2-3. Cycles 1 and 2 were alternated every 21 d. After the hyper-CVAD/MA regimen, high-dose chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT) was performed in 8 patients. Allogeneic PBSCT was carried out in one patient for relapse after the hyper-CVAD/MA regimen.

For OS, only the therapeutic regimen (hyper CVAD/MA regimen *vs* other treatment) had a significant impact in the univariate Cox regression analysis (Table 3). For EFS, neither sex, Lugano stage (I and II *vs* III and IV), LDH levels, white blood cell count, bone marrow involvement, Ki-67 positivity, IPI (high risk *vs* other), nor MIPI score showed prognostic relevance in the univariate analysis. In contrast, age and therapeutic regimen (hyper CVAD/MA regimen *vs* other treatment) had a significant impact on EFS (Table 4), whereas in the multiple Cox regression, neither age nor the therapeutic regimen was of prognostic relevance (Table 5).

Survival curves are shown in Figure 5. Median OS had not been reached after a median follow-up of 33.8 mo, and the 3-year OS rate was 61.1%. Median EFS was 15.2 mo, and the 3-year EFS rate was 44.4%. As shown in Figure 5, patients treated with the hyper-CVAD/MA regimen had both markedly longer OS and longer EFS than the group without hyper-CVAD/MA; the 3-year OS rate and 3-year EFS rate of the patients treated with hyper-CVAD/MA were 83.3% and 66.7%, respectively, whereas those of the patients without hyper-CVAD/MA were 46.4% and 33.8%. The differences between the two groups were statistically significant.

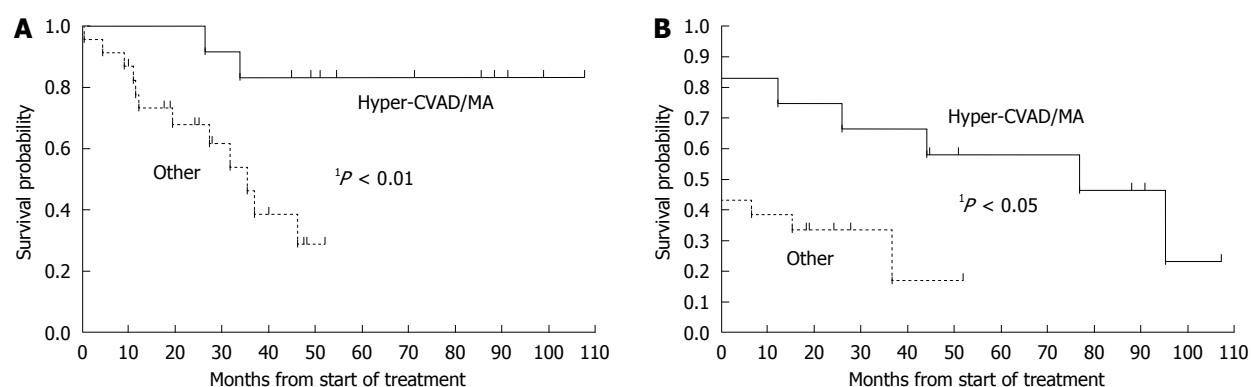


Figure 5 Overall survival (A) and event-free survival (B) according to administration of the hyper-CVAD/MA regimen. <sup>†</sup>Log-rank test.

Table 3 Prognostic relevance of overall survival according to the univariate Cox regression

Prognostic factor	Comparison	n	RR	95% LCL	95% UCL	P
Age (yr)	≥ 60 vs < 60	35	3.00	0.81	19.42	0.107
Sex	Female vs male	35	3.42	0.53	12.88	0.167
LDH	Elevated vs normal	32	1.72	0.57	4.97	0.324
WBC count	Elevated vs normal	32	1.32	0.36	4.06	0.649
Stage	III and IV vs I and II	32	0.34	0.07	2.37	0.237
Bone marrow involvement	Present vs absent	35	1.21	0.40	3.51	0.720
Ki-67 positivity	High vs low	19	1.17	0.19	8.91	0.863
IPI	High risk vs other	32	0.49	0.03	2.55	0.450
MIPI	Other vs low risk	31	1.38	0.35	9.04	0.674
MIPI	High risk vs other	31	1.12	0.29	3.73	0.857
Treatment	Other vs hyper-CVAD/MA	35	6.18	1.64	40.21	0.005

RR: Relative risk; LCL: Lower confidence limit; UCL: Upper confidence limit; IPI: International prognostic index; MIPI: Mantle cell lymphoma international prognostic index; WBC: White blood cell; LDH: Lactate dehydrogenase.

Table 4 Prognostic relevance of event-free survival according to the univariate Cox regression

Prognostic factor	Comparison	n	RR	95% LCL	95% UCL	P
Age (yr)	≥ 60 vs < 60	35	5.27	1.47	33.77	0.007
Sex	Female vs male	35	2.67	0.61	8.39	0.170
LDH	Elevated vs normal	32	1.64	0.67	3.88	0.274
WBC count	Elevated vs normal	32	1.53	0.57	3.76	0.377
Stage	III and IV vs I and II	32	0.83	0.27	3.60	0.772
Bone marrow involvement	Present vs absent	35	1.24	0.49	2.95	0.639
Ki-67 positivity	High vs low	19	0.62	0.16	2.19	0.459
IPI	High risk vs other	32	1.07	0.25	3.24	0.918
MIPI	Other vs low risk	31	2.54	0.72	16.09	0.164
MIPI	High risk vs other	31	0.75	0.24	1.98	0.580
Treatment	Other vs hyper-CVAD/MA	35	2.81	1.02	9.25	0.044

RR: Relative risk; LCL: Lower confidence limit; UCL: Upper confidence limit; IPI: International prognostic index; MIPI: Mantle cell lymphoma international prognostic index; WBC: White blood cell; LDH: Lactate dehydrogenase.

Table 5 Prognostic relevance of event-free survival according to the multiple Cox regression

Prognostic factor	Comparison	RR	95% LCL	95% UCL	P
Age (yr)	≥ 60 vs < 60	4.17	0.95	29.25	0.059
Treatment	Other vs hyper-CVAD/MA	1.51	0.52	5.5	0.474

RR: Relative risk; LCL: Lower confidence limit; UCL: Upper confidence limit.

## DISCUSSION

In our patients, the gastric lesions varied in form; superficial, protruded, fold thickening, and ulcerative lesions appeared equally. On the other hand, intestinal involvement showed a clear predominance of MLP. Cornes described gastric lesions as pale folds, like the convolutions of the brain, with some larger lobules standing out like solitary tumors<sup>[2]</sup>. Ruskoné-Fourmestraux *et al*<sup>[4]</sup> also characterized gastric lesions as having large cerebroid folds; this is equal



to the fold thickening type in our study. Romaguera *et al*<sup>[5]</sup> reported that the most frequent abnormal findings in the upper GI tract in MCL cases were nodules and inflammation. A recent report by Salar *et al*<sup>[6]</sup> described 3 cases of gastric lesions, with antral gastritis in 2 and pangastritis in 1. Thus, the gastric involvement of MCL shows diverse forms in endoscopic examinations.

In this study, esophageal, gastric, and intestinal lesions were found by endoscopic examinations in 2 (5.7%), 26 (74.3%), and 22 (62.9%) patients, respectively. The prevalence of gastric lesions seems to be higher than the reported incidence of 46%-49%, whereas the prevalence of intestinal lesions is compatible with the reported rate of 38%-62%<sup>[5,6]</sup>. Importantly, histological evidence of MCL involvement reportedly exists in most cases even those with endoscopically intact mucosa<sup>[5,6]</sup>. Therefore, random biopsies by endoscopy at the time of diagnosis will probably reveal a higher incidence of GI involvement in MCL patients. Nevertheless, the impact of microscopic involvement in the outcome of MCL patients has not yet been elucidated<sup>[6]</sup>.

MALT lymphomas and follicular lymphomas are classified as small B-cell neoplasms as well as MCL. It is well known among endoscopists that MALT lymphomas exhibit various lesions in the stomach including erosions, ulcers, polyps, protruded tumors, and swollen mucosal folds, but the involvement of other parts of the GI tract, such as the small intestine, colon, and rectum, is uncommon<sup>[20,23]</sup>. Follicular lymphomas often arise in the duodenum around the ampulla of Vater with multiple whitish granules, and they rarely form bulky masses or ulcers<sup>[24]</sup>. Endoscopists should bear in mind that MALT lymphomas and follicular lymphomas can affect the entire GI tract and even form MLP<sup>[25-27]</sup>. Thus, evaluation of the entire GI tract enables endoscopists to discriminate MCL from other small B-cell neoplasms, although a differential diagnosis is sometimes difficult and requires immunostaining for CD5, CD10, cyclin D1, and BCL2.

The prognosis of patients with GI MCL has not yet been thoroughly discussed. The present study revealed that the hyper-CVAD/MA regimen plus rituximab and PBSCT is effective for MCL patients with GI involvement as well as for systemic MCL. The prognosis of MCL patients is poorest among those with B-cell lymphoma<sup>[28]</sup>. Conventional chemotherapeutic regimens such as CHOP, with or without rituximab, obtained only short (less than 2 years) remission periods, despite a high remission rate (75%-96%)<sup>[29-32]</sup>. To overcome the unfavorable outcomes of CHOP-like regimens, a hyper-CVAD/MA regimen was established as an effective cytoreductive regimen for MCL patients<sup>[33,34]</sup>. An excellent response rate, over 90%, and a CR rate of 38%-68% were achieved by this intensified initial chemotherapy. Additionally, rituximab in combination with hyper-CVAD/MA has augmented CR rates to 87%<sup>[35]</sup>. High-dose chemotherapy with PBSCT after hyper-CVAD/MA with or without rituximab could extend the CR period and achieve 3-year OS of 72%-92%<sup>[33,36]</sup>. In this study, the hyper-CVAD/MA regimen exhibited a su-

perior response and higher rates of survival among MCL patients over other regimens. Therefore, this regimen is a promising therapeutic option for MCL patients with GI involvement as well as for systemic MCL. We believe the hyper-CVAD/MA regimen plus rituximab and PBSCT should be administered to MCL patients with GI involvement who are young (< 60-65 years) and fit (no relevant co-morbidity).

A small subset of patients with MCL may show indolent behavior and have extended survival even with little or no treatment<sup>[28]</sup>. To identify this subset of patients and classify MCL patients according to their prognoses, several researchers have attempted to establish a prognostic index. Ki-67 positivity, which represents cell proliferation, has been reported as a predictor; high mitotic rates were associated with adverse prognoses<sup>[17,18]</sup>. The recently introduced MIPI scoring system successfully differentiated OS based on four independent prognostic factors: age, performance status, LDH, and leukocyte count<sup>[16]</sup>. In this study, however, Ki-67 positivity and MIPI score failed to classify our patients' prognoses. We speculate that any one of several factors may explain this. First, MCL patients with GI involvement might have different prognoses from all other MCL patients. In this study, all but 3 patients were at advanced stages (II-2 or IV). GI involvement of MCL might represent a more advanced disease status, but the impact of these GI findings on the outcomes of MCL patients is not known<sup>[6]</sup>. Second, because this study was retrospective and the treatment regimens administered to patients were not uniform, the non-uniform backgrounds might have distorted analysis. Further investigation concerning the prognosis of MCL with GI involvement is required in a study using a larger patient group.

In conclusion, 35 cases of MCL with GI involvement were included in this report. Esophageal, gastric, and intestinal lesions were identified in 2 (5.7%), 26 (74.3%), and 22 (62.9%) patients, respectively. MLP was a representative form of intestinal involvement, whereas a variety of lesions were found in the stomach. Prompt diagnosis based on the above findings and administration of initial cytoreductive chemotherapy, such as the hyper-CVAD/MA regimen followed by PBSCT, may improve the survival of MCL patients.

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## COMMENTS

### Background

Mantle cell lymphoma (MCL) is clinically more aggressive and has a shorter median survival, only 3-5 years, as compared with other types of small B-cell neoplasms. MCL can affect the gastrointestinal (GI) tract and its frequency is reportedly up to 60% in patients undergoing endoscopic examinations. However, the prognosis of MCL patients with GI involvement has not yet been revealed in detail.

### Research frontiers

Recently, the hyper-CVAD/MA regimen was established as an effective cytoreductive regimen for MCL patients. An excellent response rate, over 90%, and a complete remission (CR) rate of 38%-68% were achieved by this intensified initial chemotherapy. Additionally, rituximab in combination with hyper-CVAD/MA has augmented the CR rates to 87%. High-dose chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT) after hyper-CVAD/MA with or without rituximab could extend the CR period and achieve 3-year overall survival (OS) of 72%-92%.

### Innovations and breakthroughs

Patients treated with the hyper-CVAD/MA regimen had both markedly longer OS and longer event-free survival (EFS) than the group without hyper-CVAD/MA; the 3-year OS rate and 3-year EFS rate of the patients treated with hyper-CVAD/MA were 83.3% and 66.7%, respectively, whereas those of the patients without hyper-CVAD/MA were 46.4% and 33.8%, respectively. The differences between the two groups were statistically significant.

### Applications

Hyper-CVAD/MA regimen plus rituximab and PBSCT is effective for MCL patients with GI involvement as well as for systemic MCL. The hyper-CVAD/MA regimen plus rituximab and PBSCT should be administered to MCL patients with GI involvement who are young (< 60-65 years) and fit (no relevant comorbidity).

### Terminology

In the hyper-CVAD/MA regimen, cycles 1, 3, 5, 7 (Hyper-CVAD) consisted of cyclophosphamide, doxorubicin, vincristine, and dexamethasone. Cycles 2, 4, 6, 8 (MA) consisted of methotrexate and cytarabine. Cycles 1 and 2 were alternated every 21 d. Rituximab is a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells. Rituximab is used for the treatment of many lymphomas, leukemias, and some autoimmune disorders.

### Peer review

This is a multi-institutional retrospective review of 35 MCLs of the GI tract. Its strength is the multiple institutions that patients were treated allowing for comparison of different therapeutic regimens.

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