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The Role of Radical Gastrectomy With Systematic Lymphadenectomy for the Diagnosis and Treatment of Primary Gastric Lymphoma

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Objective
We evaluated the therapeutic efficacy of radical gastrectomy for primary B-cell lymphoma of the stomach and attempted to identify patients who could be adequately treated with surgery alone.

Summary Background Data
Several recent gastric lymphoma reports have discussed the therapeutic benefits of various treatment strategies for stage IE and IIE lymphoma. However, few studies have been based on patients accurately staged by systematic lymphadenectomy with subsequent pathologic examination.

Methods
A retrospective study was performed to evaluate the survival and biologic behavior of lesions in 60 patients with gastric lymphoma who were treated by radical gastrectomy alone. Tumors were classified according to the histopathologic concept of mucosa-associated lymphoid tissue (MALT)-derived lymphoma.

Results
A low histopathologic grade was associated with a significantly lower incidence of nodal metastasis ($p = 0.07$) and less extensive infiltration of the gastric wall ($p < 0.005$) despite larger tumor size. A 5-year survival rate of >95% was attained with surgery alone for MALT lymphoma and for true stage IE lymphoma diagnosed by pathologic examination of up to N2 lymph nodes routinely performed after radical gastrectomy.

Conclusions
Surgery alone is adequate treatment for stage IE or pure MALT lymphoma, provided that the staging is performed after radical gastrectomy.

Primary gastric non-Hodgkin's lymphoma is a rare tumor, representing <5%[1] to 8%[2] of gastric malignancies in the United States and Canada. This percentage is even lower in Japan, where adenocarcinoma of the stomach remains the most common malignancy. An increased incidence, however, has been documented recently by several institutions in the West[1,3] and in Japan.[4] Gastrectomy usually is considered an essential component of multimodal treatment,[1,2,5–9] and patients with Ann Arbor stage IE disease may be candidates for gastrectomy alone, with a reported 5-year survival rate of >80%.[6] However, completely nonsurgical treatment strategies have now been proposed even for stage IE and IIE disease[10,11] and for low-grade mucosa-associated lymphoid tissue (MALT)-derived lymphoma.[12] No single treatment strategy is universally accepted, even for early-stage primary gastric lymphoma.

This report reviews the clinicopathologic data for stage IE and IIE gastric lymphoma treated by curative surgery alone in an institution in Japan. The surgical procedure performed in all cases was radical gastrectomy, which historically has been a standard approach to treating gastric carcinoma in Japan[13] and currently is being evaluated in randomized trials in several European countries.[14] This study, however, had additional goals as well. The meticulous lymphadenectomy performed as an essential part of this procedure also serves as an excellent staging tool,[15] providing ample histopathologic data on perigastric nodal involvement and enabling discrimination between Ann Arbor stages IIE and IE with absolute accuracy. This procedure also allows more sophisticated stage classification by the Japanese Classification of Gastric Carcinoma.[16] The utility of the Japanese staging scheme as a prognostic indicator is discussed. Lymphomas in this study also have been classified histopathologically according to the concept of MALT-derived gastric lymphoma.[17] The value of this classification as a prognostic determinant is also reviewed.

Because outcomes in this study were not influenced by factors such as differences in treatment strategy, multidrug resistance, or radiosensitivity, the results are more likely to reflect the true biologic behavior of each histopathologic type than are previous reports of lymphomas.

METHODS

Between 1967 and 1993, 112 patients with primary B-cell gastric lymphoma were operated on at Aichi Cancer Center Hospital (Aichi, Japan); 104 of them (93%) underwent gastrectomy. Of these, the 60 patients who were treated solely with standard radical gastrectomy form the basis of this study. A standard radical gastrectomy consists of a gastrectomy with D2 lymphadenectomy and resection of N1 and N2 lymph nodes, defined by the Japanese Classification of Gastric Carcinoma.[16] These patients underwent surgery alone because their preoperative examinations and intraoperative findings indicated that the disease was confined to the perigastric region. Surgery was considered to be potentially curative in all patients (except for one patient, who was later found to have a positive microscopic margin). Partial gastrectomy was performed in 27 patients and was considered the treatment of choice when total gastrectomy was considered unnecessary by pre- and intraoperative criteria. Total gastrectomy was performed in the remaining 33 patients. Preoperative evaluation included bone marrow aspiration and endoscopic and barium studies of the gastrointestinal tract. Recent patients were evaluated by computed tomography of the chest, abdomen, and cervical regions, and biopsies were performed where appropriate to ensure that the gastric lesion was not a part of, or had not developed into, a systemic lymphoma. Staging was performed according to the Ann Arbor system[18] and the Japanese Classification of Gastric Carcinoma.[16] Information concerning the clinical course of all 60 patients was available from their medical records.

Resected gastric lymphoma specimens were fixed in 10% formalin, embedded in paraffin, and stained with Giemsa, hematoxylin and eosin (H&E), periodic acid–Schiff, and Gomori silver impregnation. All surgically dissected regional lymph nodes from the adipose and connective tissue of the specimen were sent for similar histologic examination. In all cases, T-cell and B-cell immunologic characteristics of the infiltrates were evaluated using the indirect immunoperoxidase technique[19] with a panel of antibodies including L26, UCHL-1 (DAKO Japan, Kyoto, Japan) and MT1 (BioScience Products, Emmenbrucke, Switzerland). The sections from all 60 tumors were recently reexamined by a pathologist with extensive experience in the diagnosis of lymphoma. The pathologic classification, depth of invasion, and extent of nodal metastasis were reevaluated and updated. One of the patients was diagnosed as having follicular type. The remaining 59 patients were reclassified into the following four types,[4] according to the concept of MALT-derived lymphoma[17]: type I, pure low-grade B-cell lymphoma of MALT type; type II, low-grade B-cell lymphoma of MALT type with small areas of high-grade lymphoma; type III, high-grade lymphoma with small areas of low-grade MALT component; and type IV, pure high-grade lymphoma.

Survival curves were drawn by the Kaplan–Meier method, and the difference between curves was evaluated by the generalized Wilcoxon's test. Three deaths that ap-

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Table 1. CORRELATION OF DEPTH OF INFILTRATION WITH OTHER PROGNOSTIC FACTORS

Prognostic Factor	t1	t2	t3	p
Nodal metastasis				0.064
Negative	21	11	1	
Positive	15	6	6	
Tumor grade (based on the MALT concept)				
Type I	21	5	0	
Types II and III	10	7	4	0.024
Type IV	4	5	3	

t1–t3 are from the Japanese Classification of Gastric Carcinoma and are equivalent to pT1 through pT3 in the UICC TNM system. t1 = infiltration up to the submucosa; t2 = infiltration beyond the submucosa but not invading the serosa; t3 = infiltration of the entire gastric wall. Types I–IV are histopathologic grades according to the MALT concept. Type I = pure low-grade B-cell lymphoma of MALT type; Type II = low-grade B-cell lymphoma of MALT type with small areas of high-grade lymphoma; Type III = high-grade lymphoma with small areas of low-grade MALT component; Type IV = pure high-grade lymphoma.

peared to be caused by other diseases (myocardial infarction, breast cancer, and gallbladder cancer) were treated as censored cases. The chi square test was performed to assess the correlation between several prognostic factors.

RESULTS

Clinicopathologic Findings for Primary Gastric Lymphoma

The study included 45 men and 15 women, with a median age of 54 years (range, 21 to 78). The incidence of pathologically confirmed regional nodal metastasis (stage IIE) was 27 of 60 patients (45%). There were 35 cases of "early lymphoma,"[6,20] with depth of infiltration limited to the mucosa and submucosa. Serosal invasion was observed in seven cases, but invasion to adjacent viscera was not pathologically confirmed in any patient. Limited lymphoma infiltration correlated significantly with a low degree of malignancy ($p < 0.05$). The correlation between depth of infiltration and nodal metastasis was of borderline significance ($p = 0.064$) (Table 1).

According to histopathologic grading based on the MALT concept, 26 cases were classified as pure MALT lymphoma (type I), whereas 21 had components of high-grade lymphoma (types II and III) and 12 were considered high-grade lymphoma (type IV). A low histopathologic grade (type I) correlated weakly with a lower incidence of nodal metastasis ($p = 0.068$) and less extensive infiltration of the gastric wall ($p < 0.005$), despite significantly larger tumor size (Table 2).

Table 2. CORRELATION OF HISTOPATHOLOGIC CLASSIFICATION ACCORDING TO THE MALT CONCEPT WITH OTHER PROGNOSTIC FACTORS*

Prognostic Factor	Type I	Types II, III, and IV	p
Nodal metastasis			
Negative	18	15	0.068
Positive	8	18	
Depth of infiltration			
t1	21	14	
t2	5	12	<0.01
t3	0	7	
Tumor size (cm) (mean ± standard deviation)	15.2 ± 5.1	10.0 ± 5.1	<0.0005

* See Table 1 for definitions.

Survival of Patients With Gastric Lymphoma Treated by Radical Gastrectomy Alone

Unlike previous reports, tumor size[9] and age >65 years[1] had no influence on survival. Depth of infiltration correlated significantly with survival ($p < 0.05$), and "early lymphoma" cases invading no further than the submucosa had a 5-year survival rate of 100% (Fig. 1). Ann Arbor stage IE cases had a better survival (5-year survival rate of almost 100%) than did stage IIE cases (Fig. 2), but the difference was not statistically significant. Stage classification according to the Japanese Classifica-

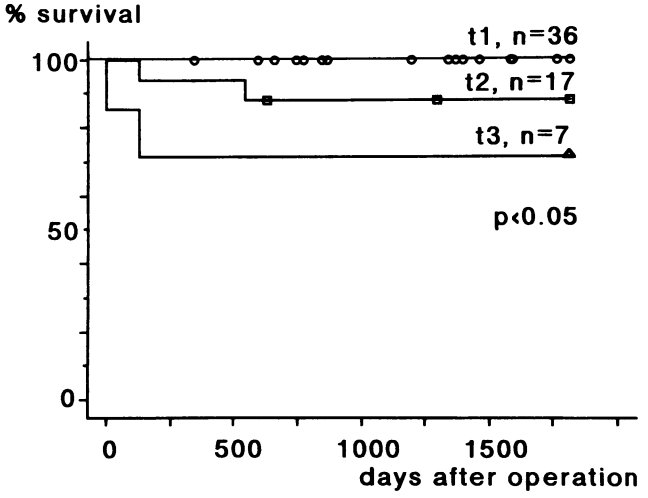

Figure 1. Survival curves for 60 cases of primary gastric lymphoma classified according to the depth of gastric infiltration. Depth of infiltration correlated significantly with survival ($p < 0.05$).

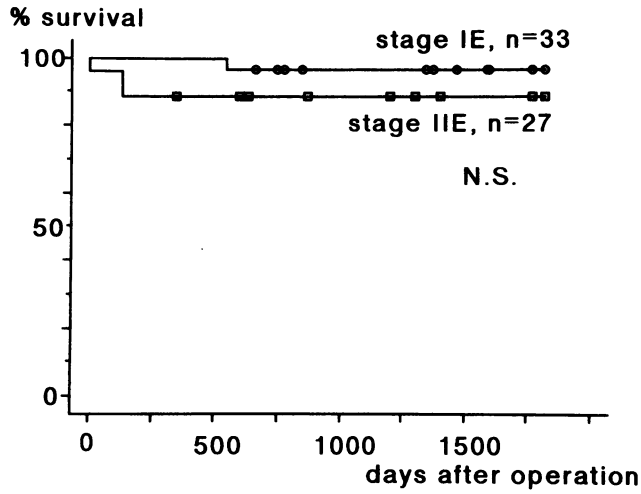

Figure 2. Comparison of survival curves of stages IE and IIE primary gastric lymphoma. The difference was not statistically significant.

tion of Gastric Carcinoma[16] might be a more sensitive indicator of prognosis, because a statistical significance was observed between survival curves for stages I and III ($p < 0.05$) (Fig. 3). Pure MALT cases (type I) had a 5-year survival rate of 95%, but little survival difference was observed compared with high-grade lymphomas (Fig. 4).

Mortality

One perioperative death occurred, secondary to cardiac failure, with a subsequent mortality rate of 1.6%.

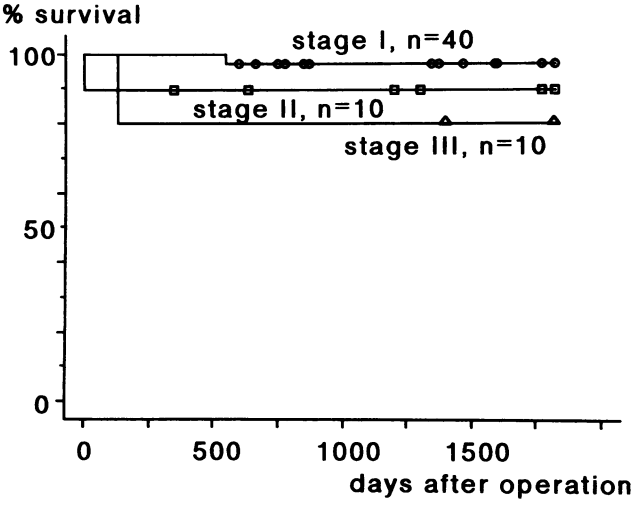

Figure 3. Stage classification of primary gastric lymphoma according to the Japanese Classification of Gastric Carcinoma. Survival decreased with progressive stages, and the difference between the curves for stages I and III was statistically significant ($p < 0.05$).

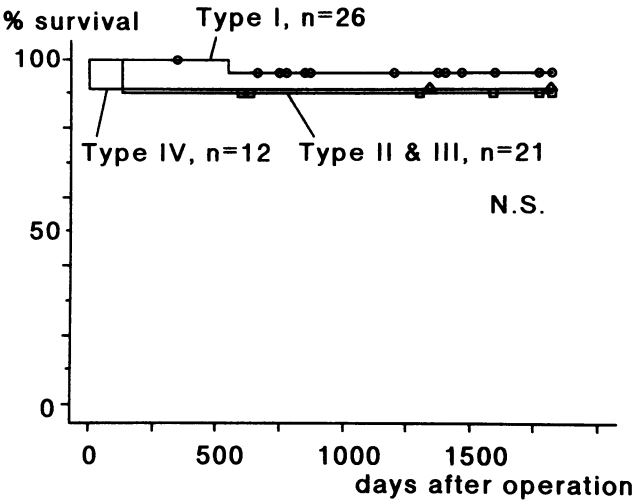

Figure 4. Survival curves for primary gastric lymphoma classified according to the histopathologic MALT concept. Type I, pure low-grade B-cell lymphoma of MALT type; type II, low-grade B-cell lymphoma of MALT type with small areas of high-grade lymphoma; type III, high-grade lymphoma with small areas of low-grade MALT component; type IV, pure high-grade lymphoma.

DISCUSSION

Surgical resection is generally considered to have a definitive role in the treatment of primary gastric lymphoma.[1,2,5–9] Attempts have been made to treat early-stage gastric lymphoma with chemotherapy with and without radiation therapy,[10,11,12] under the rationale that gastrectomy is associated with considerable mortality. The advantage of avoiding gastrectomy and sparing the stomach, however, must be balanced carefully against the toxicity of aggressive chemotherapy and the risk of emergency surgery for iatrogenic complications.[6] Radical gastrectomy, originally a procedure practiced widely in Japan for gastric carcinoma, can now be performed safely in experienced facilities outside Japan.[21,22] In the current study, only one perioperative death (mortality rate of 1.6%) was recorded. The incidence of treatment-related death secondary to chemotherapy is reported to be 1% to 10%, depending on the aggressiveness of the regimen[6]; induction of secondary malignancies, such as acute non-lymphocytic leukemia and bladder cancer, also has been documented.[23,24] The advantage of radiation therapy as an adjuvant to surgery has been refuted[7] or remains unproven.[9] Therefore, we advocate surgical treatment alone in cases where a cure can be expected by complete resection.

The therapeutic benefits of radical gastrectomy, currently undergoing randomized trials in Europe for the treatment of gastric carcinoma,[14] have not been fully elucidated in the treatment of primary gastric lymphoma. Although surgical treatment of lymph node involvement

is often hindered by peritoneal dissemination in patients with adenocarcinoma,[13] resection of nodes might be beneficial for patients with gastric lymphoma for the following reasons. First, the incidence of nodal metastasis in this study was as high as 42%, even for "early" gastric lymphoma not infiltrating beyond the submucosa. Second, gastric lymphoma is not commonly associated with peritoneal dissemination. The 5-year survival rate for stage IIE gastric lymphoma actually exceeded 85% in this study, representing one of the best results reported thus far.[6] This result implies that limited nodal involvement in gastric lymphoma can be controlled surgically. Before appraising the survival data for radical gastrectomy, however, the reader should understand that our study excluded several stage IIE patients with bulky masses and extensive lymphatic spread to the abdominal cavity that precluded curative resection and necessitated multimodal treatment. Inclusion of these cases would have exacerbated the survival rates of the stage IIE group dramatically. Moreover, the 27 stage IIE patients without massive lymphatic extension in this study might have been classified as stage IE in several institutions that do not perform radical gastrectomy, because of insufficient pathologic information regarding nodal involvement. Such stage misestimation,[15] termed the Will Rogers phenomenon,[25] could worsen the prognosis data of both stage IE and stage IIE patients in these institutions.

Although no statistically significant difference was identified, the prognosis of stage IIE patients in this study appeared worse than that of stage IE patients. No currently available methodology can exclude residual disease beyond the surgical lymphadenectomy margin once nodal involvement is confirmed. This fact, together with the excellent results reported from several institutions,[26,27] convinced us to administer adjuvant chemotherapy for a stage IIE patient, even after a potentially curative resection. Accurate staging by detection of nodal involvement, then, is a prerequisite when selecting patients for treatment with chemotherapy.

Radical gastrectomy with subsequent pathologic examination is a reliable staging tool, providing critical information about nodal involvement. After radical gastrectomy, therefore, accurate staging is provided. Stage IE patients classified in this way had a 5-year survival rate of >95% in this study, and surgical treatment alone might be appropriate.

Depth of infiltration was found to correlate well with survival. The TNM staging system and the Japanese Classification of Gastric Carcinoma include data regarding both depth of invasion and nodal status, and the TNM system has already been acknowledged as an appropriate staging system for primary gastric lymphoma.[28] In the current study, the Japanese classification discerned a significant difference in survival between stages I and III and was found to be a more sensitive indicator of prognosis than the Ann Arbor classification.

Several institutions, including ours, have recently reported that grading according to the histopathologic concept of MALT has great prognostic relevance[4,5,29,30] for primary gastric lymphoma. Such grading classifies B-cell lymphomas into low-grade lymphomas of MALT type and high-grade lymphomas with or without evidence of a low-grade component. In this study, however, such grading revealed no significant differences in survival between groups for gastric lymphoma, perhaps because patients evaluated in this study had good overall prognoses related to their early clinical stage and curative resection. Pure MALT lymphoma was found to have indolent biologic behavior, with no serosal involvement and a lower incidence of nodal metastasis, despite larger tumor diameter. As reported elsewhere,[4] the presence of even small areas of high-grade component seemed to determine the malignant potential of the whole mass, and types II, III, and IV in this study eventually had similar outcomes that were distinct from that of type I. The presence of minute elements of high-grade component could easily be missed by endoscopic biopsy, and the diagnosis of MALT lymphoma by serial endoscopic biopsies can be misleading. Malignant transformation of MALT into large-cell type has been reported in a case treated by chemotherapy alone[12] and suggests the preexistence of this component in what appeared to be a pure MALT lymphoma. Final histopathologic diagnoses in the current study were obtained by careful scrutiny of surgically resected specimens. Patients subsequently confirmed as having MALT lymphoma almost invariably were cured by surgery. Surgery, therefore, is beneficial not only as a staging tool, but also for obtaining accurate pathologic diagnoses.

With technologic advances and improved expertise, more cases of "early" lymphoma with depth of infiltration limited to the mucosa and submucosa have been endoscopically detected.[6,20] In the future, we are hopeful that earlier diagnosis of gastric lymphomas potentially curable by resection will occur. We advocate treatment by surgery alone for patients diagnosed with stage IE (Ann Arbor) or pure MALT lymphoma, provided that staging was performed accurately after radical gastrectomy with histopathologic confirmation.

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