Primary Gastric Diffuse Large B-cell Lymphoma

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Background: The optimal treatment of primary gastric large-cell non-Hodgkin's lymphoma (PGL) has not been defined. Recent studies have suggested that organ-preserving treatment produces the same results as surgical treatment.

Methods: We retrospectively reviewed the data of 88 patients diagnosed with PGL between 1995 and 2003 at Chang Gung Memorial Hospital. Sixty-two patients received chemotherapy (CT), three received CT followed by radiotherapy (CT+RT), three received surgery (ST), 14 received surgery followed by CT (ST+ adjuvant CT), one patient received ST followed by radiotherapy (ST+RT), one patient received radiotherapy (RT) alone, one received eradication therapy for *Helicobacter pylori* only and 3 patients received no further therapy after diagnosis.

Results: Of the 81 patients who received endoscopic biopsy of gastric lesions, the diagnosis of PGL could be made in all but one. Seven patients were diagnosed by pathology after ST without preoperative pathologic diagnosis. The complete remission rate was 77.3%. The 5-year overall survival (OS) and disease-free survival (DFS) were 50.0% and 81.6%, respectively. There was no difference in OS (p = 0.4051) and DFS (p = 0.8519) between patients receiving mainly CT (CT or CT+RT) and those receiving primary surgery (ST, ST+ adjuvant CT or ST+RT). We found that poor performance status (p < 0.0001), elevated β2-microglobulin level (p = 0.0082) and no CT (p = 0.0002) had adverse effects on OS.

Conclusion: The present data show that CT should be the primary treatment for patients with PGL if the diagnosis can be made with endoscopic biopsy.

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Key words: non-Hodgkin's lymphoma, large cell, primary gastric lymphoma, chemotherapy

The most frequent site of primary extranodal non-Hodgkin's lymphoma is the gastrointestinal (GI) tract. The stomach is the most common site of primary GI tract lymphoma.[1-5] Primary gastric large-cell non-Hodgkin's lymphoma (PGL) has been treated by various modalities including surgery (ST) alone, chemotherapy (CT) alone, radiotherapy (RT) alone, ST plus adjuvant CT or RT, or CT plus RT. However, the best treatment for PGL has not been well defined.[6,7]

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Previously, surgery with or without adjuvant therapy has been the main treatment for PGL.[8-10] Combination CT, consisting of cyclophosphamide, doxorubicin, vincristine and prednisone, has been the most extensively used regimen for the treatment of non-Hodgkin's lymphoma since the mid 1970s. Raderer et al.[11,12] reported that localized high-grade gastric B-cell lymphoma appeared to be a highly chemosensitive disease. Several groups have described that organ-preserving therapy produced outcomes as good as that achieved by ST alone or ST with adjuvant treatment for PGL.[2,11-17] In this retrospective study, we analyzed the clinical prognostic factors, different treatment modalities and treatment outcomes of patients with PGL.

METHODS

Patients

The medical records of patients with PGL treated between January 1995 and December 2003 at Chang Gung Memorial Hospital were reviewed. Dawson's criteria[18] for PGL were used. Eighty-eight patients met the criteria for PGL: no superficial or mediastinal lymphadenopathy; no liver, spleen, bone marrow or blood involvement; no involvement beyond the stomach and/or regional lymph nodes. All patients were investigated, treated and followed up by the Hematologic Division.

Pathology

The pathological diagnosis was based on histological findings and results of immunohistochemical study of biopsy and/or surgical specimens of gastric tumors.

Staging

The Ann Arbor staging system was adopted.[19] The staging work-up included complete history taking, physical examination, complete blood cell counts, liver and renal function tests, lactate dehydrogenase (LDH) and β-2 microglobulin, chest roentgenogram, upper GI endoscopy and contrast radiographs of GI series, computed tomography of the abdomen and pelvis, and bone marrow aspiration and trephine biopsy. Patients were staged as IE if the lymphoma involved the stomach only and IIE if it involved the regional lymph nodes.

Treatment

CT with cyclophosphamide (COP 750 mg/m^2 i.v. on day 1, vincristine 1.4 mg/m^2 i.v. on day 1, maximum 2 mg, and prednisolone 60 mg/day for 7 days) or cyclophosphamide (CHOP 750 mg/m^2 i.v. on day 1, doxorubicin 50 mg/m^2 i.v. on day 1, vincristine 1.4 mg/m^2 i.v. on day 1, maximum 2 mg, and prednisolone 100 mg/day for 5 days) was used, and was repeated every three weeks. Fourteen patients underwent subtotal gastrectomy and three had total gastrectomy before referral to the Hematologic Division. Surgical indications included diagnosis of gastric tumor (n = 10), suspicion of gastric cancers (n = 6), stomach perforation, two refractory diseases and one intractable bleeding. Seven patients did not have preoperative pathologic diagnosis. Of the remainder, the pathology of preoperative biopsies was one adenocarcinoma and nine lymphomas. Local RT to the stomach was given mainly as an adjuvant treatment.

Statistical analysis

Overall survival (OS) was calculated from the date of diagnosis to the date of last follow-up as of December 31, 2005 or to the date of death. Disease-free survival (DFS) was calculated from the date of complete remission to the date of last follow-up in remission or to the date of relapse. The survival curves were plotted according to the Kaplan-Meier method, and the significance of differences between curves was estimated by the log-rank test. Statistical analyses were performed using SPSS software version 10.0 for Windows (SPSS Inc., Chicago, IL, U.S.A.).

RESULTS

The clinical features and laboratory findings of the 88 patients with PGL are shown in Table 1. The female to male ratio was 1:1.15. The median age of the patients was 61 years. Stage IE disease affected 71.6% of the patients. The Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1 in 90% of patients. Moderate anemia [hemoglobin (Hb) < 10 g/dl] was present in 23 patients (26.1%). The LDH level was elevated in 14 (17.1%) of 82 patients tested. An elevated β2-microglobulin level was found in 23 (27.7%) of 83 patients tested.

Eighty-one patients received endoscopic exami-

nation with biopsy taken from their stomach lesions, from which the diagnosis could be made in all but one patient. Seven patients received endoscopic examination without biopsy and then underwent ST because the gastric lesions or ulcers were highly suspected of malignancy. In total, 14 patients received subtotal gastrectomy and three patients received total gastrectomy. One patient received total gastrectomy for gastric perforation before diagnosis. Nine patients had lymphoma diagnosed before ST, and another one received subtotal gastrectomy because of gastric perforation after two cycles of CT.

Sixty-two of 88 (70.5%) patients received CT alone and three patients received CT+RT. Three patients underwent ST alone. Fourteen patients received ST+CT and one patient had ST+RT. One patient was treated with RT alone and another one with only eradication therapy for *Helicobacter pylori*. Three patients did not receive any treatment after diagnosis.

No acute bleeding occurred before or after CT in the present series. One patient presented with stomach perforation before treatment and another patient had stomach perforation after two cycles of CT. They were treated successfully with surgery. One of our three patients who received total gastrectomy died of massive bleeding following surgery. There was no difference between patients who received surgical intervention and CT with respect to gender, age, stage, performance status, and Hb or β2-microglobulin level. All patients had normal LDH levels in the ST group compared with 79% in the CT group (Table 2). As of December 31, 2005, 14 patients were lost to follow-up (median follow-up time 104.75 months) and 39 patients were still alive, with a median survival time of 62.70 months.

The complete response rate of all of our patients with PGL was 77.3%. Their 5-year OS was 50.5%

Table 1. Clinical Features of Patients with Primary Gastric Large-cell Lymphoma

Feature	No. of patients	%
Gender		
M	41	46.6
F	47	53.4
Age (median, range)	61, 18 – 88	
> 60 years	46	52.3
< 60 years	42	47.7
Stage		
IE	63	71.6
IIE	25	28.4
PS (ECOG)		
0, 1	79	89.8
2-4	9	10.2
Hb (median, range)	11.5, 4.5 – 15.3	
≥ 10 g/dl	65	73.9
< 10 g/dl	23	26.1
LDH (median, range)	63, 12 – 611	
Normal (47-140 u/l)	68	82.9
Elevated	14	17.1
β2-MG (median, range)	1865, 861 – 6414	
Normal (800-2400 μg/l)	60	72.3
Elevated	23	27.7

Abbreviations: M: male; F: female; PS: performance status; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; LDH: lactate dehydrogenase; β2-MG: β2-microglobulin.

Table 2. Comparison of Characteristics of Patients Receiving Surgical Treatment and Chemotherapy Alone for Primary Gastric Large-cell Lymphoma

Feature	STG + TG (n = 17)	CT alone (n = 62)
Gender		
M	10 (58.8%)	28 (45.2%)
F	7 (41.2%)	34 (54.8%)
Age		
> 60 years	10 (58.8%)	32 (51.6%)
< 60 years	7 (41.2%)	30 (48.4%)
Stage		
IE	12 (70.6%)	45 (72.6%)
IIE	5 (29.4%)	17 (27.4%)
PS (ECOG)		
0, 1	15 (88.2%)	58 (93.5%)
2-4	2 (11.8%)	4 (96.5%)
Hb (g/dl)		
> 10	12 (70.6%)	49 (79.0%)
< 10	5 (29.4%)	13 (21.0%)
LDH		
Normal (47-140 u/l)	15 (100%)	48 (81.4%)
Elevated	0 (0%)	11 (18.6%)
β2-MG		
Normal (800-2400 μg/l)	10 (66.7%)	44 (74.6%)
Elevated	5 (33.3%)	15 (25.4%)

Abbreviations: STG: subtotal gastrectomy; TG: total gastrectomy; CT: chemotherapy; M: male; F: female; PS: performance status; ECOG: Eastern Cooperative Oncology Group; Hb: hemoglobin; LDH: lactate dehydrogenase; β2-MG: β2-microglobulin.

[95% confidence interval (CI): 39.2 ~ 61.9%] and 5-year DFS was 82.6% (95% CI: 72.4 ~ 93.0%) (Figures 1A and 1B). There was no difference in OS (p = 0.4051) or DFS (p = 0.8519) between patients receiving CT as their main therapy (CT or CT+RT) and those receiving primary surgery (ST, ST+CT and ST+RT) (Figures 2A and 2B). No difference in OS (p = 0.9654) and DFS (p = 0.1755) was observed between patients receiving CT alone and those receiving ST+CT (Figures 3A and 3B).

Outcome was analyzed for correlation with clinical and laboratory findings including age, gender, disease stage, performance status, and Hb, LDH and β2-microglobulin levels, as well as treatment modalities of CT(+) or CT(–), and ST(+) or ST(–) (Table 3). The results showed that poor performance ($p < 0.0001$), elevated β2-microglobulin level (p = 0.0082) and no CT (p = 0.0002) had adverse effects on OS.

DISCUSSION

Surgery was previously regarded as the treatment of choice for PGL: the rationale was that diag-

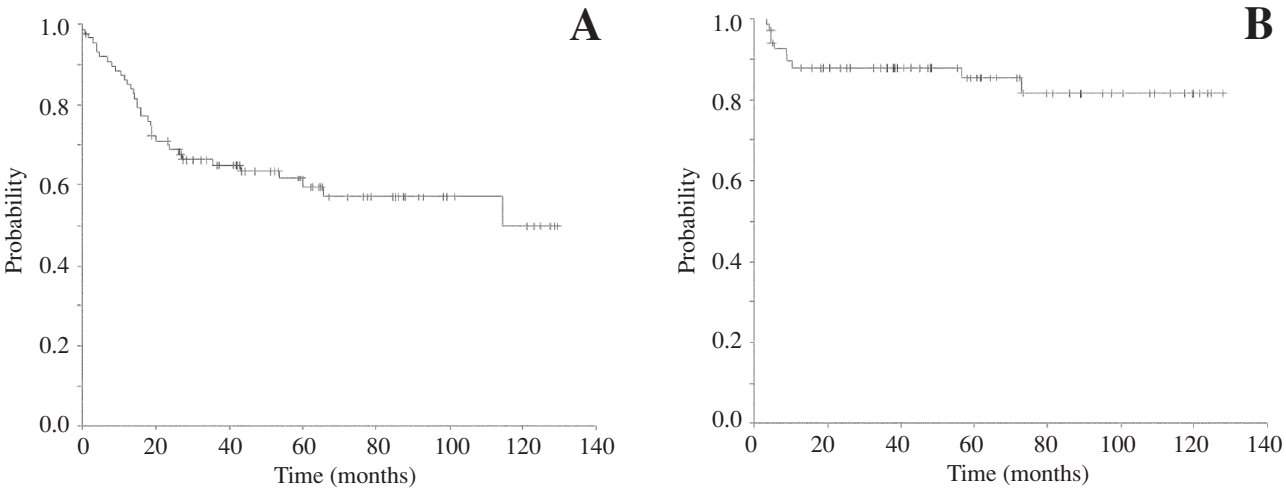

Fig. 1 Kaplan-Meier estimates of 5-year overall survival (50.5%) (A) and 5-year disease-free survival (82.6%) (B) of 88 patients with primary gastric large-cell lymphoma.

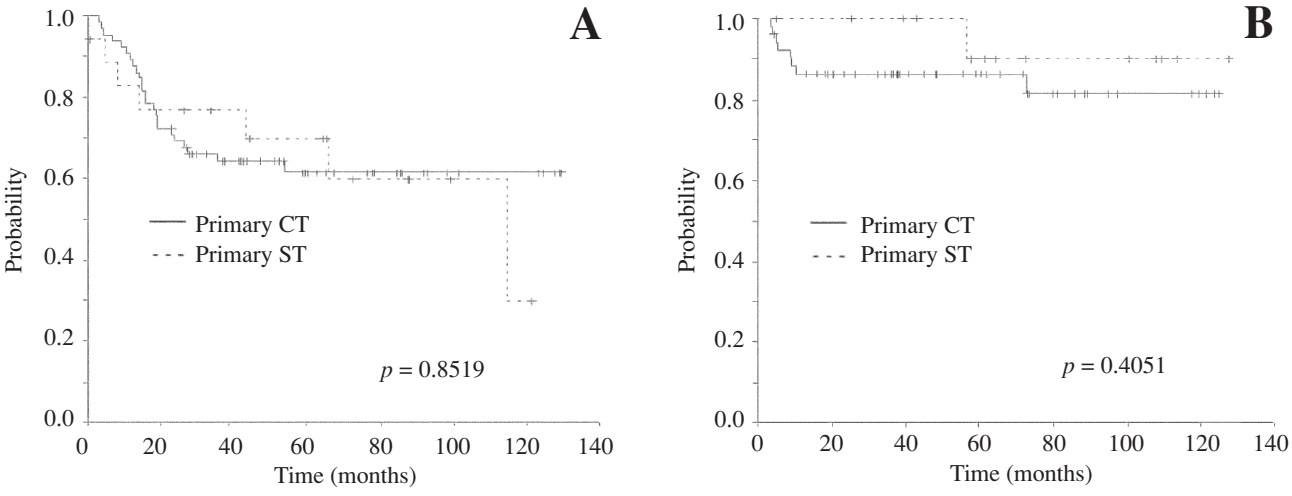

Fig. 2 Kaplan-Meier estimates of overall survival of patients with primary gastric large-cell lymphoma according to treatment with primary chemotherapy (n = 65) or primary surgery (n = 18) (A), and disease-free survival (B).

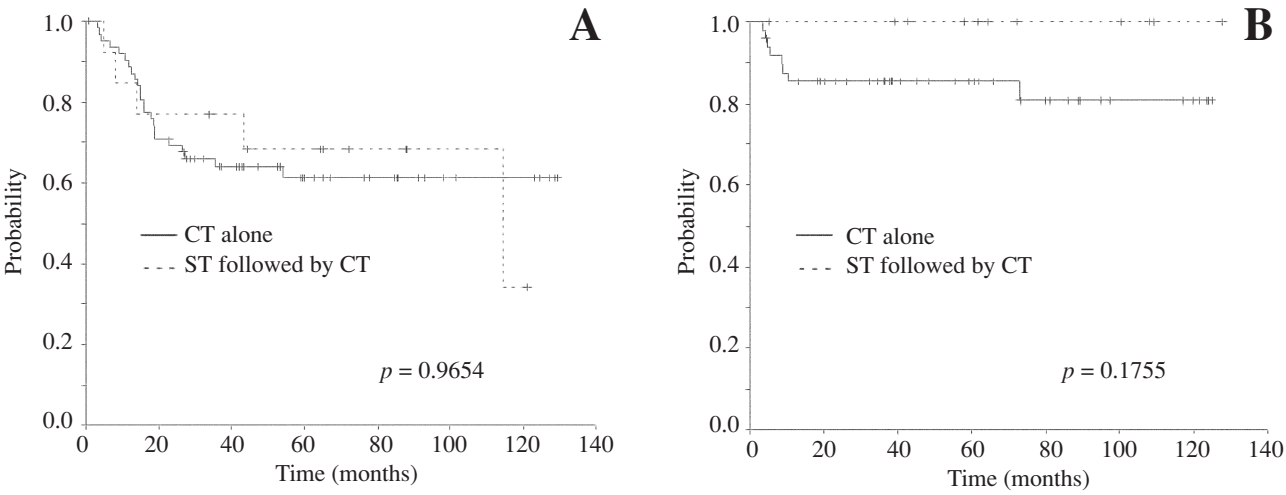

Fig. 3 Kaplan-Meier estimates of overall survival of patients with primary gastric large-cell lymphoma according to treatment with chemotherapy alone (n = 62) or surgery followed by chemotherapy (n = 14) (A), and disease-free survival (B).

Table 3. Comparison of Clinical and Laboratory Findings of Patients with Primary Gastric Large-cell Lymphoma

Factors	Median OS, months (95% CI)	*p* value	Median DFS, months (95% CI)	*p* value
Gender		0.0690		0.3484
M	44.30 (0.1-90.54)		Not reached	
F	86.00 (40.03-131.97)		Not reached	
Age		0.6622		0.8982
> 60 years	51.80 (8.11-95.49)		Not reached	
< 60 years	70.90 (34.09-107.71)		Not reached	
Hb		0.2430		0.5293
> 10g/dl	70.90 (26.40-115.40)		Not reached	
< 10g/dl	46.50 (7.02-85.98)		Not reached	
Stage		0.3666		0.6619
IE	70.90 (24.14-117.66)		Not reached	
IIE	46.50 (5.95-87.05)		Not reached	
PS		< 0.0001		0.4742
0,1	70.90 (35.86-105.94)		Not reached	
2-4	10.60 (0.1-22.58)		–	
LDH		0.4449		
normal	70.90 (18.64-123.16)		Not reached	0.1838
elevated	46.56 (3.2-100.10)		–	
β2-MG		0.0082		0.5330
normal	86.0 (43.43-128.57)		Not reached	
elevated	44.3 (4.34-84.26)		Not reached	
With ST	64.50 (23.32-105.68)	0.4873	Not reached	0.2396
Without ST	59.7.0 (16.05-103.35)		Not reached	
With CT	86.0 (42.05-129.95)	0.0002	53.90 (3.80-53.90)	0.0027
Without CT	13.80 (0.1-34.54)		Not reached	

Abbreviations: OS: overall survival; DFS: disease-free survival; CI: confidence interval; M: male; F: female; Hb: hemoglobin; PS: performance status; LDH: lactate dehydrogenase; β2-MG: β2-microglobulin; ST: surgery; CT: chemotherapy.

nosis, staging and treatment could be achieved at the same time. In the earlier series, early and accurate diagnosis of PGL was difficult because of non-specific presenting symptoms and low diagnostic rate by barium contrast study of the upper GI tract. Therefore, surgical resection was required for both diagnosis and treatment. However, recent evidence has shown that the diagnostic accuracy of endoscopic examination with biopsy of the gastric malignancy is over 90%.[20] In the current study, all patients except one were diagnosed by endoscopic biopsy of gastric lesions. Furthermore, the extent of disease can be accurately staged by computed tomography, magnetic resonance imaging or endoscopic ultrasonogram, thus avoiding the necessity of staging laparotomy.

The risk of tumor bleeding or stomach perforation during or after CT has been a concern. However, these complications have been generally overestimated.[21,22] CT-related mortality has been reported to be about 0%-2%.[22-25] Surgical indications in patients who have received chemotherapy as the first-line treatment include refractory gastric bleeding or gastric outlet obstruction under medical treatment. Spectre G. et al.[26] reported only one of 73 patients (1.3%) receiving ST for resistant disease after CT, and no stomach perforation occurred during or after CT. In our series, no patient had acute bleeding following CT, two patients (3.1%) received ST for refractory disease and only one of 65 patients (1.5%) receiving CT had perforation of the stomach. Another one had perforation before any treatment was given. These patients were successfully treated with prompt surgical intervention following gastric perforation. One of our three patients who received total gastrectomy as the primary therapy died of massive bleeding following surgery. Viste A. et al.[27] reported that the postoperative mortality rate of gastric resection was 8.3%, and was highest in patient undergoing proximal resection (16%) compared with total gastrectomy (8%), subtotal gastrectomy (10%) or distal resection (7%). The complications of gastrectomy are both short- and long-term, and have included early satiety, abdominal discomfort, afferent loop syndrome, mal-absorption and dumping syndrome.[14,28,29] All such gastrectomy-related morbidity and mortality will delay postoperative CT.

Several groups have reported that the response to CT or RT alone or in combination was as effective as that of surgery for PGL.[21-25, 30] Their observations suggested that surgery did no benefit patients with PGL if the diagnosis could be made by endoscopic biopsy. Moreover, CT and RT will preserve the function of the stomach. Our results showed that there was no difference in OS or DFS between patients receiving surgery followed by CT and those receiving CT alone. These data suggest that surgery was of limited value in the initial treatment of PGL. In the present series, the number of patients undergoing surgical resection was relatively small during the study period, which reduces the power to reach statistical significance.

In conclusion, the current study confirmed that surgery should not be the initial treatment of PGL. Stomach preservation with CT alone or CT followed by RT is favored.

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胃部原發性大細胞淋巴瘤

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背 景： 分析胃部原發性惡性淋巴瘤之治療與預後。

方 法： 本回顧性研究共分析 88 例於 1993 年 1 月至 2003 年 12 月在林口長庚紀念醫院診斷爲胃部原發性大細胞淋巴瘤患者，評估治療方式與預後。

結 果： 全部 88 例胃部原發性大細胞淋巴瘤患者，有 62 例接受化學治療，3 例接受化學治療與放射治療，3 例接受切除手術，14 例於手術切除後接受化學治療，一例手術後接受放射治療，一例只接受放射治療，一例接受抗幽門螺旋桿菌抗生素治療，有三例患者在診斷後未接受任何治療。胃部原發性惡性淋巴瘤治療完全緩解率爲 77.3%，五年存活率爲 50.5%，五年疾病無復發率爲 82.6%。僅接受化學治療或合併放射治療，與接受手術切除或合併術後化學治療／放射治療者的五年存活率或五年疾病無復發率沒有差別。病患若有較差的生活機能，較高 $\beta 2$ 微小球蛋白值或未接受化學治療者，其五年存活率較差。病患接受化學治療者五年疾病無復發率較高。

結 論： 化學治療可以保全胃部功能，並獲得好的療效。手術治療對於胃部原發性大細胞淋巴瘤不是首選的治療方式。

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關鍵詞： 非何杰金氏淋巴瘤，大細胞，胃部原發性淋巴瘤，化學治療

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