Clinicopathological Characteristics and Therapeutic Outcomes of Synchronous Gastric Adenocarcinoma and Gastric Lymphoma

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Abstract. *Background: Synchronous primary gastric adenocarcinoma and lymphoma is a rare occurrence. The aim of the present retrospective study was to analyze the clinicopathological characteristics and therapeutic outcomes of patients with this rare condition to identify post-therapeutic prognostic factors. Patients and Methods: A PubMed and MEDLINE search was performed to identify relevant articles, using the keywords 'gastric cancer' and 'gastric malignant lymphoma', while additional articles were obtained from references within these papers. A total of 57 patients who were treated for synchronous primary gastric adenocarcinoma and lymphoma were included in the study. A retrospective review was performed on the clinical characteristics of this disease. Results: The median survival time for patients in this study was 81 months and the overall 1- and 5-year survival rates after therapy were 77.6% and 69.0%, respectively. The median survival period of patients with an advanced gastric cancer was significantly shorter than for early gastric cancer (p<0.001), while the depth of gastric lymphoma invasion did not significantly affect survival time. The median survival period of patients who underwent total gastrectomy was significantly shorter than that of those who underwent distal gastrectomy (p=0.035). Gastric lymphomas were significantly larger than the gastric adenocarcinomas (6.0 vs. 2.7 cm, respectively; p=0.012). Conclusion: The prognosis for synchronous gastric adenocarcinoma and lymphoma might depend more on the behavior of the adenocarcinoma than on the lymphoma, in which case the treatment and therapeutic outcomes could depend on the adenocarcinoma status.*

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Key Words: Gastric cancer, gastric lymphoma, mucosal-associated lymphoid tissue lymphoma, synchronous gastric neoplasia.

Recently, *Helicobacter pylori* was confirmed to play a key pathogenic role in a number of gastroduodenal and non-gastroduodenal diseases, such as gastric cancer, malignant lymphoma, peptic ulcer, and idiopathic thrombocytopenic purpura (1, 2). Although adenocarcinoma and lymphoma represent the two most common malignant tumors of the stomach, with both neoplasms associated with infection by *H. pylori*, the presence of lymphoma and adenocarcinoma in the same patient is rare (3). Gastric marginal zone B-cell mucosal-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell lymphoma derived from MALT that is rarely associated with gastric carcinoma (4).

We recently encountered a patient with simultaneously occurring superficial spreading-type early gastric cancer (EGC) and MALT lymphoma (5). Based on this case, we further investigated the clinical characteristics of these synchronous tumors, starting with a literature review. There are very few case reports of these types of tumors occurring together, and, since the literature contains mostly isolated case reports, the clinicopathological features of these tumors when found together in the stomach remain unclear. We herein summarize the clinical features of synchronous gastric carcinoma and lymphoma, and discuss the clinical outcome after treatment.

Patients and Methods

Literature search. We performed a search of the English literature published from 1990 to 2013 in MEDLINE and PubMed for articles on the simultaneous occurrence of primary gastric adenocarcinoma and lymphoma using the keywords 'gastric cancer' and 'gastric malignant lymphoma'. The reference lists of the articles identified in this manner were then manually searched to find any additional

references; articles published only in abstract form were excluded. From this search, we identified 57 cases of synchronous primary gastric adenocarcinoma and lymphoma (3, 5-26).

We retrospectively reviewed 57 patients who were diagnosed with the simultaneous occurrence of primary gastric adenocarcinoma and lymphoma, comprising the 57 cases described in past reports including a patient who was treated in our hospital. For each patient, we obtained data on age, gender, tumor location, tumor size, histological type, treatment method, and outcome. We analyzed these data to identify possible relationships between the clinical variables and survival.

Statistical analysis. We used the Mann-Whitney *U*-test to evaluate differences in the ordinal and continuous variables for various groupings, and the chi-square test to compare the categorical variables. We used the Kaplan-Meier method to generate cumulative survival rates and compared them using the log–rank test to evaluate significant differences. $p<0.05$ was considered to indicate a statistically significant result. Statistical analysis was performed using the SPSS for Windows version 13.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinical characteristics. The clinical features of the 57 reported cases are listed in Table I. The median age of patients was 62 years (range=27-85 years) and there was a male predominance, with a male-to-female ratio of 39:18. Gastric carcinoma lesions in the upper third of the stomach were reported in 9 cases, 23 had lesions in the middle third, and 19 had lesions in the lower third of the stomach.

The median tumor size for gastric adenocarcinoma was 2.7 cm (range, 0.3-15 cm), which was significantly smaller than that for gastric lymphoma (6.0 cm; range=0.4-11 cm; $p=0.012$). In addition, the median gastric adenocarcinoma tumor size was significantly greater in patients with multiple metastases than in those with a solitary metastasis (4 *vs*. 2 cm, respectively; $p=0.036$). Based on gross appearance, we divided gastric adenocarcinomas into depressed and elevated types, revealing 31 cases of depressed type and 16 cases of elevated type.

The gastric adenocarcinomas had invaded to varying depths, with lesions confined to the mucosa in 18 cases, but invading the submucosa in 20 cases, muscularis propria in 2, subserosa in 6, and penetrating the serosa in 8 cases. Gastric lymphoma was confined to the mucosa in 9 cases, but had invaded the submucosa in 22, muscularis propria in 4, subserosa in 3, serosa in 6, and adjacent structures in 1 case. Histological analysis of gastric cancer revealed 33 intestinal-type and 22 diffuse-type carcinomas; for gastric lymphoma there were 47 MALT lymphomas, 5 diffuse large B-cell lymphomas, and 5 cases of other types of lymphoma. Treatment comprised total gastrectomy in 28 patients, distal gastrectomy in 16, proximal gastrectomy in 1, and chemotherapy in 2 patients.

Comparison of intestinal- and diffuse-type gastric carcinoma. Table II shows a comparison of clinical characteristics between intestinal- and diffuse-type gastric carcinoma among the cases of synchronous gastric adenocarcinoma and lymphoma. The median tumor size of the diffuse-type gastric adenocarcinoma tended to be larger than that of the intestinal-type (4.3 cm *vs*. 2.5 cm, respectively), although the difference did not reach significance ($p=0.058$). There were no significant differences in age, gender, tumor depth of adenocarcinoma or lymphoma, or treatment, between the intestinal- and diffuse-type gastric adenocarcinomas.

Survival analysis. The median survival time was 81 months (range= 1-132 months) and the overall 1- and 5-year survival rates after therapy were 77.6% and 69.0%, respectively (Figure 1). The clinical characteristics of patients with synchronous gastric adenocarcinoma and MALT lymphoma are shown in Table III, together with a comparison of survival rates among subgroups of prognostic factors. The median survival period of patients with an advanced gastric cancer was significantly shorter than that of those with an EGC ($p<0.001$) (Figure 2). The median survival period of patients who underwent total gastrectomy was also significantly shorter than that of those who underwent distal gastrectomy ($p=0.035$) (Figure 3).

When patients were divided into two groups depending on the depth of lymphoma invasion (*i.e*., the lesion was confined to the mucosal or submucosal layer, or the lesion was deeper than the muscularis propria), the median survival time was not reached for patients with mucosal or submucosal lymphoma, compared to 10 months for those with deeper-invading lymphomas ($p=0.061$) (Figure 4). However, while advanced gastric cancer was significantly associated with a poorer outcome, the relationship between depth of gastric lymphoma invasion and survival rate did not reach significance.

There were no significant influences on survival rate by age, gender, tumor location, tumor size, or histological type. No independent prognostic factors were identified by multivariate analysis, probably due to the small patient number.

Discussion

This retrospective cohort study of synchronous primary gastric adenocarcinoma and lymphoma found that the prognosis of this rare disease depends on the status of the adenocarcinoma. Namely, advanced gastric cancer was significantly associated with a poorer outcome compared to EGC, while there was no association between prognosis and the degree of lymphoma progression. These results suggest that treatment of such synchronous cases should be generally directed at the gastric adenocarcinoma.

The gastrointestinal tract, mainly the stomach, is the most common site for extra-nodal lymphoma, of which gastric MALT lymphoma is the most common histological subtype. Both gastric carcinoma and gastric MALT lymphoma are

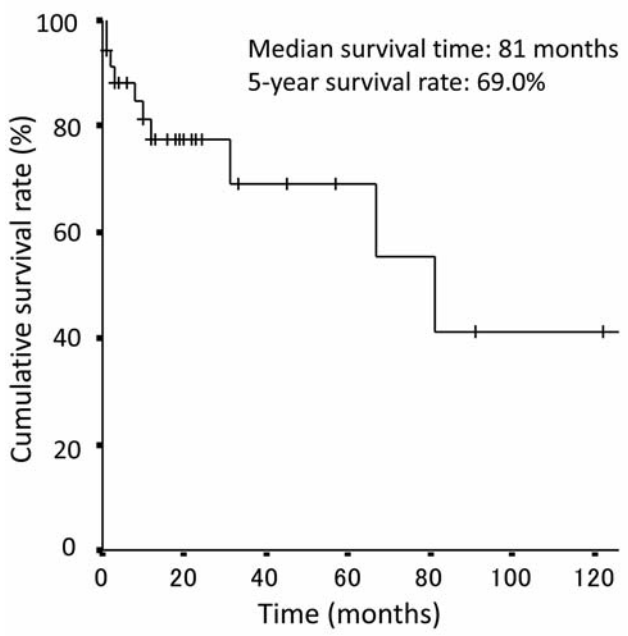

Figure 1. *Kaplan-Meier survival curve for 57 patients with synchronous gastric adenocarcinoma and mucosal-associated lymphoid tissue lymphoma. The median survival time was 81 months and 5-year survival rate was 69.0%.*

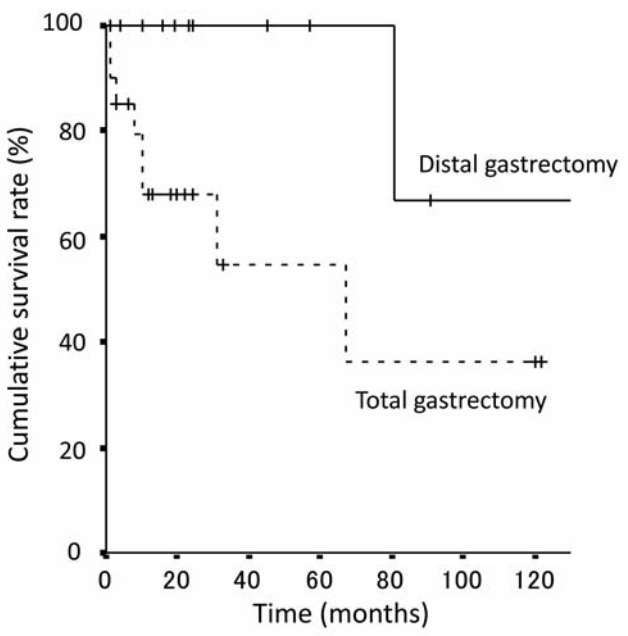

Figure 3. *Kaplan-Meier survival curves for 16 patients who underwent distal gastrectomy (solid line) and 28 patients who underwent total gastrectomy (dotted line). There was a significant difference in survival between the groups (p=0.035). Data were analyzed using the log-rank test.*

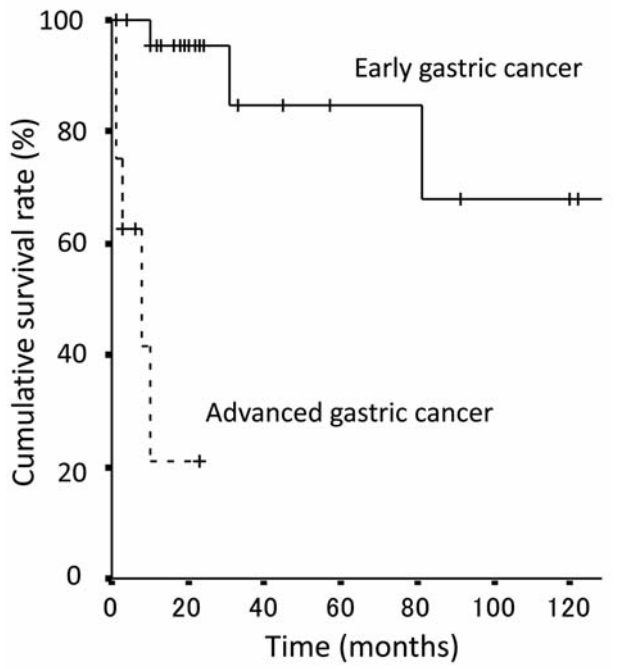

Figure 2. *Kaplan-Meier survival curves for 38 patients with synchronous early gastric cancer and mucosal-associated lymphoid tissue lymphoma (solid line) and 16 patients with synchronous advanced gastric cancer and mucosal-associated lymphoid tissue lymphoma (dotted line). There was a significant difference in survival between the groups (p<0.001). Data were analyzed using the log-rank test.*

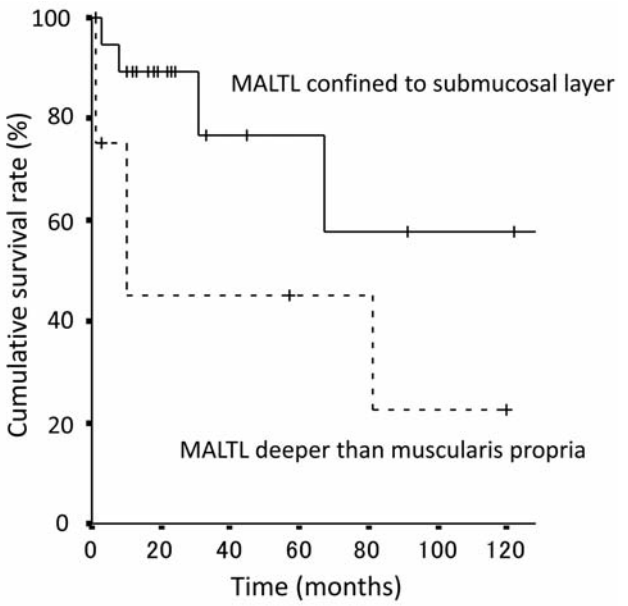

Figure 4. *Kaplan-Meier survival curves for 31 patients with synchronous gastric adenocarcinoma and mucosal-associated lymphoid tissue lymphoma (MALTL), with MALTL confined to the submucosal layer (solid line) and 15 patients with synchronous gastric adenocarcinoma and MALTL, with MALTL invading deeper than the muscularis propria. There was no significant difference in survival between the groups (p=0.061). Data were analyzed using the log-rank test.*

Table I. *Reported cases of synchronous gastric adenocarcinoma and gastric lymphoma.*

Author	Year	Age	Gender	Gastric adenocarcinoma				Gastric lymphoma				Treatment	Outcome
				Tumor location	Tumor size (cm)	Tumor depth	Histological type	Tumor location	Tumor size (cm)	Tumor depth	Histological type		
Kelly (6)	1994	85	Male	M, L	ND	ND	Intestinal	M, L	ND	ND	MALTL	BSC	DOD at 2 months
von Herbay (7)	1995	79	Female	M	ND	sm	Intestinal	M	8	mp	MALTL	Distal gastrectomy	ND
Wotherspoon (8)	1995	55	Female	A	ND	se	Diffuse	A	ND	sm	MALTL	ND	ND
		55	Female	M	ND	sm	Intestinal	M	4	se	MALTL	ND	ND
		ND	Male	ND	ND	se	Intestinal	ND	ND	se	MALTL	ND	ND
		60	Female	ND	ND	se	Intestinal	ND	ND	sm	MALTL	ND	ND
		34	Female	M	ND	se	Diffuse	ND	ND	se	MALTL	ND	ND
		67	Female	L	ND	m	Intestinal	ND	ND	sm	MALTL	ND	ND
		55	Female	ND	ND	sm	Intestinal	ND	ND	m	MALTL	ND	ND
		55	Female	L	ND	sm	Diffuse	ND	ND	se	MALTL	ND	ND
		69	Female	ND	ND	se	Intestinal	ND	ND	sm	MALTL	ND	ND
Greiner (9)	1996	65	Male	M	ND	ss	Diffuse	M	ND	sm	MALTL	Total gastrectomy	ND
Nishino (10)	1996	71	Male	U	ND	sm	Intestinal	U	7	si	DLBCL	Total gastrectomy	Alive at 120 months
Nakamura (3)	1997	27	Male	L	0.7	m	Intestinal	M	11	mp	MALTL	Distal gastrectomy	Alive at 57 months
		38	Male	M	0.7	sm	Diffuse	M	4	sm	MALTL	Distal gastrectomy	Alive at 45 months
		70	Male	L	1.2	m	Intestinal	M	8	mp	MALTL	Distal gastrectomy	DOD at 81 months
		72	Male	L	6	se	Intestinal	U	6	se	MALTL	Total gastrectomy	DOD at 1 month
		75	Female	L	1.6	m	Intestinal	U	3	sm	MALTL	Total gastrectomy	Alive at 13 months
		42	Male	M	4.5	sm	Diffuse	M	8	sm	IblL	Distal gastrectomy	Alive at 91 months
		47	Male	L	4	m	Diffuse	L	10	sm	MALTL	Distal gastrectomy	Alive at 24 months
		53	Male	M	0.9	sm	Intestinal	U	9	sm	MALTL	Total gastrectomy	DOD at 67 months
		67	Female	M	5.5	sm	Intestinal	U	9	sm	MALTL	Total gastrectomy	DOD at 31 months
		78	Male	U, M	15	se	Diffuse	U	6	se	TPSL	Total gastrectomy	DOD at 1 month
Hardman (11)	1997	56	Male	M	5.9	se	Diffuse	M	ND	mp	MALTL	Total gastrectomy	ND
Goteri (12)	1997	51	Male	M	2	m	Intestinal	M	2	sm	MALTL	Total gastrectomy	Alive at 122 months
		55	Female	U	7	sm	Diffuse	U	7	sm	MALTL	Total gastrectomy	Alive at 33 months
		80	Male	L	4	sm	Intestinal	L	4	sm	MALTL	Total gastrectomy	Alive at 12 months
		57	Male	L	3	sm	Intestinal	M, L, U	7.5	ss	MALTL	Total gastrectomy	DOD at 10 months
		53	Male	M	2.5	ss	Intestinal	U	2.5	sm	MALTL	Total gastrectomy	DOD at 3 months
		66	Male	U	ND	ss	Diffuse	U	ND	ss	MALTL	Total gastrectomy	DOD at 10 months
		69	Male	U	ND	ss	Diffuse	U	ND	sm	MALTL	Total gastrectomy	DOD at 8 months
		69	Male	M, L	8	ss	Diffuse	U	9	ss	MALTL	Total gastrectomy	Alive at 3 months
Ishihama (13)	1997	68	Male	U	2.2	sm	Diffuse	M	3	m	DSCL	Total gastrectomy	ND
		61	Male	L	ND	m	Intestinal	M	ND	m	DLBCL	Total gastrectomy	ND
		61	Female	M	1.5	m	Diffuse	L	ND	m	DLCL	Distal gastrectomy	DOD at 132 months
		62	Male	M	ND	m	Intestinal	M	ND	ND	DLBCL	Total gastrectomy	ND
Kanamoto (14)	1998	47	Male	L	3.5	m	Diffuse	L	10	sm	MALTL	Total gastrectomy	Alive at 24 months

*T*able I. *continued*

Table I. *continued*

Author	Year	Age	Gender	Gastric adenocarcinoma				Gastric lymphoma				Treatment	Outcome
				Tumor location	Tumor size (cm)	Tumor depth	Histological type	Tumor location	Tumor size (cm)	Tumor depth	Histological type		
Montalbàn (15)	1999	77	Male	ND	ND	ND	ND	ND	ND	ND	MALTL	Chemotherapy	DOD
		68	Female	ND	ND	ND	ND	ND	ND	ND	MALTL	Chemotherapy	DOD
Chan (16)	2001	71	Male	L	1	sm	Intestinal	L	1	m	MALTL	Distal gastrectomy	ND
		58	Female	L	6.5	sm	Diffuse	L	6.5	ND	MALTL	Distal gastrectomy	ND
		75	Female	L	ND	m	Diffuse	L	1	ND	MALTL	Distal gastrectomy	ND
Cammarota (17)	2001	47	Male	M	4	ss	Intestinal	M	4	sm	MALTL	Total gastrectomy	ND
Kaffes (18)	2002	78	Male	L	ND	sm	Diffuse	M, U	ND	ND	MALTL	Total gastrectomy	Alive at 20 months
Tang (19)	2002	72	Male	U	2.5	sm	Intestinal	M, U	ND	ND	MALTL	Proximal gastrectomy	Alive at 4 months
Sakai (20)	2003	51	Female	M	2.8	m	Intestinal	U	1.5	mp	MALTL	Total gastrectomy	ND
Suenaga (21)	2003	73	Male	M	2.3	mp	Intestinal	M	ND	m	MALTL	Distal gastrectomy	Multiple metastases at 23 months
Lee (22)	2005	54	Male	M	1	m	Diffuse	Multifocal	ND	sm	MALTL	Distal gastrectomy	Alive at 16 months
		60	Male	M	2.6	sm	Intestinal	Multifocal	ND	sm	MALTL	Total gastrectomy	Alive at 22 months
		62	Male	L	2	m	Intestinal	Multifocal	ND	sm	MALTL	Total gastrectomy	Alive at 18 months
		73	Male	M	2.6	m	Intestinal	M	3.1	sm	MALTL	Distal gastrectomy	Alive at 23 months
		48	Female	M	3.2	m	Diffuse	M	0.4	m	MALTL	Distal gastrectomy	Alive at 19 months
Chong (23)	2008	64	Male	U	1.5	sm	Intestinal	L	1.2	ND	MCL	Total gastrectomy	ND
Trovato (24)	2009	47	Male	L	0.3	m	Intestinal	U	ND	m	DLBCL	Distal gastrectomy	Alive at 10 months
Casas (25)	2011	81	Male	L	5.5	mp	Diffuse	L	6.5	ND	DLBCL	Total gastrectomy	Alive at 6 months
Hamabe (26)	2011	71	Male	U, L	5.5	sm	Intestinal	U, L	ND	ND	MALTL	Total gastrectomy	Alive at 24 months
Namikawa (5)	2014	61	Male	M, L	6	m	Intestinal	M	6.5	m	MALTL	Distal gastrectomy	Alive at 1 month

BSC, Best supportive care; DLBCL, diffuse large B-cell lymphoma; DLCL, diffuse lymphocytic cell-type lymphoma; DOD, dead of disease; DSCL, diffuse small cleaved-cell-type lymphoma; IblL, immunoblastic-type lymphoma; L, lower third of the stomach; M, middle third of the stomach; m, mucosa; MALTL, mucosa-associated lymphoid tissue lymphoma; MCL, mantle cell lymphoma; mp, muscularis propria; ND, not described; se, serosa; si, invasion of adjacent structures; sm, submucosa; ss, subserosa; TPSL, T-cell lymphoma of pleomorphic small cell-type lymphoma; U, upper third of the stomach.

Table II. *Clinical characteristics of intestinal- and diffuse-type gastric adenocarcinoma in cases of synchronous gastric adenocarcinoma and lymphoma.*

	Intestinal-type n=33	Diffuse-type n=22	*p*-Value
Age, median (range), years	63 (27-85)	57 (34-81)	0.248
Gender, n			0.475
Male	24	14	
Female	9	8	
Gastric adenocarcinoma size, median (range), cm	2.5 (0.3-6.0)	4.3 (0.7-15)	0.058
Gastric adenocarcinoma depth, n			0.132
m/sm	25	13	
mp/ss/se	7	9	
Gastric lymphoma size, median (range), cm	4.0 (1-11)	6.5 (0.4-10)	0.514
Gastric lymphoma depth, n			0.812
m/sm	19	12	
mp/ss/se	9	6	
Treatment, n			0.913
Total gastrectomy	17	11	
Distal gastrectomy	8	8	
Proximal gastrectomy	1	0	

m, Mucosa; mp, muscularis propria; se, serosa; sm, submucosa; ss, subserosa.

long-term complications of chronic *H. pylori* infection, which could, therefore, play a significant pathogenic role in the simultaneous development of both tumors (1-3). Although, traditionally, aggressive surgical resection was performed to treat gastric lymphoma, nowadays the first choice of treatment for *H. pylori* eradication is antibiotics, irrespective of *H. pylori* status or lymphoma stage because of the high rate of complete remission with such a strategy (27). Non-responders to *H. pylori* eradication are referred for radiation or chemotherapy and/or immunotherapy with anti-CD20 monoclonal antibodies. Surgery no longer plays a role in the therapy of gastric MALT lymphoma except for very rare complications such as perforation or bleeding that cannot be controlled endoscopically (27). However, regular follow-up endoscopy after remission from gastric lymphoma is still recommended to detect metachronous gastric cancer at an early stage (28).

While gastric lymphoma is usually treated non-surgically, the most effective therapy for gastric adenocarcinoma is surgical resection with lymphadenectomy, which remains the only curative therapy. In particular, the outcome of patients with EGC after curative surgery is excellent, with 5-year survival rates of more than 90% (29). Endoscopic submucosal dissection is widely-accepted as the standard treatment for EGC without lymph node metastasis enabling the clinician to resect a target lesion *en bloc*. Although there were no patients treated by endoscopic submucosal dissection in the present study, hereafter, it might be an optional treatment for patients with synchronous tumors in cases of oncological agreement. However, in the case of

Table III. *Clinical characteristics of patients with synchronous gastric adenocarcinoma and mucosal-associated lymphoid tissue lymphoma.*

Characteristics	5-year survival rate (%)	Median survival time (months)	*p*-Value
Overall	69.0	81	
Age group, years			0.098
<62	86.7	NR	
≥62	46.3	31	
Gender			0.470
Male	73.7	81	
Female	66.7	NR	
Gastric adenocarcinoma size (cm)			0.502
<2.7	65.7	67	
≥2.7	76.0	NR	
Gastric lymphoma size (cm)			0.374
<6.0	85.7	NR	
≥6.0	66.9	81	
Gastric adenocarcinoma tumor depth			<0.001
Mucosal or submucosal layer	86.1	NR	
Deeper than muscularis propria	0	8	
Gastric lymphoma tumor depth			0.061
Mucosal or submucosal layer	77.1	NR	
Deeper than muscularis propria	45.0	10	
Histological type			0.502
Intestinal-type	65.7	67	
Diffuse-type	76.0	NR	
Type of surgery			0.035
Total gastrectomy	54.4	67	
Distal gastrectomy	100.0	NR	

NR, not reached.

superficial spreading-type EGC, as in our patient, a curative approach requires appropriate extensive lymph node dissection and wide surgical resection (5,30).

In the present study, 66.7% (38 of 57) of patients with synchronous gastric adenocarcinoma and malignant lymphoma had EGC, and 82.5% (47 of 57) of patients had MALT lymphoma; these rates were remarkably high. In addition, the lymphomas were significantly larger than the adenocarcinomas found synchronously occurring. A previous report of 30 patients with metachronous gastric adenocarcinoma and lymphoma described lymphomas as the first-detected malignancy in 28 patients, with only 2 cases diagnosed with lymphoma after the treatment of gastric adenocarcinoma had begun . Taken together with our results, this suggests that lymphomas might develop before adenocarcinomas or that the presence of MALT lymphoma might increase the risk of developing gastric carcinoma. It is not clear whether the risk of MALT lymphoma increases in patients with gastric carcinoma.

Distal or total gastrectomy is performed for synchronous tumors depending on the tumor location. As the results of the present study show, the median survival period of patients undergoing total gastrectomy is significantly worse than those undergoing only distal gastrectomy. Previous analysis of the Japanese national registry data including 14,394 patients with gastric cancer showed that the 5-year survival rate was 77.7% for distal gastrectomy and 51.9% for total gastrectomy. These data suggest the survival period for all patients with gastric cancer undergoing total gastrectomy is shorter than for those undergoing distal gastrectomy, regardless of whether they have synchronous tumors.

The limitations of the present study include the errors and biases inherent in a small retrospective study design. Another limitation is the lack of consistency within the study for treatment following recurrence of the disease, as the choice of treatment for each case was made independently by each physician. Since the prognosis for patients with gastric carcinoma and lymphoma is gradually improving, it is likely that these tumors will be encountered simultaneously more frequently in the future. For this reason, special attention should be paid to the possibility of the simultaneous occurrence of both tumors during diagnosis or follow-up for each type of tumor.

In conclusion, the current study indicated that the prognosis for synchronous gastric adenocarcinoma and lymphoma might depend more on the behavior of the adenocarcinoma than on the lymphoma. Therefore, the therapeutic outcome and strategy for this disease would depend on the status of the adenocarcinoma.

Conflicts of Interest

The Authors declare no conflicts of interest.

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