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REVIEW

Synchronous and metachronous occurrence of gastric adenocarcinoma and gastric lymphoma: A review of the literature

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Abstract

The occurrence of both primary gastric lymphoma and gastric adenocarcinoma in the same patient is a rare entity. The possible causative factors of synchronous or metachronous occurrence of both malignancies and varieties in the treatment modalities are reviewed according to published cases in English language medical literature.

Key words: Gastric adenocarcinoma; Gastric lymphoma; Synchronous occurrence; Metachronous occurrence

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INTRODUCTION

Secondary malignancies associated with Hodgkin's or non-Hodgkin's lymphoma are commonly detected in relation with the improvement in overall survival rate of these patients. The most common type of secondary malignancy seen with lymphoma is acute myelogenous leukemia, however, epithelial malignancies are also reported[1-3]. Intensive radiotherapy and chemotherapy administered to these patients have raised questions about the long-term effects of these therapeutic modalities on the development of secondary malignancies. Primary gastric lymphoma is a relatively uncommon malignancy, occurring in only 1%-7% of all malignant neoplasms of the stomach[4]. The occurrence of both primary gastric lymphoma and gastric adenocarcinoma in the same patient is a rare entity. We review the possible causative factors of synchronous or metachronous occurrence of both malignancies and varieties in the treatment modalities according to published cases in English language medical literature.

INCIDENCE

Since the first description of multiple gastric cancers by *Barth* in 1855[5], case reports of benign and malignant multiple primary tumors have been appearing with an increasing frequency. The incidence of multiple simultaneous gastric cancers is high, ranging from 3.4% to 67.4%[6]. In the first published case series in Germany, authors did not mention the incidence of simultaneous occurrence of malignant lymphoma and adenocarcinoma in the stomach[7]. Thereafter, case series from Japan appeared in the literature. Kasahara *et al*[8] reviewed data of 35 Japanese patients without giving incidence rate for synchronous occurrence. Noda *et al*[9] found an association of both tumors in 2 of 2438 (0.08%) gastric carcinoma cases. The incidence of simultaneous occurrence was 3.7% (9/247) in primary gastric lymphomas and 0.098% (9/9150) in gastric carcinomas in series by Nakamura *et al*[10]. Despite definite expression of incidence rate for synchronous cases, the incidence of metachronous occurrence of both tumors has not been mentioned in the literature.

SYNCHRONOUS CASES

Since the first case reported by Rabinovitch *et al*[11], 56 cases of synchronous occurrence of gastric adenocarcinoma and lymphoma have been published in English language medical literature[7-31]. Majority of these reports included detailed analysis of histopathologic features of tumors instead of clinical follow-up of patients. Basic characteristics of the patients are summarized on Table 1. Twenty-three cases were from the Eastern and 33 cases were from the Western countries. The overall median age was 66 (range 27-85) years. The median age for the Eastern population was 67 and for the Western population was 72 years. Male predominance was observed in both the Western (1.75:1) and the Eastern (3:1) populations. Overall, 62.5% of patients had early gastric carcinoma (EGC) and 30.4% of pa-

Table 1 Synchronous cases reported in the literature

Reference	Age/sex	Lymphoma type	*H pylori*	Adenocarcinoma type	Therapy	Survival months
Rabinovitch[11]	64/m	Lymphosarcoma	NM	EGC	S. gastrectomy	NM
Jernstrom[12]	72/f	Lymphocytic lymphosarcoma	NM	AGC, I, W	S. gastrectomy and 750 R radiotherapy	10
Manier[13]	65/m	Histiocytic	NM	EGC, P	T. gastrectomy and chemotherapy	24
	72/m	Histiocytic	NM	AGC, P	T. gastrectomy	1.5
Lin[14]	56/m	Diffuse lymphocytic	NM	EGC, W	T. gastrectomy and 4500 cGy Co60 radiotherapy	24
Kane[15]	74/m	Diffuse lymphocytic	NM	EGC, P	S. gastrectomy, radiotherapy and chemotherapy	12
Planker[7]	65/m	Immunocytoma	NM	EGC, I, M	T. gastrectomy, splenectomy and 4000 cGy Co60 radiotherapy	30
Czerniak[16]	74/m	Mix type	NM	EGC, W,	S. gastrectomy, radiotherapy and chemotherapy	12
Kasahara[8]	77/m	Small cleaved	NM	AGC, W	S. gastrectomy	24
Noda[9]	61/m	Diffuse large cell	NM	EGC, W	T. gastrectomy and chemotherapy	9
Akosa[17]	79/m	MALT, LG	NM	EGC, M	No treatment	NM
Kelly[18]	85/m	MALT, LG	+	?, I, M	No treatment	2
Von Herbay[19]	79/f	MALT, LG + HG	+	EGC, I, W	T. gastrectomy	
Wotherspoon[20]	55/f	MALT, LG	+	AGC, P	NM	NM
	55/f	MALT, LG + HG	+	EGC, W	NM	NM
	NM/m	MALT, LG	-	AGC, W	NM	NM
	60/f	MALT, LG	+	AGC, W	NM	NM
	34/f	MALT, LG	+	AGC, P	NM	NM
	67/f	MALT, LG	+	EGC, W	NM	NM
	55/f	MALT, LG	+	EGC, W	NM	NM
	55/f	MALT, LG	-	EGC, P	NM	NM
	69/f	MALT, LG	+	AGC, W	NM	NM
Nishino[21]	71/m	Diffuse, large cell type	NM	EGC, tubular type, W	T. gastrectomy, splenectomy and cyclophosphamide, oncovin, prednisolone chemotherapy	120
Hardman[22]	56/m	MALT, LG	+	AGC, Signet-ring cell, P	T. gastrectomy and etoposide, cisplatin, adriamycin chemotherapy	NM
Nakamura[10]	27/m	MALT, LG	+	EGC, I, W	NM	57
	38/m	MALT, LG	+	EGC, D, P	NM	45
	70/m	MALT, HG	+	EGC, I, W	NM	81
	72/m	MALT, LG	+	AGC, I, W	NM	1
	75/f	MALT, LG	+	EGC, I, W	NM	13
	53/m	MALT, LG	+	EGC, I, W	NM	67
	67/f	MALT,LG	+	EGC, I, W	NM	31
	42/m	Immunoblastic	+	EGC, D, P	NM	91
	47/m	MALT, LG	+	EGC, D, P	NM	24
	78/m	T-cell pleomorphic	+	AGC, D, P	NM	1
Ishihama[23]	68/m	Diffuse, small cleaved	+	EGC, W	T. gastrectomy	NM
	61/m	Diffuse, large cell	+	EGC, P	T. gastrectomy	NM
	61/f	Diffuse, lymphocytic	+	EGC, P	S. gastrectomy	132
	77/m	Diffuse, large cell	+	EGC, W	Vincristine,endoxanpredonine, adriamicin chemotherapy and endoscopic mucosectomy	NM
Goteri[24]	51/M	MALT, LG + HG	+	EGC, I, W	NM	122
	55/f	MALT, LG	+	EGC, D, P	NM	33
	80/m	MALT, LG	-	EGC, I, W	NM	12
	57/m	MALT, LG	+	EGC, I, W	NM	10
	53/m	MALT, LG	+	AGC, I, W	NM	3
	66/m	MALT, LG	-	AGC, D, P	NM	10
	69/m	MALT, LG	-	AGC, D, P	NM	8
	69/m	MALT, LG	-	AGC, M, M	NM	3
Kanamoto[25]	47/m	MALT, LG	+	EGC, D, P	T. gastrectomy	24
Montalban[26]	77/m	MALT, LG	NM	GC	NM	NM
	68/f	MALT, HG	NM	GC	NM	NM
Cammarota[27]	47/m	MALT, LG	+	AGC, I, P	Etoposide, epirubicin, cisplatin chemotherapy and T. gastrectomy	NM
Chan[28]	71/m	MALT, LG	-	EGC, P	S. gastrectomy	NM
	58/f	MALT, HG	+	EGC, P	S. gastrectomy	NM
	75/f	MALT, HG	+	EGC, P	S. gastrectomy	NM
Kafes[29]	78/m	MALT, NM	+	EGC, I, P + stromal tumor	T. gastrectomy	20
Sakai[30]	51/f	MALT, LG	+	EGC, tubular, M	T. gastrectomy	NM
Suenaga[31]	73/m	MALT, LG	-	AGC, I, W	S. gastrectomy, D3 dissection	23

m: male, f: female, NM: not mentioned, EGC: early gastric carcinoma, AGC: advanced gastric carcinoma, GC: gastric carcinoma, I: intestinal type, D: diffuse type, W: well differentiated, P: poor differentiated, M: moderately differentiated, MALT: mucosa-associated lymphoid tissue, HG: high grade, LG: low grade, S. gastrectomy: subtotal gastrectomy, T. gastrectomy: total gastrectomy.

tients had advanced gastric carcinoma (AGC), the type of gastric carcinoma was undefined in the rest of the patients. EGC constituted a majority of the Eastern cases (82%), whereas 48% of cases were from the Western countries. Before the report by Kelly *et al*[18] in 1994, the presence of *H pylori* was not mentioned by the authors. Since then, reported *H pylori* infection rate reached 79%. The infection rate in the East (86%) was higher than that in the West (72%). The prevalence of *H pylori* was higher in EGC (86%) than that in AGC (64%). There was no significant correlation between the prevalence of *H pylori* and the differentiation of adenocarcinoma. The declared results of adenocarcinoma histopathology were not uniform in relation to the variations in the classification systems used by the authors. However, differentiation of the tumor was clearly revealed by all authors. Poor and well differentiated adenocarcinomas showed an equal distribution in the Eastern (43.5% and 52%, respectively) and the Western cases (42% and 42%, respectively).

Majority of the lymphomas were MALT (mucosa-associated lymphoid tissue) type lymphoma (69.6%) and low grade one (87.2%). The association of *H pylori* with MALToma was 86% in the Eastern cases and 72% in the Western cases. Six of 7 (86%) patients with other types of gastric lymphoma associated with gastric adenocarcinoma were *H pylori*-positive. There was no data about the size of the tumor found in 32% of the cases. The size of the lymphoma was larger than carcinoma in 57% of cases. Overall, lymph node metastasis was found in 41% of the cases. In patients with early carcinoma and positive lymph node metastasis, the origin of metastatic lymph node was usually lymphoma (89%). In the presence of advanced carcinoma, metastases originated from the adenocarcinoma, either alone or in combination with the lymphoma. The topographic interrelation of both tumors was also revealed in the reports (n = 53/56). Majority of the cases (n = 29, 54.7%) had independent tumors. There was no significant difference between the Eastern and the Western cases in this respect. Collision of both tumors was reported in 14 (26.4%) cases. There were 4 cases with contiguous and 5 cases with intermingling tumors.

METACHRONOUS CASES

In contrast to synchronous occurrence of gastric adenocarcinoma and lymphoma, majority of cases (90%, 27/30) with metachronous occurrence of both tumors were reported from the Western countries[10,32-47]. In 1950, McNeer *et al*[32] published the first case in the literature. The features of the 30 patients are summarized in Table 2. The median age was 50 (8-82) years. Of these patients, 18 were male and 12 were female. Previously detected malignancy in 28 patients was lymphoma. Only 2 cases reported by Nakamura *et al*[10] were diagnosed as lymphoma after the treatment of gastric adenocarcinoma. One of these tumors developed in the remnant stomach in the 7th year after subtotal gastrectomy and the other developed in the 13th month after endoscopic mucosal resection. Rest of the patients suffered from various types of lymphoma previously. Leading type of lymphoma was MALT lymphoma (30%), followed by large cell lymphoma (20%). The existence of *H pylori* was not mentioned in the reports published before 1997. Thereafter, 9 of 10 reported cases were found infected with *H pylori*. Median interval between the treatment of lymphoma and the diagnosis of gastric adenocarcinoma was 90 (6-408) mo. The reported interval after the treatment of MALToma (median 27, range 6-108 mo) was shorter than the other types of lymphoma (median 120, range 42-408 mo). Adequate description of histopathology of adenocarcinoma was determined in 26 of 30 cases. After the latent period, majority of cases suffered from advanced gastric adenocarcinomas (65%) and 9 patients had EGC.

PATHOLOGIC ASPECTS OF SYNCHRONOUS OCCURRENCE

The relation of both tumors in the stomach was classified in four categories: (1) separate tumors; (2) collision tumor; (3) contagious tumor, without any intermingling between malignant components; and (4) intermingling (admixture) of both tumors. Histological classification of gastric lymphomas is based on systems originally designed for nodal lymphomas as Musshoff modification of the Ann Arbor staging system, Working formulation or Kiel classification. However, these are not optimal for the documentation of specific relevant features of primary extranodal lymphoma in the gastrointestinal tract. Several modifications on TNM staging system and alternatives have been proposed[48,49]. Recently, the European Gastro-Intestinal Lymphoma Study Group (EGILS) proposed a new modification of TNM staging system for the gastric lymphomas[50]. In 1983, the histologic relationship of extranodal B-cell lymphomas and MALToma was recognized by Isaacson and Wright, and classification as a separate entity of MALT-NHL was proposed - the MALT lymphoma concept[51,52]. However, the first report of synchronous occurrence of MALToma with gastric adenocarcinoma appeared in the literature in 1990. Metachronous occurrence of MALToma was reported at the end of 1990's. Therefore, it is easily speculated that authors are affected by the classification systems for nodal lymphomas before 1990.

Histopathological disorders of gastric mucosa are not specific for any neoplasm, but intestinal-type adenocarcinomas frequently showed atrophy, intestinal metaplasia, and not uncommonly, dysplasia of the surrounding non-neoplastic gastric mucosa. Diffuse-type adenocarcinomas did not frequently show such lesions. Primary lymphomas displayed expansive lymphoid follicles and also a high percentage of atrophy and intestinal metaplasia of the surrounding gastric mucosa[53]. In addition to the similar histopathological findings in the surrounding gastric mucosa of intestinal-type adenocarcinoma and primary gastric lymphoma, lymphocytic gastritis was found more frequently in patients with gastric carcinoma and primary gastric lymphoma than in unselected patients undergoing endoscopy[54]. This finding suggests that these two disparate gastric tumors may share an immunological dysfunction or a common pathogenesis. Zamboni *et al*[55] pointed out that foveolar lymphoepithelial lesions or signet-ring cells were found in 37% of MALT lymphomas. Like in MALT

Table 2 Metachronous cases reported in the literature

Reference	Age/sex	Lymphoma type	Lymphoma therapy	Interval	Adenocarcinoma therapy
McNeer[32]	27/f	Reticulum cell sarcoma	S. gastrectomy; radiotherapy for local recurrence	6.5 yr	T. gastrectomy
Fleischer and Walker[33]	61/m	Lymphosarcoma	S. gastrectomy; 4000 cGy	5 yr	Supportive treatment
Bockus[34]	49/m	Lymphosarcoma	Radiotherapy	3.5 yr	T. gastrectomy
Komarov[35]	40/m	Round cell sarcoma	S. gastrectomy	19 yr	NM
Morgenstern[36]	46/f	Reticulum cell sarcoma	S. gastrectomy	25 yr	Resection
Ettinger and Carter[37]	55/m	Lymphosarcoma	S. gastrectomy; 2000-2600 cGy	16 yr	Palliative surgery
Shani[38]	47/m	Reticulum cell sarcoma	S. gastrectomy	31 yr	Resection
	29/m	Diffuse, poorly differentiated lymphocytic	S. gastrectomy; orthovoltage for whole abdomen (6 d)	34 yr	Exploration
	51/f	Diffuse, mixed lymphocytic histiocytic	S. gastrectomy; 1800 cGy X-R + 2000 cGy Co 60. [1]2030 cGy for recurrence (16 yr later)	16 yr	Exploration
	48/m	Diffuse, poorly differentiated lymphocytic	S. gastrectomy; 3000 cGy.	10 yr	Exploration; combined chemotherapy
Sellin[39]	45/m	Diffuse, large cleaved cell	2300 cGy; S. gastrectomy; 4000 cGy (4 yr later)	13 yr	Total gastrectomy
Brumback[40]	8/m	Diffuse undifferentiated (small noncleaved)	S. gastrectomy; cyclophosphamide, vincristine, prednisolone for 1 mo; 4075 cGy; 6-mercaptopurine, vincristine, prednisolone, methotrexate for 3 yr	6 yr	Gastrojejunal bypass; 5-FU, doxorubicine, mitomycin chemotherapy
	15/m	Hodgkin's disease, nodular sclerosis type	3500 cGy to upper abdomen; 2000 cGy to left axillary-cervical-supraclavicular; cyclophosphamide, vincristine, procarbazine, prednisolone, adriamycin for 2 yr	10 yr	NM
Baron[41]	58/m	Diffuse large cell	3150 cGy to upper abdomen	10 yr	S. gastrectomy
	24/f	Reticulum cell sarcoma	S. gastrectomy; 4000 cGy	15 yr	No treatment
	60/m	Diffuse large cell	S. gastrectomy; cyclophosphamide, vincristine, prednisolone, doxorubicin chemotherapy	4 yr	T. gastrectomy and S. esophagectomy
	56/m	Well differentiated lymphocytic	S. gastrectomy; 3700 cGy; oral cyclophosphamide chemotherapy	12 yr	T. gastrectomy
Zorlu[42]	43/m	Diffuse, large cleaved cell	S. gastrectomy; cyclophosphamide, vincristine, prednisolone (2 courses); 4500 cGy; cyclophosphamide, vincristine, prednisolone (4 courses)	8 yr	Near total gastrectomy; 5-FU, mitomycin
	35/f	Diffuse, large cleaved cell	S. gastrectomy; 4000 cGy; cyclophosphamide, vincristine, prednisolone (6 courses)	8 yr	T. gastrectomy
Nakamura[10][1]	69/f	Immunoblastic	NM	7 yr	S.gastrectomy
	82/f	MALT, HG	NM	13 mo	Endoscopic mucosal resection
Zauber[43]	78/f	Large cleaved cell	S. gastrectomy; 4500 cGy; i.v. cyclophosphamide chemotherapy (9 courses)	4 yr	T. gastrectomy
Montalban[26]	42/m	MALT	Cyclophosphamide, doxorubicin, vincristine, prednisone	108 mo	NM
Hasegawa[44]	72/f	MALT	Antibiotic therapy for *H pylori*	6 mo	S. gastrectomy
Morgner[45]	74/m	MALT, LG	Antibiotic therapy for *H pylori*	4 yr	Endoscopic mucosal resection
	70/m	MALT, LG	Antibiotic therapy for *H pylori*	5 yr	Endoscopic mucosal resection and argon plasma coagulation
	77/f	MALT, LG	Antibiotic therapy for *H pylori*	4 yr	Endoscopic mucosal resection
Ghosdal[46]	32/m	MALT, LG	S. gastrectomy; Antibiotic therapy for H pylori (for 2 wk);	15 mo	No treatment
Raderer[47]	67/f	MALT	Antibiotic therapy for *H pylori* (for 9 mo)	9 mo	S. gastrectomy
	61/f	MALT	Antibiotic therapy for *H pylori* (for 14 mo); 2CdA chemotherapy (4 courses)	27 mo	S. gastrectomy

m: male, f: female, NM: not mentioned, MALT: mucosa-associated lymphoid tissue, HG: high grade, LG: low grade, S. gastrectomy: subtotal gastrectomy, T. gastrectomy: total gastrectomy, [1]Only 2 cases reported by Nakamura *et al* were diagnosed as lymphoma after the treatment of gastric adenocarcinoma.

lymphomas, gastric carcinomas are invariably accompanied by lymphoid proliferations ranging from reactive lymphoid follicles to MALT lymphomas[56]. These observations also supplied the theory of common pathogenesis of MALT-type lymphoma and gastric carcinoma.

The incidence of early gastric carcinoma in synchronous tumors was remarkably high. Especially in the Eastern countries, routine screening for gastric carcinoma is practiced, and up to about 50% of gastric carcinoma diagnosed in the early stage[57]. This observation, together

with the finding that most lymphomas were larger than adenocarcinomas, suggested that lymphomas might develop before adenocarcinomas or that the presence of MALT lymphoma might increase the risk of developing gastric carcinoma.

ETIOLOGIC FACTORS OF SYNCHRONOUS OCCURRENCE

H pylori

It is tempting to hypothesize that *H pylori* is a common etiological agent for synchronous occurrence of gastric adenocarcinoma and primary gastric lymphoma. Since 1994, the existence of *H pylori* has been investigated in almost every report. In the present analysis, in areas with high prevalence (Eastern) and low prevalence (Western) of *H pylori*, synchronous tumors are associated with *H pylori* infection rates of 86% and 72%, respectively, and are similar to or higher than the reported infection rates of isolated gastric adenocarcinoma and isolated MALT lymphoma or other primary gastric non-hodgkin lymphoma[20,58-60]. Therefore, *H pylori* may have an important etiological role for synchronous tumors in both high and low prevalence areas.

H pylori plays a key role in the natural history of gastric MALT lymphoma, representing an example of antigen-mediated tissue stimulation and lymphoproliferation, with possible subsequent lymphomagenesis[58,61]. Antigenic mimicry between *H pylori* and the host mucosa was held responsible for inducing autoimmune responses which lead to development of the disease[62,63]. Kawahara *et al*[64] found that the increase of antibody titers to HCG-27 cells in *H pylori*-positive patients with MALT lymphoma compared to titers in patients with other gastroduodenal diseases and in healthy subjects. Lymphoid follicles which are not present in the normal stomach show development in the setting of chronic gastritis. Genta *et al*[65] have observed a strong correlation between follicular gastritis and *H pylori* infection. Wotherspoo*n et al*[58] suggested that *H pylori* might trigger the acquisition of MALT in the gastric mucosa, and this lymphoid tissue is thought to harbor the precursor cells in MALT-NHL. These precursor cells change gradually into malignant lymphoma cells with autonomous and uncontrolled growth by accumulation of genetic alterations such as mutations, deletions, and amplifications. *In vitro* experiments have demonstrated that in the earlier phases of development, the growth of genetically altered lymphoid cell is not yet fully autonomous, and proliferation partly depends on *H pylori*-related proteins and T cells[66-69]. On the other hand, *H pylori* infection has been linked to the intestinal-type gastric adenocarcinoma through a chain of events that starts as acute gastritis and progresses to chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and eventually, adenocarcinoma formation[70,71]. A recent meta-analysis has revealed that *H pylori* infection is associated with a 2-fold increase in developing gastric adenocarcinoma[72]. These epidemiologic and pathologic data about the relation of *H pylori* infection with gastric adenocarcinoma and primary gastric lymphoma are supported by a recent genetic study[73]. *H pylori* genotyping on archived gastric tissue revealed that *H pylori* strains with certain combinations of virulence subtypes are associated with gastric carcinoma or MALT lymphoma. Thus, the virulence subtype composition vacA s1a and iceA1 occurs mainly in gastric carcinoma, whereas the vacA s1t/m2 iceA1 combination is found in MALT lymphoma[73]. Therefore, in the future studies, the composition of virulence subtypes might be taken into account during the evaluation of possible sequelae of gastric mucosal damage caused by *H pylori* infection.

Epstein-Barr virus

Studies of Epstein-Barr virus (EBV) suggest that an aberrant antibody response to infection may occur years before the appearance of a tumor[74]. The frequency of EBV detection has been reported to be 6%-18% in gastric lymphomas[75-77] and 7%-16% in ordinary gastric adenocarcinomas without lymphoid stroma[78-80]. Whether EBV plays a pathogenic role in either of these tumors is still unclear[81]. Although any mechanism related to EBV in tumorigenesis of gastric malignancies remains highly speculative, it has been demonstrated that there is a delay in apoptosis in EBV-positive gastric carcinomas (associated with up-regulation of BCL-2 and p53) and a decrease in cellular differentiation (associated with decreased E-cadherin expression)[82]. Nakamura *et al*[10] found no specific association between EBV infection and these double malignancies.

Exposure to atomic blast

It is controversial whether the incidence of gastric carcinoma is higher in persons exposed to an atomic blast in comparison to non-exposed subjects[83-85], but Suehiro *et al*[83] suggested that the incidence is the highest in persons exposed within a 2.0-Km radius ground zero. The relation of primary gastric lymphoma and atomic bomb exposure is under debate. Recently, t (11; 18) (q21; q21) and t (1;14) (p22; q32) translocations have been reported to be associated with MALT-type lymphoma. The former translocation results in the formation of fusion protein API2-MALT1, and the latter in the fusion protein pf BCL10 and IgH. These fusion transcripts are thought to be molecular markers for MALT-type lymphoma not responding to *H pylori* eradication and highly correlated with aberrant nuclear BCL10 expression, which may serve as a screening tool for fusion[86-88]. These investigations support the etiologic role of atomic bomb blast on the formation of MALT-type lymphoma.

ETIOLOGIC FACTORS OF METACHRONOUS OCCURRENCE

Epithelial malignancies, the common cancers of adulthood, are detected rarely in the post-treatment course of Hodgkin's disease and other lymphomas[2,3,26]. However, Greene and Wilson[88,89] observed a significant increase in the incidence of gastric carcinoma in the period following the treatment of non-Hodgkin lymphomas.

Previous gastric surgery

Previous gastric surgery is a well known precancerous con-

dition[90,91]. Gastroesophageal reflux and gastritis, formation of nitrosamines due to gastric pH decrease and untreated *H pylori* infection may play a role in carcinogenesis of the gastric remnant[92]. So-called "stump carcinoma" develops between 13-27 years after resection in patients treated with gastrectomy for benign conditions[91].

Radiotherapy and chemotherapy

Though the stomach is considered relatively radio-resistant compared to other parts of the gastrointestinal tract, side effects and complications progressively increased when the total dosage delivered was above 4500 cGy[93,94]. The effects of radiotherapy on the risk of carcinogenesis are well known[95]. Hirose *et al*[96] demonstrated that localized radiation induced gastric adenocarcinoma development in an experimental model. Brown *et al*[97] reported a slight increase in the incidence of gastric adenocarcinoma in patients with ankylosing spondylitis under radiation therapy. In contrast, when the relatively low dose (less than 3400 cGy) radiotherapy was used to decrease acid production in 2049 peptic ulcer patients, only two cases of leiomyosarcoma were reported. The elapsed time between radiotherapy and the diagnosis of these cases were reported as 14 and 26 years[98].

Both series reported by Stanford and Milan concluded that combined administration of chemotherapy and radiotherapy increases the occurrence rate of secondary malignancies[1,2]. In these series, the most common secondary malignancy was especially acute myelogenous leukemia. Its occurrence was associated with the administration of alkylating agents (nitrogen mustard, vincristine, prednisone, and procarbazine in Milan series)[2]. Solid tumors were commonly associated with radiation therapy[1,2]. Brumback *et al*[40] concluded that secondary gastric adenocarcinoma occurred in one of these cases probably due to oral administration of procarbazine for Hodgkin's disease. In addition to these factors, *H pylori* infection was also held accountable for metachronous occurrence of both tumors, as discussed above.

DIFFICULTIES IN DIAGNOSIS

It may be difficult to diagnose the two different tumors in the stomach before surgery. Because most of the patients with gastric adenocarcinoma and coexisting primary gastric lymphoma are associated with *H pylori* infection, the presence of MALT-type or other types of primary gastric lymphoma should be taken into consideration when gastric adenocarcinoma with gastritis is detected on endoscopy. In surgical specimens, not only the lesions of adenocarcinoma but also the background mucosa of cancerous lesions must be examined with regard to infiltration of lymphocytes, and the presence of gastritis, as well as the presence of *H pylori*. Signet-ring cells around MALT lymphomas or lymphoid proliferations around gastric adenocarcinomas should be kept in mind against over-diagnosis during the histopathological examination. Considering the metachronous occurrence of gastric adenocarcinoma and gastric lymphoma, proper endoscopic follow-up should be performed in the remnant stomach, especially when *H pylori* infection is present.

TREATMENT

Treatment modalities for synchronous cases

Treatment of synchronous cases is generally applied according to the presence of adenocarcinoma. Distal or total gastrectomy is performed depending on the tumor localization. Preoperative chemotherapy was preferred only in two cases. Cammarota *et al*[27] decided to administer etoposide, epirubicin, cisplatin chemotherapy according to the presence of locally advanced tumor stage (T3 N1) in laparoscopic exploration. Older patients in the series by Ishihama *et al*[23] were exposed to 10 courses of vincristine, endoxan, predonisdone, adriamicin chemotherapy and endoscopic resection of the tumor. Postoperative chemotherapy was administered only to 6 (10.7%) patients.

Treatment modalities for metachronous cases

Eight of thirty patients underwent subtotal gastrectomy and radiotherapy against lymphoma. Chemotherapy was administered in different combinations with other treatment modalities in 7 patients. Two patients were treated by only chemotherapy. Radiotherapy was performed solely in 2 patients. Overall, 10 cases with lymphoma were treated without surgical treatment. All patients with MALToma were treated with antibiotic regimen against *H pylori*, except cases reported by Nakamura *et al*[10] *and* Montalban *et al*[26], the authors of both did not mention anything about the treatment of *H pylori* infection in their reports. Every patient with *H pylori* infection was eradicated and no one was re-infected or re-colonized during the follow-up period. Except cases with widespread metastasis, total gastrectomy or palliative resections were performed in patients with AGC. Patients with EGC were exposed to more conservative surgery, such as endoscopic mucosal resection[10,45].

Surgery

Clear guidelines for management have not been designed for synchronous adenocarcinoma and primary gastric lymphoma. Traditionally, aggressive surgical resection has been the mainstay of gastric lymphoma treatment because by this treatment modality it would be possible to collect definitive tissues for pathologic examination, allow exploration of the abdomen, reduce the tumor burden and obviate the concern that gastric hemorrhage or perforation would complicate medical treatment of lymphomas. Recently, radical gastrectomy is disputed and considered unnecessary for gastric lymphomas. Lesser procedures are now accepted where resection of the gross disease and involved lymph nodes will provide adequate results[99-102]. Some authors advocate wide resection and extensive lymph node dissection alone for adequate treatment of stage 1E or pure MALT lymphomas with a survival rate of > 95%[103,104]. In a retrospective study from Italy patients in different stages of gastric lymphoma who underwent surgical resection when feasible, the ten-year actuarial survival rates were markedly higher (100% and 80%, respectively) for stage IE and IIE as compared with stage IIIE and IVE (21% and 0%, respectively)[105]. Surgical resection with clear margins for lymphoma is advised in order to maximize the chance of cure[100,106]. However, others have found no difference in survival, whether the margin of resection was

clear or not, as long as post-operative chemotherapy was given[107]. Operative mortality rates for gastric lymphoma reached 25% in cases with advanced tumor stage[108]. Therefore, aggressive surgery for gastric lymphoma is not indicated due to increased morbidity which outweighs the benefit gained in terms of survival[107]. Surgery for gastric lymphoma is now often reserved for patients with localized disease, residual disease after non-surgical therapy or for rare patients with complications[109]. If the coexisting adenocarcinoma is diagnosed correctly, surgical treatment, a first-line therapy, is preferred according to adenocarcinoma treatment principles. Total or subtotal gastrectomy with D1 or D2 dissection must be performed.

In metachronous cases, generally, the occurrence of primary gastric lymphoma precedes gastric adenocarcinoma, resection of the remnant stomach must be done with or without a combination of other treatment modalities. However, a close follow-up of the patients undergoing gastric lymphoma treatment allows early detection of carcinogenesis. Limited endoscopic resections might be an alternative treatment for these cases. Similar to gastric lymphoma as a previous malignancy, patients in whom limited resection is performed for gastric adenocarcinoma should undergo a close endoscopic follow-up. The *H pylori* status with histopathologic alterations in the resected stomach and in the remnant stomach must be detected and followed up for early detection of metachronous occurrence of gastric lymphoma.

Chemotherapy

The effect of chemotherapy as a sole treatment for gastric lymphomas is still under debate. The needs behind trying chemotherapy were the considerable morbidity and mortality associated with resection[108]. Some authors reported better survival rates in patients with primary gastric lymphoma treated by chemotherapy alone or combination with radiotherapy when compared to surgical treatment alone[110,111]. Other reports showed no apparent difference in survival between patients treated by chemotherapy or surgery and chemotherapy with survival rates of 67% and 60%, respectively. The fear of chemotherapy-related complications, for instance, bleeding and perforation, has been disputed, and less significant compared with surgical resection[111,112]. Therefore, chemotherapy has been suggested and adopted as a primary mode of treatment for primary gastric lymphomas. Whereas cyclophoshamide, vincristine and prednisolone were adopted for low grade lymphomas, high grade tumors were treated with doxurubicin, teniposide, cyclophosphamide and prednisolone. The combination of both regimens with surgical resection has increased the survival rates up to 80% and 100%, respectively[113]. In contrast to primary gastric lymphomas, chemotherapy regimens have not been used as a sole therapy in the treatment of gastric adenocarcinoma, except in cases with metastatic disease. Systemic chemotherapy for metastatic disease has a marginal survival benefit when compared with best supportive care, while no standard worldwide regimen has been established yet. In Japan, especially the number of patients treated with endoscopic mucosal resection for early gastric adenocarcinoma is increasing year by year. Chemotherapy may be a more important part of treatment protocols in these patients in near future, because of the increasing survival rates. Cisplatin, 5-fluorouracil and mitomycin C were commonly used in various combinations for patients with gastric adenocarcinoma[114].

Radiotherapy

In most instances, radiotherapy is used as an adjuvant to surgery, chemotherapy or both for primary gastric lymphoma. It has rarely been tried as a single mode of therapy[115,116]. However, limited trials have suggested that radiotherapy can be utilized as a primary mode of treatment with a reasonable outcome[116,117]. Radiotherapy has been studied in comparison with other treatment modalities for stage IE and IIE of primary gastric lymphomas with a comparable outcome of 80%-89% survival[115,118,119]. Radiation was used post-operatively in high- and low-grade lymphomas, for residual tumors in stages I and II to improve the disease-free survival[120]. Combination of radiotherapy with chemotherapy might improve the chance of stomach conservation of these patients which may approach 100%[121]. Contradictory studies have found combined radiotherapy with either resection or chemotherapy no significant difference in both modalities, with a survival rate of 82%-88%[116,119]. Radiation therapy has a limited but well established role in the care of those afflicted with gastric adenocarcinoma. Radiation therapy can provide considerable relief of local gastric cancer symptoms. Approximately 50% to 75% of patients have had symptomatic improvement of problems, such as obstruction, bleeding and pain in a variety of trials[122,123].

Antibiotic therapy

Because gastric MALT lymphomas have a high association with *H pylori* infection, eradication of *H pylori* with antibiotics is very important[58,60,124,125]. Isaacson *et al*[125] suggested that antibiotic eradication of *H pylori* removes the growth stimulus from gastric MALT lymphoma without necessarily eradicating the neoplastic B-cell clone. This clone may re-expand, but in the absence of concomitant re-infection with *H pylori*, this is likely to be a self-limiting event. Short and long-term follow-up results of medical eradication of *H pylori* in patients with gastric MALT lymphoma have been published in the literature[124,125]. However, patients still require periodic surveillance endoscopies and may require more traditional treatment of their lymphoma. Antibiotic therapy may fail to cure gastric lymphomas when there is a bulky tumor with a high-grade component or when the gastric lymphoma is associated with carcinoma[126]. A combination of partial gastrectomy and antibiotic therapy might be an alternative treatment for primary gastric lymphomas. However, periodic surveillance endoscopies are required after partial gastrectomy and antibiotic therapy. There has been no defined role of antibiotic therapy against *H pylori* in the treatment of gastric adenocarcinoma. Eradication of *H pylori* infection can be placed in preventive measures of gastric adenocarcinoma. If *H pylori* infection is detected in the partially resected

stomach secondary to adenocarcinoma, the postoperative antibiotic treatment against *H pylori* may be administered for hindering metachronous occurrence of primary gastric lymphoma.

PROGNOSIS

Reported period of follow-up for synchronous cases ranged from 1 to 132 mo. Overall, data about surveillance of patients were insufficient to perform analysis. Some authors did not mention follow-up data whereas others did not report treatment modalities. However, shorter postoperative survey was observed in cases with AGC (up to 23 mo) when compared to cases with EGC. The follow-up study conducted by Nakamura *et al*[10] revealed that the survival rate of patients with synchronous occurrence of gastric lymphoma and adenocarcinoma appeared to be similar to that for previously reported patients with gastric adenocarcinoma without lymphoma, and was significantly worse than patients with primary gastric lymphoma without adenocarcinoma. As discussed above, majority of metachronous cases suffered from advanced gastric adenocarcinomas after the latent period. Eleven of 17 patients with AGC died within 18 mo. Despite incomplete survival data of cases with EGC, Zauber *et al*[42] reported 96 mo disease-free survival after total gastrectomy. Nakamura *et al*[10] did not reveal any survival data regarding primary gastric lymphoma occurring after treatment of gastric adenocarcinoma.

In summary, with the help of case reports or series, the synchronous or metachronous occurrence of primary gastric lymphoma and gastric adenocarcinoma have evolved in various aspects. Clinicians should be alert for the possible synchronous or metachronous occurrence of both tumors during diagnosis or follow-up of each other. Authors suggest the application of principles for gastric adenocarcinoma treatment to cases with synchronous occurrence. The biologic behavior of the latest diagnosed tumor determines the accurate management of metachronous occurrence of primary gastric lymphoma and gastric adenocarcinoma.

REFERENCES

1 **Coleman CN**, Williams CJ, Flint A, Glatstein EJ, Rosenberg SA, Kaplan HS. Hematologic neoplasia in patients treated for Hodgkin's disease. *N Engl J Med* 1977; **297**: 1249-1252
2 **Valagussa P**, Santoro A, Kenda R, Fossati Bellani F, Franchi F, Banfi A, Rilke F, Bonadonna G. Second malignancies in Hodgkin's disease: a complication of certain forms of treatment. *Br Med J* 1980; **280**: 216-219
3 **Neufeld H**, Weinerman BH, Kemel S. Secondary malignant neoplasms in patients with Hodgkin's disease. *JAMA* 1978; **239**: 2470-2471
4 **Nakamura S**, Akazawa K, Yao T, Tsuneyoshi M. A clinicopathologic study of 233 cases with special reference to evaluation with the MIB-1 index. *Cancer* 1995; **76**: 1313-1324
5 **Barth.** (Abstract of presentation). *Bull Soc Anat Paris* 1855; **30**: 1
6 **Ostertag H**, Georgii A. Early gastric cancer: a morphological study of 144 cases. Pathol Res Pract 1979; **164**: 294-315
7 **Planker M**, Fischer JT, Peters U, Borchard F. Synchronous double primary malignant lymphoma of low grade malignancy and early cancer (collision tumor) of the stomach. *Hepatogastroenterology* 1984; **31**: 144-148
8 **Kasahara Y**, Takemoto M, Morishita A, Kuyama T, Takahashi M, Tanji K. Coexisting adenocarcinoma and malignant lymphoma of the stomach: case report and review of the Japanese literature. *Am J Gastroenterol* 1988; **83**: 190-193
9 **Noda T**, Akashi H, Matsueda S, Katsuki N, Shirahashi K, Kojiro M. Collision of malignant lymphoma and multiple early adenocarcinomas of the stomach. *Arch Pathol Lab Med* 1989; **113**: 419-422
10 **Nakamura S**, Aoyagi K, Iwanaga S, Yao T, Tsuneyoshi M, Fujishima M. Synchronous and metachronous primary gastric lymphoma and adenocarcinoma: a clinicopathological study of 12 patients. *Cancer* 1997; **79**: 1077-1085
11 **RABINOVITCH J**, PINES B, GRAYZEL D. Coexisting lymphosarcoma and ulcer-carcinoma of the stomach. *AMA Arch Surg* 1952; **64**: 185-191
12 **Jernstrom P**, Murray GC. Synchronous double primary lymphosarcoma and adenosarcoma (collision tumor) of the stomach with cancer to cancer metastasis. *Cancer* 1966; **19**: 60-66
13 **Manier JW**, Reyes CN. Collision tumor of the stomach: Report of two cases. *Gastroenterology* 1974; **67**: 1011-1015
14 **Lin JI**, Tseng CH, Chow S, Weisberg J, Guzman L. Coexisting malignant lymphoma and adenocarcinoma of the stomach. *South Med J* 1979; **72**: 619-622
15 **Kane EP**, Weingarten LA, Payson BA, Mori K, Sarlin JG. Synchronous ulcerating adenocarcinoma and malignant lymphoma of the stomach. *Am J Gastroenterol* 1982; **77**: 461-463
16 **Czerniak A**, Lotan G, Engelberg IS, Rabau MY, Avigad I, Schachter P, Wolfstein I. The simultaneous coexistence of adenocarcinoma and primary malignant lymphoma in the stomach. *J Surg Oncol* 1985; **30**: 42-45
17 **Akosa AB**, Clark DM, Desa L. Synchronous adenocarcinoma and primary malignant lymphoma of the stomach. *Postgrad Med J* 1990; **66**: 778-780
18 **Kelly SM**, Geraghty JM, Neale G. *H pylori*, gastric carcinoma, and MALT lymphoma. *Lancet* 1994; **343**: 418
19 **von Herbay A**, Schreiter H, Rudi J. Simultaneous gastric adenocarcinoma and MALT-type lymphoma in *Helicobacter pylori* infection. *Virchows Arch* 1995; **427**: 445-450
20 **Wotherspoon AC**, Isaacson PG. Synchronous adenocarcinoma and low grade B-cell lymphoma of mucosa associated lymphoid tissue (MALT) of the stomach. *Histopathology* 1995; **27**: 325-331
21 **Nishino N**, Konno H, Baba S, Aoki K, Nishimura T, Arai T, Kino I. Synchronous lymphoma and adenocarcinoma occurring as a collision tumor in the stomach: report of a case. *Surg Today* 1996; **26**: 508-512
22 **Hardman WJ 3rd**, Gal AA, Pascal RR. Gastric adenocarcinoma and low-grade B-cell lymphoma of mucosa-associated lymphoid tissue. *South Med J* 1997; **90**: 426-430
23 **Ishihama T**, Kondo H, Saito D, Yamaguchi H, Shirao K, Yokota T, Hosokawa K, Ono H, Iwabuchi M, Gotoda T, Matsuno Y, Boku N, Ohtsu A, Yoshida S. Clinicopathological studies on coexisting gastric malignant lymphoma and gastric adenocarcinoma: report of four cases and review of the Japanese literature. *Jpn J Clin Oncol* 1997; **27**: 101-106
24 **Goteri G**, Ranaldi R, Rezai B, Baccarini MG, Bearzi I. Synchronous mucosa-associated lymphoid tissue lymphoma and adenocarcinoma of the stomach. *Am J Surg Pathol* 1997; **21**: 505-509
25 **Kanamoto K**, Aoyagi K, Nakamura S, Hizawa K, Suekane H, Sakamoto K, Fujishima M. Simultaneous coexistence of early adenocarcinoma and low-grade MALT lymphoma of the stomach associated with *Helicobacter pylori* infection: a case report. *Gastrointest Endosc* 1998; **47**: 73-75
26 **Montalbàn C**, Castrillo JM, López-Abente G, Abraira V, Serrano M, Bellas C, Piris MA, Carrion R, Cruz MA, García-Laraña J, Menarguez J, Rivas C. Other cancers in patients with gastric MALT lymphoma. *Leuk Lymphoma* 1999; **33**: 161-168
27 **Cammarota G**, Larocca LM, D'Ugo D, Persiani R, Cianci R, Nocente R, Picciocchi A, Gasbarrini G. Synchronous gastric adenocarcinoma and MALT lymphoma in a patient with H. pylori infection. Could the two neoplasms share a common

pathogenesis? *Hepatogastroenterology* 2001; **48**: 104-106
28 **Chan AO**, Chu KM, Yuen ST, Leung SY, Lam SK, Wong J. Synchronous gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma in association with *Helicobacter pylori* infection: comparing reported cases between the East and West. *Am J Gastroenterol* 2001; **96**: 1922-1924
29 **Kaffes A**, Hughes L, Hollinshead J, Katelaris P. Synchronous primary adenocarcinoma, mucosa-associated lymphoid tissue lymphoma and a stromal tumor in a *Helicobacter pylori*-infected stomach. *J Gastroenterol Hepatol* 2002; **17**: 1033-1036
30 **Sakai T**, Ogura Y, Narita J, Suto T, Kimura D, Ainai S, Fujita H, Kamada M. Simultaneous early adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach associated with *Helicobacter pylori* infection. *Gastric Cancer* 2003; **6**: 191-196
31 **Suenaga M**, Ohta K, Toguchi M, Sato T, Ohyama S, Yamaguchi T, Muto T, Yanagisawa A, Kato Y. Colliding gastric and intestinal phenotype well-differentiated adenocarcinoma of the stomach developing in an area of MALT-type lymphoma. *Gastric Cancer* 2003; **6**: 270-276
32 **McNEER G**, BOOHER RJ, BOWDEN L. The resectability of recurrent gastric carcinoma. *Cancer* 1950; **3**: 43-55
33 **FLEISCHER N**, WALKER R. Gastric carcinoma following successful therapy for primary gastric lymphosarcoma. *South Med J* 1960; **53**: 965-968
34 **Bockus HL**. Carcinoma of the stomach. In: Bockus H. Gastroenterology, vol. 1, ed. 2" Philadelphia, W.B. Saunders Company, 1963: 747
35 **Komarov AS**. [Cancer of the gastric stump 19 years after its resection for sarcoma]. *Khirurgiia (Mosk)* 1969; **45**: 131-133
36 **Morgenstern L**, Yamakawa T, Seltzer D. Carcinoma of the gastric stump. *Am J Surg* 1973; **125**: 29-38
37 **Ettinger DS**, Carter D. Gastric carcinoma 16 years after gastric lymphoma irradiation. *Am J Gastroenterol* 1977; **68**: 485-488
38 **Shani A**, Schutt AJ, Weiland LH. Primary gastric malignant lymphoma followed by gastric adenocarcinoma: report of 4 cases and review of the literature. *Cancer* 1978; **42**: 2039-2044
39 **Sellin J**, Levin B, Reckard C, Riddell R. Gastric adenocarcinoma following gastric lymphoma. Role of partial gastrectomy. *Cancer* 1980; **45**: 996-1000
40 **Brumback RA**, Gerber JE, Hicks DG, Strauchen JA. Adenocarcinoma of the stomach following irradiation and chemotherapy for lymphoma in young patients. *Cancer* 1984; **54**: 994-998
41 **Baron BW**, Bitter MA, Baron JM, Bostwick DG. Gastric adenocarcinoma after gastric lymphoma. *Cancer* 1987; **60**: 1876-1882
42 **Zorlu AF**, Atahan IL, Gedikoglu G, Ruacan S, Sayek I, Tekuzman G. Does gastric adenocarcinoma develop after the treatment of gastric lymphoma? *J Surg Oncol* 1993; **54**: 126-131
43 **Zauber NP**, Berman EL. Synchronous and metachronous primary gastric lymphoma and adenocarcinoma: a clinicopathologic study of 12 patients. *Cancer* 1998; **82**: 226-227
44 **Hasegawa N**, Kato K, Yamada K, Morita K, Kuroiwa M, Ito H, Kamioka T, Matsuura T, Taguchi A, Ono K, Suzuki Y, Goto H. Early-stage gastric adenocarcinoma: revealed after anti-*Helicobacter pylori* therapy of MALT lymphoma. *Gastrointest Endosc* 2001; **53**: 495
45 **Ghoshal UC**, Guha D, Bandyopadhyay S, Pal C, Chakraborty S, Ghoshal U, Ghosh TK, Pal BB, Banerjee PK. Gastric adenocarcinoma in a patient re-infected with H. pylori after regression of MALT lymphoma with successful anti-H.pylori therapy and gastric resection: a case report. *BMC Gastroenterol* 2002; **2**: 6
46 **Raderer M**, Püspök A, Stummvoll G, Längle F, Chott A. Early cancer of the stomach arising after successful treatment of gastric MALT lymphoma in patients with autoimmune disease. *Scand J Gastroenterol* 2003; **38**: 294-297
47 **Lim FE**, Hartman AS, Tan EG, Cady B, Meissner WA. Factors in the prognosis of gastric lymphoma. *Cancer* 1977; **39**: 1715-1720
48 **Shimodaira M**, Tsukamoto Y, Niwa Y, Goto H, Hase S, Hayakawa T, Nagasaka T. A proposed staging system for primary gastric lymphoma. *Cancer* 1994; **73**: 2709-2715
49 **Ruskoné-Fourmestraux A**, Dragosics B, Morgner A, Wotherspoon A, De Jong D. Paris staging system for primary gastrointestinal lymphomas. *Gut* 2003; **52**: 912-913
50 **Isaacson P**, Wright DH. Malignant lymphoma of mucosa-associated lymphoid tissue. A distinctive type of B-cell lymphoma. *Cancer* 1983; **52**: 1410-1416
51 **Isaacson P**, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. *Cancer* 1984; **53**: 2515-2524
52 **Arista-Nasr J**, Jiménez-Rosas F, Uribe-Uribe N, Herrera-Goepfert R, Lazos-Ochoa M. Pathological disorders of the gastric mucosa surrounding carcinomas and primary lymphomas. *Am J Gastroenterol* 2001; **96**: 1746-1750
53 **Griffiths AP**, Wyatt J, Jack AS, Dixon MF. Lymphocytic gastritis, gastric adenocarcinoma, and primary gastric lymphoma. *J Clin Pathol* 1994; **47**: 1123-1124
54 **Zamboni G**, Franzin G, Scarpa A, Bonetti F, Pea M, Mariuzzi GM, Menestrina F. Carcinoma-like signet-ring cells in gastric mucosa-associated lymphoid tissue (MALT) lymphoma. *Am J Surg Pathol* 1996; **20**: 588-598
55 **Ioachim HL**, Hajdu C, Giancotti FR, Dorsett B. Lymphoid proliferations and lymphomas associated with gastric metaplasia, dysplasia, and carcinoma. *Hum Pathol* 1999; **30**: 833-842
56 **Endo M**, Habu H. Clinical studies of early gastric cancer. *Hepatogastroenterology* 1990; **37**: 408-410
57 **Wotherspoon AC**, Ortiz-Hidalgo C, Falzon MR, Isaacson PG. *Helicobacter pylori*-associated gastritis and primary B-cell gastric lymphoma. *Lancet* 1991; **338**: 1175-1176
58 **Loffeld RJ**, Willems I, Flendrig JA, Arends JW. *Helicobacter pylori* and gastric carcinoma. *Histopathology* 1990; **17**: 537-541
59 **Parsonnet J**, Hansen S, Rodriguez L, Gelb AB, Warnke RA, Jellum E, Orentreich N, Vogelman JH, Friedman GD. *Helicobacter pylori* infection and gastric lymphoma. *N Engl J Med* 1994; **330**: 1267-1271
60 **Isaacson PG**. Mucosa-associated lymphoid tissue lymphoma. **Semin Hematol** 1999; **36**: 139-147
61 **Negrini R**, Savio A, Poiesi C, Appelmelk BJ, Buffoli F, Paterlini A, Cesari P, Graffeo M, Vaira D, Franzin G. Antigenic mimicry between *Helicobacter pylori* and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology* 1996; **111**: 655-665
62 **Cammarota G**, Gasbarrini G. *Helicobacter pylori* infection and autoimmune pathogenesis of gastric neoplasias. *Gut* 2000; **46**: 295
63 **Kawahara Y**, Yokota K, Mizuno M, Yunoki N, Uesu T, Okada H, Kobayashi K, Hirai Y, Oguma K, Tsuji T. Antibodies to human gastric epithelial cells and heat shock protein 60 in *Helicobacter pylori* positive mucosa associated lymphoid tissue lymphoma. *Gut* 1999; **45**: 20-23
64 **Genta RM**, Hamner HW. The significance of lymphoid follicles in the interpretation of gastric biopsy specimens. *Arch Pathol Lab Med* 1994; **118**: 740-743
65 **Hussell T**, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. *Lancet* 1993; **342**: 571-574
66 **Hussell T**, Isaacson PG, Crabtree JE, Spencer J. *Helicobacter pylori*-specific tumour-infiltrating T cells provide contact dependent help for the growth of malignant B cells in low grade gastric lymphoma of mucosa-associated lymphoid tissue. *J Pathol* 1996; **178**: 122-127
67 **Morgner A**, Bayerdörffer E, Neubauer A, Stolte M. Malignant tumors of the stomach. Gastric mucosa-associated lymphoid tissue lymphoma and *Helicobacter pylori*. *Gastroenterol Clin North Am* 2000; **29**: 593-607
68 **Zucca E**, Bertoni F, Roggero E, Bosshard G, Cazzaniga G, Pedrinis E, Biondi A, Cavalli F. Molecular analysis of the progression from *Helicobacter pylori*-associated chronic gastritis to mucosa-associated lymphoid-tissue lymphoma of the stomach. *N Engl J Med* 1998; **338**: 804-810
69 **Correa P**, Ruiz B. *Helicobacter pylori* and gastric cancer.

In: Rathbone BJ, Heatley RV. *Helicobacter pylori* and gastroduodenal diseases. 2nd Ed. Oxford: Blackwell Scientific, 1992: 158-164
70 **Asaka M**, Takeda H, Sugiyama T, Kato M. What role does *Helicobacter pylori* play in gastric cancer? *Gastroenterology* 1997; **113**: S56-S60
71 **Eslick GD**, Lim LL, Byles JE, Xia HH, Talley NJ. Association of *Helicobacter pylori* infection with gastric carcinoma: a meta-analysis. *Am J Gastroenterol* 1999; **94**: 2373-2379
72 **Koehler CI**, Mues MB, Dienes HP, Kriegsmann J, Schirmacher P, Odenthal M. *Helicobacter pylori* genotyping in gastric adenocarcinoma and MALT lymphoma by multiplex PCR analyses of paraffin wax embedded tissues. *Mol Pathol* 2003; **56**: 36-42
73 **Mueller N**, Mohar A, Evans A, Harris NL, Comstock GW, Jellum E, Magnus K, Orentreich N, Polk BF, Vogelman J. Epstein-Barr virus antibody patterns preceding the diagnosis of non-Hodgkin's lymphoma. *Int J Cancer* 1991; **49**: 387-393
74 **Ott G**, Kirchner T, Seidl S, Müller-Hermelink HK. Primary gastric lymphoma is rarely associated with Epstein-Barr virus. *Virchows Arch B Cell Pathol Incl Mol Pathol* 1993; **64**: 287-291
75 **Hui PK**, Tokunaga M, Chan WY, Ng CS, Chow J, Lee JC. Epstein-Barr virus-associated gastric lymphoma in Hong Kong Chinese. *Hum Pathol* 1994; **25**: 947-952
76 **Liu Q**, Ohshima K, Masuda Y, Kikuchi M. Detection of the Epstein-Barr virus in primary gastric lymphoma by in situ hybridization. *Pathol Int* 1995; **45**: 131-136
77 **Shibata D**, Weiss LM. Epstein-Barr virus-associated gastric adenocarcinoma. *Am J Pathol* 1992; **140**: 769-774
78 **Tokunaga M**, Land CE, Uemura Y, Tokudome T, Tanaka S, Sato E. Epstein-Barr virus in gastric carcinoma. *Am J Pathol* 1993; **143**: 1250-1254
79 **Nakamura S**, Ueki T, Yao T, Ueyama T, Tsuneyoshi M. Epstein-Barr virus in gastric carcinoma with lymphoid stroma. Special reference to its detection by the polymerase chain reaction and in situ hybridization in 99 tumors, including a morphologic analysis. *Cancer* 1994; **73**: 2239-2249
80 **Thompson MP**, Kurzrock R. Epstein-Barr virus and cancer. *Clin Cancer Res* 2004; **10**: 803-821
81 **Wu MS**, Shun CT, Wu CC, Hsu TY, Lin MT, Chang MC, Wang HP, Lin JT. Epstein-Barr virus-associated gastric carcinomas: relation to H. pylori infection and genetic alterations. *Gastroenterology* 2000; **118**: 1031-1038
82 **Suehiro S**, Nagasue N, Abe S, Ogawa Y, Sasaki Y. Carcinoma of the stomach in atomic bomb survivors. A comparison of clinicopathologic features to the general population. *Cancer* 1986; **57**: 1894-1898
83 **Kai M**, Luebeck EG, Moolgavkar SH. Analysis of the incidence of solid cancer among atomic bomb survivors using a two-stage model of carcinogenesis. *Radiat Res* 1997; **148**: 348-358
84 **Little MP**, Muirhead CR, Charles MW. Describing time and age variations in the risk of radiation-induced solid tumour incidence in the Japanese atomic bomb survivors using generalized relative and absolute risk models. *Stat Med* 1999; **18**: 17-33
85 **Maes B**, Demunter A, Peeters B, De Wolf-Peeters C. BCL10 mutation does not represent an important pathogenic mechanism in gastric MALT-type lymphoma, and the presence of the API2-MLT fusion is associated with aberrant nuclear BCL10 expression. *Blood* 2002; **99**: 1398-1404
86 **Nakamura T**, Nakamura S, Yokoi T, Suzuki H, Ohashi K, Seto M. Clinicopathologic comparison between the API2-MALT1 chimeric transcript-positive and –negative gastric low-grade B-cell lymphoma of mucosa-associated lymphoid tissue type. *Jpn J Cancer Res* 2002; **93**: 677-684
87 **Okabe M**, Inagaki H, Ohshima K, Yoshino T, Li C, Eimoto T, Ueda R, Nakamura S. API2-MALT1 fusion defines a distinctive clinicopathologic subtype in pulmonary extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue. *Am J Pathol* 2003; **162**: 1113-1122
88 **Greene MH**, Wilson J. Second cancer following lymphatic and hematopoietic cancers in Connecticut, 1935-82. *Natl Cancer Inst Monogr* 1985; **68**: 191-217
89 **Caygill CP**, Hill MJ, Hall CN, Kirkham JS, Northfield TC. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. *Gut* 1987; **28**: 924-928
90 **Stalnikowicz R**, Benbassat J. Risk of gastric cancer after gastric surgery for benign disorders. *Arch Intern Med* 1990; **150**: 2022-2026
91 **Pointner R**, Schwab G, Königsrainer A, Bodner E, Schmid KW. Gastric stump cancer: etiopathological and clinical aspects. *Endoscopy* 1989; **21**: 115-119
92 **Kellum JM**, Jaffe BM, Calhoun TR, Ballinger WF 2nd. Gastric complications after radiotherapy for Hodgkin's disease and other lymphomas. *Am J Surg* 1977; **134**: 314-317
93 **Roswit B**, Malsky SJ, Reid CB. Severe radiation injuries of the stomach, small intestine, colon and rectum. Am J Roentgenol Radium *Ther Nucl Med* 1972; **114**: 460-475
94 National Research Council: Committee on the biological effects of ionising radiation. The Effects on Populations of Exposure to Low Levels of Ionising Radiation. Washington, DC: National Academy Press, 1980
95 **Hirose F**. Induction of gastric adenocarcinoma in mice by localized x-irradiation. *Gann* 1969; **60**: 253-260
96 **Brown WM**, Doll R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965; **2**: 1327-1332
97 **Lieber MR**, Winans CS, Griem ML, Moossa R, Elner VM, Franklin WA. Sarcomas arising after radiotherapy for peptic ulcer disease. *Dig Dis Sci* 1985; **30**: 593-599
98 **Al-Akwaa AM**, Siddiqui N, Al-Mofleh IA. Primary gastric lymphoma. *World J Gastroenterol* 2004; **10**: 5-11
99 **Rackner VL**, Thirlby RC, Ryan JA Jr. Role of surgery in multimodality therapy for gastrointestinal lymphoma. *Am J Surg* 1991; **161**: 570-575
100 **Maor MH**, Velasquez WS, Fuller LM, Silvermintz KB. Stomach conservation in stages IE and IIE gastric non-Hodgkin's lymphoma. *J Clin Oncol* 1990; **8**: 266-271
101 **Liang R**, Todd D, Chan TK, Chiu E, Lie A, Kwong YL, Choy D, Ho FC. Prognostic factors for primary gastrointestinal lymphoma. *Hematol Oncol* 1995; **13**: 153-163
102 **Kitamura K**, Yamaguchi T, Okamoto K, Ichikawa D, Hoshima M, Taniguchi H, Takahashi T. Early gastric lymphoma: a clinicopathologic study of ten patients, literature review, and comparison with early gastric adenocarcinoma. *Cancer* 1996; **77**: 850-857
103 **Kodera Y**, Yamamura Y, Nakamura S, Shimizu Y, Torii A, Hirai T, Yasui K, Morimoto T, Kato T, Kito T. The role of radical gastrectomy with systematic lymphadenectomy for the diagnosis and treatment of primary gastric lymphoma. *Ann Surg* 1998; **227**: 45-50
104 **Lucandri G**, Stipa F, Mingazzini PL, Ferri M, Sapienza P, Stipa S. The role of surgery in the treatment of primary gastric lymphoma. *Anticancer Res* 1998; **18**: 2089-2094
105 **Vaillant JC**, Ruskoné-Fourmestraux A, Aegerter P, Gayet B, Rambaud JC, Valleur P, Parc R. Management and long-term results of surgery for localized gastric lymphomas. *Am J Surg* 2000; **179**: 216-222
106 **Popescu RA**, Wotherspoon AC, Cunningham D, Norman A, Prendiville J, Hill ME. Surgery plus chemotherapy or chemotherapy alone for primary intermediate and high-grade gastric non-Hodgkin's lymphoma: the Royal Marsden Hospital experience. *Eur J Cancer* 1999; **35**: 928-934
107 **Law MM**, Williams SB, Wong JH. Role of surgery in the management of primary lymphoma of the gastrointestinal tract. *J Surg Oncol* 1996; **61**: 199-204
108 **Yoon SS**, Coit DG, Portlock CS, Karpeh MS. The diminishing role of surgery in the treatment of gastric lymphoma. *Ann Surg* 2004; **240**: 28-37
109 **Salvagno L**, Sorarù M, Busetto M, Puccetti C, Sava C, Endrizzi L, Giusto M, Aversa S, Chiarion Sileni V, Polico R, Bianco A, Rupolo M, Nitti D, Doglioni C, Lise M. Gastric non-Hodgkin's lymphoma: analysis of 252 patients from a multicenter study. *Tumori* 1999; **85**: 113-121
110 **Raderer M**, Valencak J, Osterreicher C, Drach J, Hejna M, Kornek G, Scheithauer W, Brodowicz T, Chott A, Dragosics B.

Chemotherapy for the treatment of patients with primary high grade gastric B-cell lymphoma of modified Ann Arbor Stages IE and IIE. *Cancer* 2000; **88**: 1979-1985

111 **Liu HT**, Hsu C, Chen CL, Chiang IP, Chen LT, Chen YC, Cheng AL. Chemotherapy alone versus surgery followed by chemotherapy for stage I/IIE large-cell lymphoma of the stomach. *Am J Hematol* 2000; **64**: 175-179

112 **Ruskoné-Fourmestraux A**, Aegerter P, Delmer A, Brousse N, Galian A, Rambaud JC. Primary digestive tract lymphoma: a prospective multicentric study of 91 patients. Groupe d' Etude des Lymphomes Digestifs. *Gastroenterology* 1993; **105**: 1662-1671

113 **Ohtsu A**. The latest advances in chemotherapy for gastrointestinal cancers. *Int J Clin Oncol* 2003; **8**: 234-238

114 **Sutherland AG**, Kennedy M, Anderson DN, Park KG, Keenan RA, Davidson AI. Gastric lymphoma in Grampian Region: presentation, treatment and outcome. *J R Coll Surg Edinb* 1996; **41**: 143-147

115 **Kocher M**, Müller RP, Ross D, Hoederath A, Sack H. Radiotherapy for treatment of localized gastrointestinal non-Hodgkin's lymphoma. *Radiother Oncol* 1997; **42**: 37-41

116 **Pinotti G**, Zucca E, Roggero E, Pascarella A, Bertoni F, Savio A, Savio E, Capella C, Pedrinis E, Saletti P, Morandi E, Santandrea G, Cavalli F. Clinical features, treatment and outcome in a series of 93 patients with low-grade gastric MALT lymphoma. *Leuk Lymphoma* 1997; **26**: 527-537

117 **Chandran RR**, Raj EH, Chaturvedi HK. Primary gastrointestinal lymphoma: 30-year experience at the Cancer Institute, Madras, India. *J Surg Oncol* 1995; **60**: 41-49

118 **Ferreri AJ**, Cordio S, Paro S, Ponzoni M, Freschi M, Veglia F, Villa E. Therapeutic management of stage I-II high-grade primary gastric lymphomas. *Oncology* 1999; **56**: 274-282

119 **Fischbach W**, Dragosics B, Kolve-Goebeler ME, Ohmann C, Greiner A, Yang Q, Böhm S, Verreet P, Horstmann O, Busch M, Dühmke E, Müller-Hermelink HK, Wilms K, Allinger S, Bauer P, Bauer S, Bender A, Brandstätter G, Chott A, Dittrich C, Erhart K, Eysselt D, Ellersdorfer H, Ferlitsch A, Fridrik MA, Gartner A, Hausmaninger M, Hinterberger W, Hügel K, Ilsinger P, Jonaus K, Judmaier G, Karner J, Kerstan E, Knoflach P, Lenz K, Kandutsch A, Lobmeyer M, Michlmeier H, Mach H, Marosi C, Ohlinger W, Oprean H, Pointer H, Pont J, Salabon H, Samec HJ, Ulsperger A, Wimmer A, Wewalka F. Primary gastric B-cell lymphoma: results of a prospective multicenter study. The German-Austrian Gastrointestinal Lymphoma Study Group. *Gastroenterology* 2000; **119**: 1191-1202

120 **Lin KM**, Penney DG, Mahmoud A, Chae W, Kolachalam RB, Young SC. Advantage of surgery and adjuvant chemotherapy in the treatment of primary gastrointestinal lymphoma. *J Surg Oncol* 1997; **64**: 237-241

121 **Mantell BS**. Radiotherapy for dysphagia due to gastric carcinoma. *Br J Surg* 1982; **69**: 69-70

122 **Henderson IW**, Lipowska B, Lougheed MN. Clinical evaluation of combined radiation and chemotherapy in gastrointestinal malignancies. *Am J Roentgenol Radium Ther Nucl Med* 1968; **102**: 545-551

123 **Bayerdörffer E**, Neubauer A, Rudolph B, Thiede C, Lehn N, Eidt S, Stolte M. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type after cure of *Helicobacter pylori* infection. MALT Lymphoma Study Group. *Lancet* 1995; **345**: 1591-1594

124 **Isaacson PG**, Diss TC, Wotherspoon AC, Barbazza R, De Boni M, Doglioni C. Long-term follow-up of gastric MALT lymphoma treated by eradication of *H. pylori* with antibodies. *Gastroenterology* 1999; **117**: 750-751

125 **Pescatore P**, Heine M, Manegold BC. Cure of gastric lymphoma with antibiotics. *Gastroenterology* 1995; **109**: 334-335

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