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Original Article

Nonmucosa-associated lymphoid tissue lymphomas of gastric and intestinal origin differ in their clinical features: A single institute experience

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Abstract

Background: The treatment policy and disease process of mucosa-associated lymphoid tissue (MALT) lymphomas are different from those of other gastrointestinal lymphomas. Chemotherapy has replaced curative surgery as the treatment of choice in gastric lymphomas but the optimal frontline treatment of intestinal lymphomas has yet to be defined. Hence, we attempted to identify the difference in features between gastric and intestinal nonMALT lymphomas.

Methods: Patients who were newly diagnosed with nonMALT lymphomas of gastrointestinal origin in our hospital between January 2001 and February 2010 were included in our study. Patient characteristics and outcomes were retrospectively analyzed.

Results: Among 59 gastric lymphoma patients and 25 intestinal lymphoma patients, the intestinal group were significantly younger and had better performance ($p = 0.002$ and 0.042). Whereas gastrointestinal obstruction and intussusception were more common in the intestinal group ($p = 0.024$ and 0.024), more bleeding episodes were displayed in the gastric counterpart ($p = 0.042$). Histologically, diffuse large B-cell lymphoma was more prevalent in the stomach, and enteropathy associated T-cell lymphoma was found only in the intestine ($p = 0.006$ and 0.024). Despite more intestinal lymphoma patients receiving surgery ($p = 0.002$), the response rate, overall survival and progression-free survival were similar to the gastric counterpart ($p = 0.1060$, 0.7758 and 0.1248). In the multivariate analysis of overall survival, chemotherapy (hazard ratio [HR] 0.2; 95% confidence interval [CI] 0.091–0.440; $p < 0.001$) and International Prognostic Index (HR 1.7; 95% CI 1.181–2.448; $p = 0.004$) proved prognostic in gastric lymphomas. Furthermore, T-cell lineage (HR 8.615; 95% CI 2.165–34.288; $p = 0.002$) and poor performance (HR 9.374; 95% CI 1.497–58.712; $p = 0.017$) were poor predictors in the intestinal counterpart.

Conclusion: Intestinal lymphomas differ from gastric lymphomas in manifestation, histology, management and prognosis. Surgery still plays a role in intestinal lymphomas because presentations of surgical emergencies are more common. In addition, the outcome of gastric lymphomas compared with intestinal lymphomas is no longer superior if patients with MALT lymphomas are excluded. Because of the limited number of enrolled patients, further large-scale studies are warranted to validate these results.

Keywords: diffuse large B-cell lymphoma; gastric lymphoma; gastrointestinal lymphoma; intestinal lymphoma; mucosa-associated lymphoid tissue lymphoma

1. Introduction

Gastrointestinal lymphomas account for 10–15% of all non-Hodgkin's lymphomas and 30–40% of extranodal lymphomas[1] but the incidence is increasing.[2] The most common site of gastrointestinal lymphoma involvement is the stomach (60–75%) followed by the small intestine, ileum, cecum, colon and rectum.[3] The major histological subtypes are diffuse large B-cell lymphoma (DLBCL) and mucosa-associated lymphoid tissue (MALT) lymphoma. *Helicobacter pylori* eradication is the treatment of choice in MALT lymphoma, which usually has superior outcomes compared with other subtypes.[4,5] Except for MALT lymphoma, immunochemotherapy with or without

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involved field radiation (IFRT) has replaced curative surgery as the frontline treatment in gastric lymphomas. An operation is reserved simply for surgical complications or localized residual disease after first-line conservative treatment.[6,7] By contrast, the most appropriate treatment modality for intestinal lymphoma is still controversial.[8,9] Patients with MALT lymphoma were excluded from the study because of the individual treatment policy and natural course of MALT lymphomas. The clinical manifestations, managements and survival outcomes between gastric and intestinal nonMALT lymphomas were investigated here. Only a single similar comparison study has been reported.[10]

2. Methods

2.1. Patients

The enrollment criterion was histologically proven non-Hodgkin's lymphoma that was considered to originate from the gastrointestinal tract, either with main lesions or at least with adequate gastrointestinal specimens for pathological review. The earlier biopsies were classified according to the now obsolete Working Formulation and the Revised European–American Lymphoma classification. Later, World Health Organization classification system was used. Patients with MALT lymphomas and those without adequate clinical information in our hospital were excluded. Among 972 newly diagnosed lymphoma patients in our hospital, 84 patients with nonMALT lymphomas of gastrointestinal origin between January 2001 and February 2010 were included in our study.

Staging procedures included physical examination, complete blood cell count with differential count, blood chemistry, and computed tomography of the chest, abdomen and pelvis. Bone marrow aspiration and biopsy were essential for staging but some patients who received only surgery or palliative treatment did not undergo bone marrow examination. Endoscopic examinations and positron emission tomography were optional choices. The clinical evaluations included the performance status based on the Eastern Cooperative Oncology Group scale, B symptoms (tumor fever, night sweating and loss of more than 10% of body weight), the International Prognostic Index (IPI) and bulky lesions (mass of 10 cm or more in the longest diameter).

Clinical stage was defined according to the Musshoff modification of the Ann Arbor system. Stage I disease was defined as single gastrointestinal lesion. Stage II was defined as disease extending into either local or distant abdominal lymph nodes. Stage III denoted nodal involvement above and below the diaphragm. Stage IV denoted noncontinuous visceral organs or bone marrow involvement. For response evaluation, disappearance of all lesions for a period of 4 weeks with negative endoscopic finding (if done) was defined as complete remission (CR). At least 50% decrease in mass was defined as partial remission (PR). New lesions or increased size of lesions were classified as progressive disease (PD). Patients who were not classified as CR, PR or PD were classified as stable disease.

Table 1
Clinical characteristics of patients with gastric and intestinal lymphomas

Parameters (median; range)	Classification	No. of patients (%)		*p*
		Gastric lymphoma ($n = 59$)	Intestinal lymphoma ($n = 25$)	
Gender	Male	36 (61)	15 (60)	NS
	Female	23 (39)	10 (40)	
Age (69 years; 20–87 years)	≦60 years	14 (23.7)	15 (60)	0.002
	>60 years	45 (76.3)	10 (40)	
Histology	B-cell	57 (96.6)	18 (72)	0.002
	T-cell	2 (3.4)	7 (28)	
Low-grade component		5 (8.5)	2 (8)	NS
Musshoff staging	I	11 (18.6)	6 (24)	NS
	II	11 (18.6)	5 (20)	
	III	10 (16.9)	3 (12)	
	IV	27 (45.8)	11 (44)	
B symptoms		10 (16.9)	8 (32)	NS
Bulky lesions	≧10 cm	3 (5.2)	4 (16)	NS
Performance status	0, 1	35 (59.3)	21 (84)	0.042
	2–4	24 (40.7)	4 (16)	
IPI	Low	13 (22.0)	10 (40)	NS
	Low-intermediate	17 (28.8)	9 (36)	
	High-intermediate	11 (18.6)	4 (16)	
	High	18 (30.5)	2 (8)	
Hemoglobin (11.1 g/dL; 6.1–15.2 g/dL)	≧12 g/dL	22 (37.3)	11 (44)	NS
	<12 g/dL	37 (62.7)	14 (56)	
LDH (267 U/L; 129–3540 U/L)	≦205 U/L	16 (31.4)	9 (56.3)	NS
	>205 U/L	35 (68.6)	7 (43.8)	
Albumin (3.2 g/dL; 1.8–4.5 g/dL)	≧3.7 g/dL	10 (19.2)	8 (38.1)	NS
	<3.7 g/dL	42 (80.8)	13 (61.9)	

IPI = International Prognostic Index; LDH = lactate dehydrogenase; NS = not significant.

2.2. Statistical analysis

The categorical variables were compared using Fisher's exact test and Chi-square test as appropriate. Overall survival (OS) was recorded from the date of diagnosis to the date of death or last follow-up alive. Progression-free survival (PFS) was the time from the start of curative treatment to the time of disease progression or persisting CR until last follow-up. The Kaplan–Meier method was used to calculate OS and PFS, and the comparison between groups was performed through the logrank test. The univariate and multivariate analyses of prognostic factors were estimated using Cox's proportional hazards model. A $p < 0.05$ was taken to be two-tailed statistically significant. Statistical analyses were performed using SPSS software Version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

The entire population was divided into groups of gastric lymphomas ($n = 59$) and intestinal lymphomas ($n = 25$). Two patients revealed noncontinuous gastric and duodenal involvement. Another four patients had separate lesions of the intestine. They were classified as gastric and intestinal lymphoma, respectively. One patient had acquired immunodeficiency syndrome, and two patients had autoimmune diseases. Intestinal lymphoma patients were significantly younger and had better performance ($p = 0.002$ and 0.042). The other characteristics disclosed no significant difference between these two groups (Table 1).

The common manifestations of enrolled patients included abdominal pain (61.9%), nonspecific complaints (45.2%), bleeding (33.3%), body weight loss (27.4%) and anemia (22.6%). However, gastrointestinal obstruction and intussusception were significantly more common in the intestinal group than in the gastric counterpart ($p = 0.024$ and 0.024). By contrast, manifestation of various degrees of bleeding was significantly more frequent in gastric lymphomas than in the intestinal counterpart ($p = 0.042$) (Table 2). Histologically, 73.8% of all patients were classified as DLBCL, which was more common in the gastric group ($p = 0.006$). Of the total patients, 10.7% had T-cell type lymphoma, and all enteropathy associated T-cell lymphomas originated from the intestine ($p = 0.024$). However, the other histological subtypes demonstrated equal distribution in these subgroups (Table 3). In total, 8.3% ($n = 7$) of patients showed evidence of transformation from low-grade MALT lymphoma.

Of all the patients, 28.6% received chemotherapy only, 26.2% had an operation followed by chemotherapy, 19% underwent single surgery, and 16.7% received palliative treatment for old age, poor performance or refusal of aggressive treatment. In total, 34.5% underwent multimodality treatment. Between the subgroups, no statistical significance was displayed in these managements (Table 4). In the analysis of individualized modality, 50% of all patients received surgery, and the percentage was significantly higher in the intestinal group ($p = 0.002$) (Table 5). Among intestinal

Table 2
The initial presentations of gastric and intestinal lymphoma patients

Manifestations	No. of patients (%)		p
	Gastric lymphoma ($n = 59$)	Intestinal lymphoma ($n = 25$)	
Abdominal pain	35 (59.3)	17 (68)	NS
Nonspecific complaints	25 (42.4)	13 (52)	NS
Bleeding	24 (40.7)	4 (16)	0.042
Body weight loss	15 (25.4)	8 (32)	NS
Anemia	13 (22)	6 (24)	NS
Perforation	4 (6.8)	2 (8)	NS
Dysphagia	4 (6.8)	1 (4)	NS
Fever	4 (6.8)	0 (0)	NS
Constipation	3 (5.1)	1 (4)	NS
Mass	1 (1.7)	2 (8)	NS
Intestinal obstruction	0 (0)	3 (12)	0.024
Intussusception	0 (0)	3 (12)	0.024
Sweating	1 (1.7)	1 (4)	NS
Diarrhea	1 (1.7)	1 (4)	NS

NS = not significant.

Table 3
The histological subtypes of gastric and intestinal lymphomas

Classifications	No. of patients (%)		p
	Gastric lymphoma ($n = 59$)	Intestinal lymphoma ($n = 25$)	
Diffuse large B-cell lymphoma	49 (83.1)	13 (52)	0.006
Peripheral T-cell lymphoma	2 (3.4)	4 (16)	NS
Mantle cell lymphoma	1 (1.7)	2 (8.0)	NS
Enteropathy associated T-cell lymphoma	0 (0)	3 (12)	0.024
Follicular lymphoma	1 (1.7)	1 (4.0)	NS
B-cell lymphoma, unclassified	4 (6.8)	0 (0)	NS
Diffuse large lymphoma	1 (1.7)	1 (4.0)	NS
Diffuse mixed small and large cell lymphoma	0 (0)	1 (4.0)	NS
High-grade B-cell lymphoma	1 (1.7)	0 (0.0)	NS

NS = not significant.

Table 4
Treatment modalities and overall response of included patients

Treatment modalities	No. of patients (%)		
	Gastric lymphoma ($n = 59$)	Intestinal lymphoma ($n = 25$)	Response rate
Chemotherapy alone	19 (32.2)	5 (20)	14/15 (93.3)
Surgery & chemotherapy	13 (22)	9 (36)	16/19 (84.2)
Surgery	8 (13.6)	8 (32)	5/8 (62.5)
Surgery & chemotherapy & radiotherapy	1 (1.7)	1 (4.0)	2/2 (100)
Chemotherapy & salvage surgery	2 (3.4)	0 (0)	2/2 (100)
Chemotherapy & transplantation	1 (1.7)	1 (4.0)	2/2 (100)
Chemotherapy & radiotherapy	1 (1.7)	0 (0)	1/1 (100)
Radiation	1 (1.7)	0 (0)	1/1 (100)
Supportive care	13 (22)	1 (4)	—

All p values were not significant ($p > 0.05$).

Table 5
Individualized interventions performed in gastric and intestinal lymphomas

Treatment modalities	No. of patients (%)		p
	Gastric lymphoma ($n = 59$)	Intestinal lymphoma ($n = 25$)	
Surgery	24 (40.7)	18 (72)	0.002
Chemotherapy	37 (62.7)	16 (64)	NS
Radiotherapy	3 (5.4)	1 (4)	NS
Rituximab	18 (30.5)	6 (24)	NS
Transplantation	1 (1.7)	1 (4)	NS

NS = not significant.

lymphoma patients who received resection, 16.7% ($n = 3$) manifested with obstruction, 16.7% ($n = 3$) with intussusception, 16.7% ($n = 3$) with perforation, 16.7% ($n = 3$) with bleeding and 11.1% ($n = 2$) with masses for exploratory laparotomy. Actually, only 22.1% ($n = 4$) received intended curative surgery.

3.2. Outcome

The median duration of follow-up was 10.2 months (0.1−104.9 months). During the observation period, 41 patients (48.8%) died and 24 patients (28.6%) suffered from disease progress or relapse. The most common causes of death were infection (58.5%), disease progress (24.3%) and bleeding (14.6%). The CR and PR rate in all patients receiving interventions and restaging were 66.7% (34 out of 51) and 17.6% (9 out of 51), respectively. In the subgroup analysis, gastric and intestinal lymphoma were 68.6% (24 out of 35) and 62.5% (10 out of 16) for the CR rate, and 22.9% (8 out of 35) and 6.3% (1 out of 16) for the PR rate ($p = 0.1060$). The rates of 1-year and 2-year OS were 57.7% and 47.1% in the gastric group, and 64.7% and 48.5% in the intestinal counterpart ($p = 0.7758$). The percentages of 1-year and 2-year PFS were 74.2% and 70.6% in gastric lymphomas and 51.3% and 30.8% in intestinal lymphomas ($p = 0.1248$). The overall response rates were similar under different combinations of treatment modalities (Table 3). In the Kaplan−Meier analysis of the whole population, the administration of chemotherapy and rituximab significantly prolonged the OS ($p = 0.0002$ and 0.0018) but surgery did not ($p = 0.1704$). Instead of chemotherapy and surgery ($p = 0.6116$ and 0.2892), the introduction of rituximab significantly extended the PFS ($p = 0.0254$; Fig. 1). The complications of all treatments included neutropenic fever (28.6%), hemorrhage (3.6%), perforation (3.6%), obstruction (2.4%), congestive heart failure (1.2%) and chronic hepatitis B with reactivation (1.2%) but no significant difference was noted between the gastric and intestinal groups.

In the univariate analysis of OS for gastric lymphomas, poor performance status, high IPI, low albumin, no chemotherapy and no rituximab were poor prognostic factors. However, chemotherapy administration (hazard ratio [HR]:

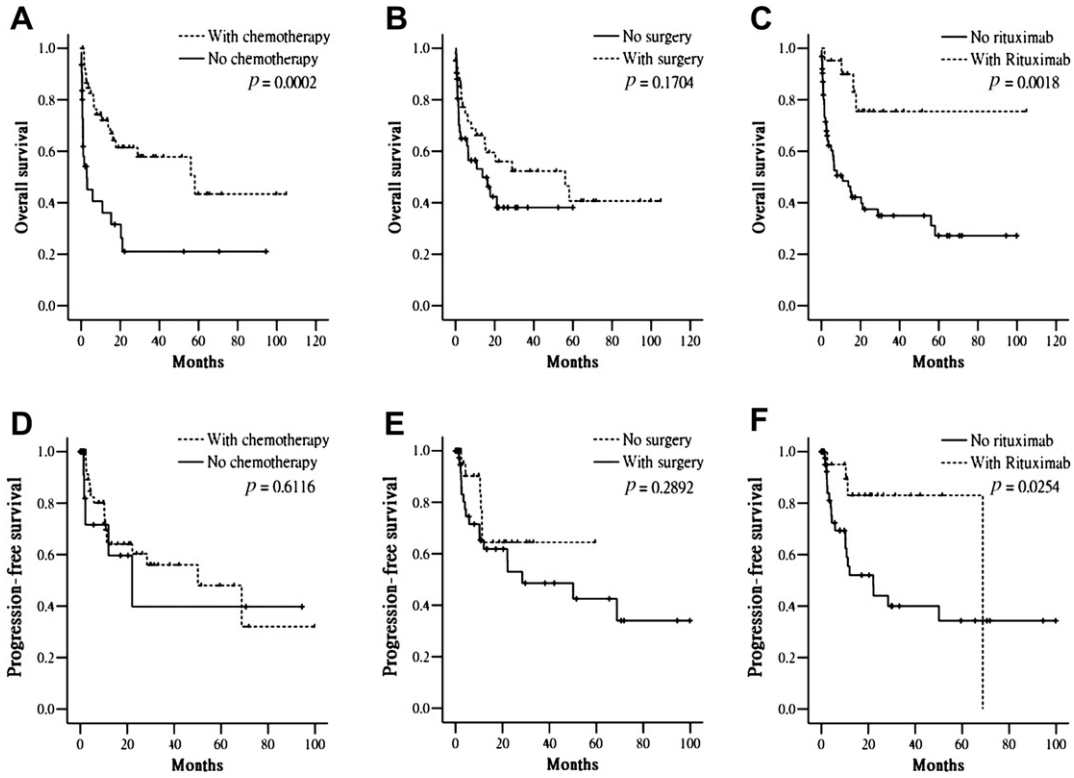

Fig. 1. Whole population treatment outcomes demonstrated by Kaplan−Meier survival curves. (A−C) The administration of chemotherapy and rituximab significantly prolonged the overall survival ($p = 0.0002$ and 0.0018) but surgery did not ($p = 0.1704$). (D−F) The undergoing or not of chemotherapy and surgery had no significant impact on progression-free survival ($p = 0.6116$ and 0.2892 respectively). However, patients receiving rituximab had a superior progression-free survival in comparison with those without rituximab ($p = 0.0254$).

0.2; 95% confidence interval [CI]: 0.091–0.440; $p < 0.001$) and high IPI (HR: 1.7; 95% CI: 1.181–2.448; $p = 0.004$) proved to have independently prognostic significance in multivariate analysis of OS in gastric lymphomas. In the multivariate analysis of intestinal lymphomas, T-cell lineage (HR: 8.615; 95% CI: 2.165–34.288; $p = 0.002$) and poor performance (HR: 9.374; 95% CI: 1.497–58.712; $p = 0.017$) were demonstrated to be significantly poor predictors of OS. In the univariate analysis of OS in the pooling of all patients, T-cell histology, poor performance status, high IPI, low albumin, no chemotherapy and no rituximab were poor prognostic factors. Furthermore, poor performance status (HR: 4.276; 95% CI: 2.062–8.867; $p < 0.001$) and low albumin (HR: 4.725; 95% CI: 1.072–20.830; $p = 0.04$) confirmed the statistical significance in the multivariate analysis of OS (Table 6). Rather, no single factor showed predictive values of PFS in the gastric group, the intestinal group, and even in all patients.

4. Discussion

The principles of lymphoma management are based on histological classifications. Because of the unique pathogenesis, *H pylori* eradication is the standard frontline treatment of most gastric MALT lymphomas. According to the recommendation of the National Comprehensive Cancer Network, treatments of gastric MALT lymphomas should be individualized in clinical practice and have been isolated from the other non-Hodgkin's lymphomas. At the same time, interventions at diagnosis of gastrointestinal lymphomas are usually proposed to prevent possible lethal complications (gastrointestinal obstruction, bleeding and perforation), even in indolent diseases other than gastric MALT lymphomas.[11,12] Therefore, the separation of MALT lymphomas from other gastrointestinal lymphomas was reasonable, and the comparison between gastric and intestinal nonMALT lymphomas was informative.

Histological classification also determines a major part of the clinical course and treatment response in gastrointestinal lymphomas. Chemotherapy shows high activity in B-cell lymphomas, and the role of surgery is limited. By contrast, T-cell intestinal lymphoma usually presents with severe surgical complications, advanced stage, aggressive course and poor response to treatment.[13,14] In our study, DLBCL was the most common histological subtype in either gastric or intestinal lymphomas but the percentage was significantly higher in the gastric group (83.1% vs. 52.0%; $p = 0.006$). However, T-cell lymphoma was significantly more common in intestinal than in gastric lymphomas (28.0% vs. 3.4%; $p = 0.002$). T-cell lineage adversely affected the OS and PFS in the intestinal group ($p = 0.0011$ and 0.0405) but the impact was not as demonstrated in the gastric counterpart (Fig. 2) because of inadequate numbers of T-cell gastric lymphoma patients ($n = 2$; $p = 0.9662$ and 0.3358).

In gastric lymphomas, the role of first-line immunochemotherapy has been well established, and surgical intervention has shifted to become the salvage treatment of unsatisfactory conservative treatments or complications.[15–17] Owing to

Table 6
Univariate and multivariate analysis of overall survival

Parameters	All patients ($n = 84$)						Gastric lymphoma ($n = 59$)						Intestinal lymphoma ($n = 25$)					
	Univariate			Multivariate			Univariate			Multivariate			Univariate			Multivariate		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Gastric origin	0.907	0.463–1.778	0.776	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
T-lineage	2.325	1.024–5.279	0.044	—	—	—	0.957	0.128–7.148	0.966	—	—	—	6.401	1.843–22.231	0.003	8.615	2.165–34.288	0.002
Female	0.714	0.379–1.345	0.297	—	—	—	0.454	0.204–1.012	0.054	—	—	—	1.884	0.592–6.001	0.284	—	—	—
Age > 60 y	1.349	0.686–2.651	0.385	—	—	—	1.567	0.595–4.126	0.364	—	—	—	1.181	0.373–3.739	0.777	—	—	—
Advanced stage	1.326	1.001–1.756	0.050	—	—	—	1.388	0.985–1.957	0.061	—	—	—	1.146	0.697–1.883	0.592	—	—	—
B symptoms	1.793	0.893–3.600	0.101	—	—	—	2.064	0.871–4.891	0.100	—	—	—	1.426	0.413–4.924	0.574	—	—	—
No bulky lesions	0.496	0.119–2.056	0.333	—	—	—	0.785	0.105–5.840	0.813	—	—	—	0.352	0.045–2.740	0.318	—	—	—
Poor PS	1.887	1.475–2.413	<0.001	4.276	2.062–8.867	<0.001	4.643	2.128–10.130	<0.001	—	—	—	7.516	2.059–27.437	0.002	9.374	1.497–58.712	0.017
High IPI	1.678	1.323–2.130	<0.001	—	—	—	1.913	1.342–2.727	<0.001	1.700	1.181–2.448	0.004	1.676	0.900–3.121	0.104	—	—	—
Hemoglobin < 12 g/dL	1.799	0.899–3.600	0.097	—	—	—	1.622	0.717–3.673	0.246	—	—	—	2.223	0.588–8.405	0.239	—	—	—
LDH > 205 U/L	1.827	0.861–3.873	0.116	—	—	—	2.600	0.965–7.009	0.059	—	—	—	0.846	0.201–3.556	0.819	—	—	—
Albumin < 3.7 g/dL	8.320	1.994–34.716	0.004	4.725	1.072–20.830	0.040	9.512	1.288–70.217	0.027	—	—	—	5.886	0.732–47.355	0.096	—	—	—
Surgery	0.648	0.346–1.211	0.174	—	—	—	0.589	0.273–1.274	0.179	—	—	—	0.841	0.245–2.892	0.784	—	—	—
Chemotherapy	0.321	0.173–0.596	<0.001	—	—	—	0.163	0.076–0.350	<0.001	0.200	0.091–0.440	<0.001	1.543	0.415–5.743	0.517	—	—	—
Rituximab	0.221	0.079–0.623	0.004	—	—	—	0.145	0.034–0.610	0.008	—	—	—	0.501	0.108–2.332	0.378	—	—	—
Radiation	1.019	0.311–3.336	0.975	—	—	—	1.016	0.241–4.292	0.982	—	—	—	0.964	0.115–8.087	0.973	—	—	—
SCT	0.047	0–94–565	0.431	—	—	—	0.048	0.513–6.204	0.607	—	—	—	0.045	0.207–0.094	0.571	—	—	—

CI = confidence interval; HR = hazard ratio; IPI = International Prognostic Index; LDH = lactate dehydrogenase; PS = performance status; SCT = autologous stem cell transplantation.

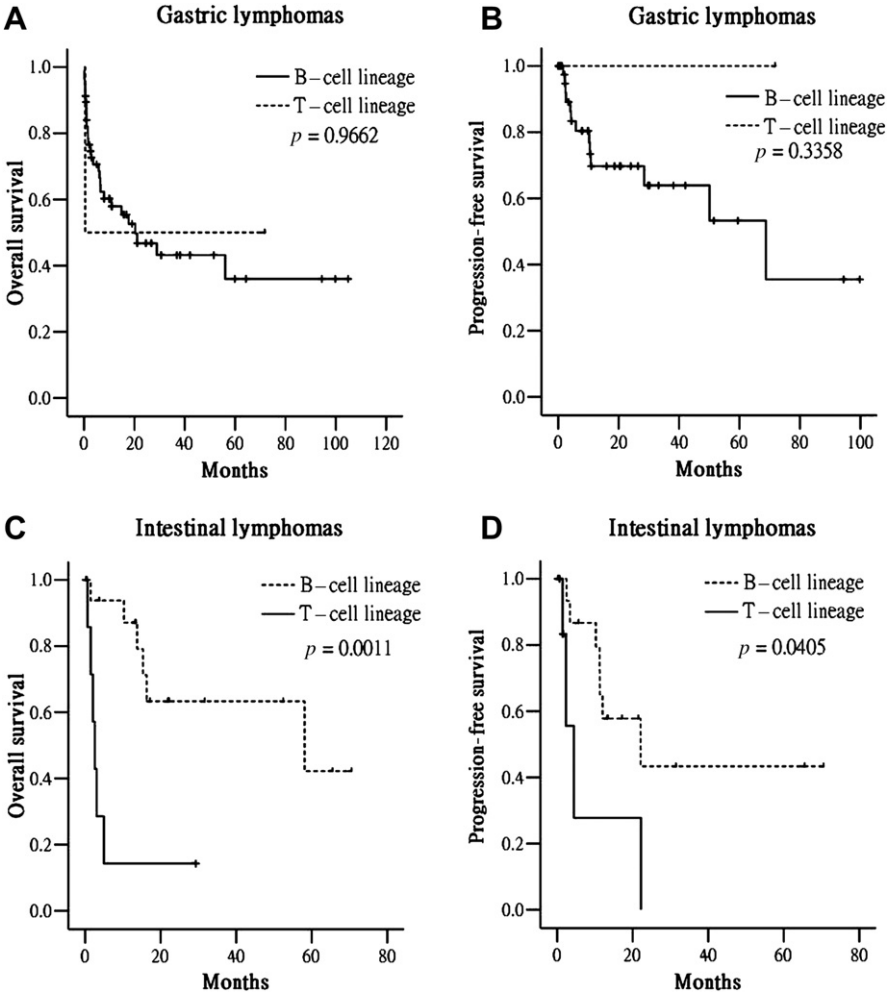

Fig. 2. Survival, outcomes analyzed between histological subgroups. (A, B) Because of limited numbers of T-cell lymphomas, similar overall survival and progression-free survival rates were demonstrated between B- and T-cell gastric lymphomas ($p = 0.9662$ and 0.3358 respectively). (C, D) By contrast, intestinal lymphomas with T-cell lineage had significantly inferior overall survival and progression-free survival rates compared to those with B-cell lineage ($p = 0.0011$ and 0.0405, respectively).

tumor histology and the study covering a period of 10 years, 33.9% ($n = 20$) received chemotherapy with cyclophosphamide, anthracycline, vincristine and prednisolone (CHOP) and 25.6% ($n = 15$) of patients received rituximab plus CHOP as first-line chemotherapy. Chemotherapy, rather than surgery and rituximab, was proven to have protective significance for OS in gastric lymphoma. Also, there was no significant increase in complications for those patients receiving chemotherapy with CHOP, even after adding rituximab.[18] Nevertheless, the importance of rituximab might be underestimated because the sample size was limited.

In some studies of intestinal lymphomas, surgical resection has proven to be beneficial for local control but controversies still exist concerning chemotherapy.[9,19,20] In another study, the combination of surgery and chemotherapy showed good management of complications and obtained a high remission rate in localized intestinal lymphomas.[21] In this study, the manifestations of surgical emergencies of intestinal obstruction and intussusception were significantly more common ($p = 0.024$ and 0.024), and therefore more patients received surgical resection ($p = 0.002$). In addition, intestinal perforation, bleeding and masses for exploratory laparotomy were also important indications for operations. In total, 55.6% ($n = 14$) of intestinal lymphoma patients receiving surgery were also prescribed chemotherapy. However, neither surgery nor chemotherapy proved beneficial in the OS or PFS of intestinal lymphomas. Rather, it was proved that histological subtypes and performance status were the significant prognostic indicators in the multivariate analysis of OS. From the results, it was inconclusive whether the therapeutic efficacy came from chemotherapy, operation or both. In short, there is still a role for surgery in intestinal lymphomas because the manifestations of surgical emergencies are more common than in gastric lymphomas. The current trend of treatment tends to combine surgical resection and chemotherapy in localized intestinal lymphoma but it is still not well documented.

In this study, the locations of gastrointestinal lymphomas, in order of frequency, were the stomach (70.2%), small intestine (13.2%), ileocecal region (10.6%), colon (3.6%), appendix, (1.2%) and rectum (1.2%). Neither overall response, PFS nor

OS showed a significant difference between the gastric and intestinal groups ($p = 0.106$, 0.7758 and 0.1248, respectively). The site of lymphoma origin was prognostic in a previous report but the superiority of outcome was not echoed in our study even though the tumor distribution was similar.[22] The major explanation for this finding might be the exclusion of MALT lymphoma patients from the study and therefore the survival rate of patients with gastric lymphomas decreased. The minor explanation is likely to be the bias of younger and better performance status in the intestinal group. In the literature review, four lymphoma subgroups were analyzed in a German study: the stomach, ileococeal region, small bowel and multiple sites of origin. Superior survival outcomes were confirmed in the gastric and ileocecal subgroups.[22] If the gastric and ileocecal lymphoma subgroups had better outcomes than others, the inclusion of ileocecal lymphoma patients into the intestinal group should lengthen the survival of the intestinal group and thus make its survival comparable with that of patients with gastric lymphoma in the present study. In addition, the fact that tumor location had no significant impact on outcomes was shown in the study of gastrointestinal DLBCL.[20] This indirect evidence further supported our result because DLBCL was the predominate subtype in both groups.

However, there are some limitations to this study. Firstly, it was a small-scale retrospective analysis with some missing data. Secondly, different histological classification systems were used at different time points and hence the true incidence of DLBCL may be underestimated. Thirdly, we could not validate the role of surgery in intestinal lymphoma directly through lack of head-to-head comparison. Fourthly, no significant prognostic factor of PFS was found; the assumed probable reason was inadequately analyzed parameters. Some other factors, such as pathological characteristics,[23,24] cytogenetic abnormalities,[25] beta-2 microglobulin[26] and absolute lymphocyte count[27] might also have had an impact on the outcomes. Finally, the number of patients receiving IFRT and autologous stem cell transplantation was extremely low.

In conclusion, intestinal lymphomas differ from gastric lymphomas in manifestation, histology, management and prognosis. Surgery still plays a role in intestinal lymphomas because the initial presentations of surgical emergencies are more common, especially those of intestinal obstruction and intussusception. In addition, the outcome of gastric lymphomas compared with intestinal lymphomas is no longer superior if patients with MALT lymphomas are excluded. Because of the limited number of enrolled patients, further large-scale studies are warranted to validate these results.

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