

SURGICAL TREATMENT OF PRIMARY GASTRIC LYMPHOMA : A RETROSPECTIVE STUDY OF 13 CASES

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Abstract : A retrospective study of 13 patients who were operated on primary gastric lymphoma was made to evaluate the influence of clinicopathologic features and method of treatment on survival. There was an association found between tumor size and depth of invasion, or lymph node involvement especially in the localized type. More specifically, when the tumor measured 10 cm or more in diameter, the tumor stage advanced except for the infiltrative-flat type. The estimated 5-year survival rates were 75 % for stage I, 66.7 % for stage II and 50 % for stage IV, respectively. We experienced a case of recurrence in the remnant stomach after resection for an early stage lymphoma of the infiltrative-flat type, and two cases of over 10-year survival after extended resection with adjuvant chemotherapy for advanced stage IV lymphoma. Therefore, we concluded that adequate resection should be performed even for early lymphoma, and also that adjuvant chemotherapy be given for advanced lymphoma.

Index Terms

primary gastric lymphoma, surgical treatment

INTRODUCTION

Primary gastric lymphoma has been reported to be the most common among the gastric sarcomas in Japan and its incidence has been increasing in recent years. However, it constitutes only 1 to 5 % of all gastric malignancies. Because of its rarity, the optimum strategy for the treatment of primary gastric lymphoma remains to be clarified.

In the present study, we clinicopathologically investigated 13 cases of primary gastric lymphoma operated on at our department and discussed the policy for the treatment of this disease.

PATIENTS AND METHODS

Between 1975 and 1992, 13 cases of primary gastric lymphoma (PGL) were surgically resected at the 1st Department of Surgery, Nara Medical University. These cases constituted 1.1 % (13/1182) of all gastric malignancies treated during that period. In this study, PGL was defined according to the criteria of Dawson et al¹⁾ : no palpable superficial lymphadenopathy on initial presentation, no mediastinal lymphnode involvement on chest radiography, white blood cell count and differential counts within normal limits, predominant gastric lesions with only adjacent lymphnodes obviously affected on laparotomy, and no tumor in the spleen or the liver. Staging, depth of invasion and lymphnode metastasis were determined by the General Rules for

the Gastric Cancer Study of the Japanese Research Society for Gastric Cancer²⁾. The LSG classification³⁾ was used for histological analysis. Survival period was determined as the period from the operative day to the date of the patient's death or to December 31, 1993. Survival curves were obtained by the Kaplan-Meier method. Statistical analyses were performed with the generalized Wilcoxon test or the Chi-squared test.

RESULTS

There were six male and seven female patients whose ages ranged from 27 to 76 (mean, 55.5) years. Sixty-nine percent of PGL patients complained of abdominal pain, mainly in the epigastric region. Six cases (46 %) were preoperatively diagnosed as malignant lymphoma, five cases (38 %) as cancer, one as ulcer and one as submucosal tumor. Only 6 of 11 patients who underwent gastroscopy with biopsy were successfully diagnosed as malignant lymphoma. Concerning the operative procedure, six patients had total gastrectomy, four patients had distal subtotal gastrectomy and three patients had distal gastrectomy. There were no operative deaths nor surgical complications.

The pathological characteristics are summarized in Table 1. Seven of 13 tumors (53.8 %) were located in the middle third of the stomach and 3 each (23.1 %) in the upper and lower thirds of the stomach. Macroscopically, there were three cases of infiltrative-flat type in which tumors spread widely and did not form ulcers or elevation clearly, five cases of localized ulcerated types, and five cases of localized elevated types. The maximum diameter of the tumor ranged from 2 to 17 cm and nine (69.2 %) were over 5 cm. Histologically, all tumors were B cell lymphomas and classified as diffuse lymphoma and 5 were the large cell type, 2 the medium-sized cell type, 2 the small cell type, 3 the mixed typed and 1 the pleomorphic type. Depth of invasion was sm in 5 patients, pm in 2, ss in 2, se in 1 and si in 3. Lymph node metastases were n0 in 5 patients, n1 in 2, n3 in 3 and n4 in 1. A significant relationship between tumor size and depth of invasion, or lymph node metastasis was observed in this study. When the localized type tumors reached 10 cm in diameter or larger, tumors invaded beyond the serosa and metastases were detected in the group 3 or 4 lymph nodes (Fig. 1). On the other

Table 1. Pathological characteristics of the primary gastric lymphoma

Stage	Depth of invasion	Lymphnode metastasis	Macroscopic type	Tumor size(cm)	Histological type	Survival period(m)	Dead or Alive
I	sm	0	ulcerated	2	large	86	Alive
I	sm	0	ulcerated	8.5	mixed	69	Alive
I	sm	0	infiltrative-flat	10	large	25	Dead
I	sm	0	infiltrative-flat	11	mixed	58	Alive
I	pm	0	elavated	3.5	small	18	Alive
I	pm	0	elavated	5	small	16	Alive
II	sm	1	infiltrative-flat	8	mixed	83	Alive
II	ss	0	ulcerated	3	pleomorphic	37	Dead
II	ss	0	elavated	6	large	54	Alive
IV	se	3	elavated	13	medium	139	Dead
IV	si	3	ulcerated	11	large	4	Dead
IV	si	3	elavated	14.5	large	121	Alive
IV	si	4	ulcerated	17	medium	3	Dead

m : months

hand, all the infiltrative-flat type tumors were confined to the submucosa, and two of three were 10 cm and over, and n 0.

The estimated 5-year survival rates were 75 % for stage I, 66.7% for stage II and 50 % for stage IV (Fig. 2). The 5-year survival rate among the n 0, 1 patients was 71.4%, and higher than 50 % among the n 3, 4 patients.

All tumors of nine patients who had absolute curative resection were stage I or II. Two of 9 patients died with recurrence or metastasis. Of the 6 stage I patients, only one patient died. She was a 46-year-old woman who had been diagnosed as SLE and Sjögren syndrome with no need for treatment. The tumor was 10 cm in diameter, and was classified the infiltrative-flat

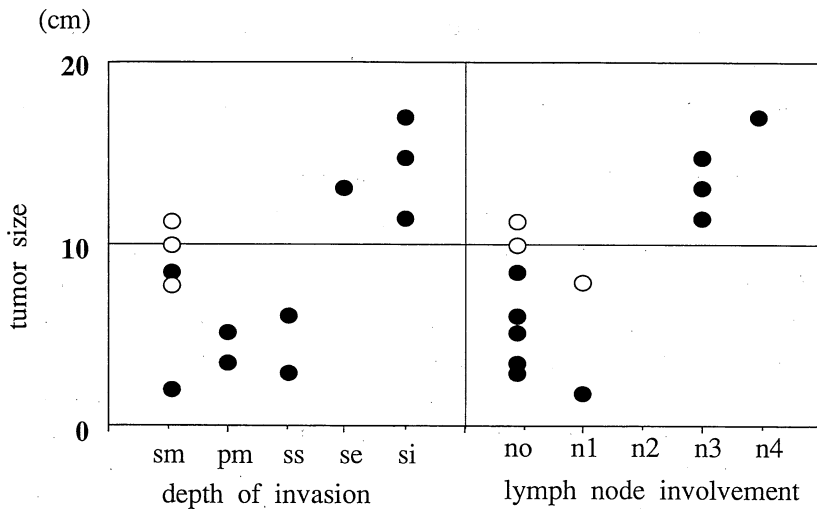


Fig. 1. Relation between tumor size, depth of invasion and lymph node involvement (●: localized type, ○: infiltrating-flat type).

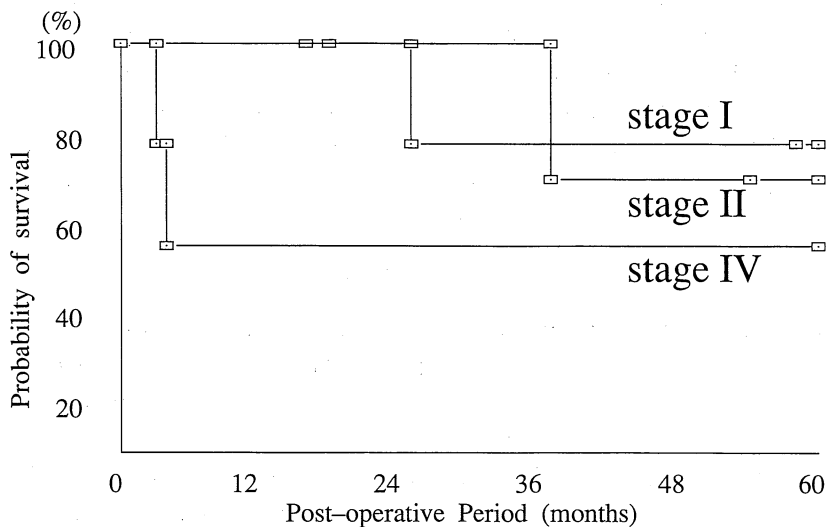


Fig. 2. Survival rate of patients with PGL, according to the stage of disease.

type located in the middle third of the stomach. Distal gastrectomy with lymph node dissection (R2) was performed. Pathologic diagnosis was stage I (P0, H0, n(-), sm), large cell type lymphoma and no lymphoma cells were detected at the proximal margin or distal margin (ow(-), aw(-)). She received chemotherapy with 1 cycle of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone). Malignant lymphoma recurred in the remnant stomach 12 months after the operation. After that she was treated with several cycles of CHOP, but this treatment was not very effective. Subsequently, pulmonary metastasis occurred 19 months later and she died 25 months postoperatively. One of the three stage II patients died. She was a 55-year-old woman. The tumor was 3 cm in diameter and an ulcerated type located in the lower third of the stomach. Distal gastrectomy was performed. Pathologic diagnosis was a stage II (P0, H0, n(-), ss) pleomorphic type lymphoma, which was a relatively rare type. She received chemotherapy for cyclophosphamide (100 mg/day), but died of metastases to mediastinal lymph nodes and bone 37 months postoperatively. Tumors of two patients who received no chemotherapy were stage I, and they were alive and disease-free for 58 and 86 months respectively, postoperatively.

Operation on four advanced lymphoma patients were non-curative resections. The reasons for non-curative resection were lymph node metastasis or tumor invasion into other organs. Of these four stage IV patients, two died of the disease at 3 and 4 months postoperatively, but the other two patients survived for over 10 years after operation. One was a 58-year-old woman, who had 13 cm giant elevated type lymphoma extending from the upper portion to the middle portion, and received subtotal gastrectomy and splenectomy. Pathologically, the lymphoma was a medium-sized cell type with lymph node metastasis (n3). She received postoperative chemotherapy (vincristine, cyclophosphamide), but malignant lymphoma recurred at the inguinal lymph nodes 9 years later and at the cervical lymph nodes 11 years postoperatively. She died 11 years and 7 months postoperatively. Another case was a 27-year-old woman. An elevated type lymphoma extended from the cardia to the body of the stomach and invaded the left lobe of the liver directly. Combined resection (total gastrectomy, distal esophagectomy and splenectomy) with lymph node dissection (R3) was performed. Pathologically the tumor was a large cell type with lymph node metastasis (n3). She was treated postoperatively with 8 cycles of CHOP-B (cyclophosphamide, doxorubicin, vincristine, prednisolone, bleomycin), then cyclophosphamide (100 mg/day) was given for four years. She has survived free of disease for 10 years and 1 month. Two patients who died at 3 and 4 months postoperatively had total gastrectomy and distal gastrectomy, respectively, with adjuvant chemotherapy, but these treatments were not effective.

DISCUSSION

PGL has been reported to represent 1 to 5 % of all gastric malignancies⁴⁾⁵⁾⁶⁾⁷⁾⁸⁾. It constituted 1.1 % in our 18-year study period. Hayes stated that the incidence of PGL had increased and that it was difficult to explain but must be recognized by surgeons and endoscopists⁹⁾. Of our 13 cases, 3 cases were operated on in the first half of the 1975-1983 period and 10 cases in the latter half of the 1984-1992 period. The incidence may be expected to increase still more in the future. However, the biological behavior differs considerably from that of gastric cancer, and so the optimal approach to treatment PGL remains unclear.

The diagnosis of PGL has increasingly improved. The accuracy of diagnosis on endoscopic biopsies was reported to be 33 % by Fleming⁸⁾ in 1983, 37.5 % by Jones¹⁰⁾ in 1988. Schwarz reported in 1993 that the correct diagnosis by endoscopic biopsy had been made in 64 % of their patients and endoscopy was the diagnostic procedure of choice¹¹⁾. In our study, the accuracy was 54.5 % in 11 patients who underwent gastroscopy with biopsy. Of five patients who were misdiagnosed, three patients were diagnosed as having no malignancy and two were diagnosed as having poorly differentiated adenocarcinoma. It is important to take numerous deep biopsies and to have an experienced pathologist available.

The most common location was the middle third of the stomach in our series. Other authors have reported similar results⁸⁾¹¹⁾. However, others have reported that it was the lower third portion⁴⁾⁵⁾⁷⁾. In any report, the most frequent site of PGL was the distal site of the stomach. The mean maximal tumor diameter was reported to be 6-10 cm, ranging from 1.7 cm to 30 cm⁴⁾⁵⁾⁷⁾¹¹⁾. In our study, the mean size was 8.5 cm (range : 2-17 cm). Rosen reported that increased tumor size, increased tumor penetration, and lymph node involvement decreased the probability of survival and that resectability was associated with increased patient survival independent of other prognostic factors⁷⁾. In this study there seemed to be a relation between tumor size and depth of invasion, or lymph node involvement especially in the localized type. In tumors measuring 10 cm or more in diameter, the tumor-grade was highly advanced (se or si, n 3 or n 4).

Surgery is considered to have several advantages for both therapeutic and diagnostic purposes. The first advantage is that surgical exploration affords an opportunity for accurate clinical and pathologic staging. The second advantage is that surgical resection prevents some of the complications like hemorrhage or perforation which may occur during chemotherapy or radiotherapy. And the last advantage is that because gastrectomy removes the bulky primary lesion, the subsequent chemotherapy or radiotherapy becomes more effective. Therefore, surgical resection have been accepted generally as the treatment of first choice for PGL in many reports⁴⁾⁵⁾⁷⁾⁸⁾¹²⁾¹³⁾. Tumors limited to the gastric mucosa or submucosa may be managed by curative resection alone without additional therapy⁴⁾¹⁰⁾¹²⁾. In our series, two of 9 stage I or II patients died of recurrence or metastasis. One of had an infiltrative-flat type lymphoma macroscopically and the other had a pleomorphic type pathologically. The infiltrative-flat type lymphoma seemed to differ considerably from the localized type lymphoma in the clinicopathological features. Seifert reported that infiltrative-flat type lymphomas, which accounted for 23 (34.8 %) of their 66 cases, usually showed low-grade malignancy on histology and had an excellent prognosis; however, they were difficult to diagnose and multiple biopsies were needed to confirm PGL¹⁴⁾. We experienced recurrence from an infiltrative-flat type of stage I tumor one year after distal gastrectomy. The cause for recurrence in the remnant stomach remained unknown. It may have been due to the development of another new lesion or skip lesion. Adequate resection should be carefully considered even for early lymphomas. On the other hand, two stage I patients who did not receive adjuvant chemotherapy were alive and disease-free 58 and 86 months after operation, respectively. Therefore, the role of adjuvant chemotherapy after curative resection for an early stage lymphoma remains unclear.

For an advanced stage lymphoma, extensive surgical procedure, including combined resection and postoperative adjuvant chemotherapy are required. There is general agreement that

chemotherapy is necessary for patients with wide-spread disease. Although there are occasional long-term survivors reported with chemotherapy without resection¹⁵⁾, that modality has not demonstrated sufficiently consistent results to be regarded as a primary treatment. Many other studies have reported an improved survival rate when adjuvant chemotherapy is employed⁴⁾¹⁰⁾¹³⁾. In our series, two of four stage IV patients survived over 10 years with such treatment.

The role of radiotherapy in PGL remains controversial. Some investigators have reported increased survival with radiotherapy⁶⁾¹⁰⁾¹²⁾¹⁶⁾. Others have reported no significant benefit from radiotherapy⁵⁾⁷⁾⁸⁾¹¹⁾. We performed radiation therapy for the metastatic cervical lymph node in only one case. That treatment decreased the tumor size, but the effect on survival was unclear.

CONCLUSION

We regard surgical resection as the treatment of first choice for PGL. For an early lymphoma confined to the mucosa or submucosa, a careful, adequate resection is needed in order to prevent recurrence in the remnant stomach, especially in the infiltrative-flat type. When lymph node involvement is proved pathologically, we should also consider the use of adjuvant chemotherapy. For an advanced lymphoma, we recommend an aggressive extended resection and postoperative multi-agent chemotherapy in expectation of long-term survival. However, further study is needed to fully elucidate the biological behavior of the gastric lymphoma and optimal treatment.

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