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Therapeutic Comparison of Chemotherapy and Surgery for Early Stage Diffuse Large B-cell Gastric Lymphoma

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Purpose: The use of surgery versus stomach-preserving treatment for primary gastric lymphoma has caused controversy among doctors. This retrospective, single center study aims to evaluate the efficacy and benefit of stomach-preserving treatment against surgery for early stage diffuse large B-cell lymphoma of stomach. **Materials and Methods:** From August 1991 to January 2006, 43 cases of early-stage diffuse large B-cell gastric lymphoma were reviewed. **Results:** Eleven cases were treated with chemotherapy or chemotherapy plus radiation (CT ± RT), 17 were treated with surgery alone (OP), and 15 were treated with surgery plus adjuvant chemotherapy (OP + CT). The complete remission and response rates were 63.6% and 90.9% in those treated with CT ± RT (7 complete responders, 3 partial responders, 1 non-responder), 100% and 100% in those treated with OP, and 100% and 100% in those treated with OP + CT, respectively. Five-year overall survival rates were 85.7%, 87.5%, and 100% in those treated by CT ± RT, OP, and OP + CT, respectively ($p = 0.76$). The five-year disease free survival rates were 100%, 87.5% and 100% in those treated by CT ± RT, OP, and OP + CT, respectively ($p = 0.99$). There was no significant difference in overall survival and disease free survival between modalities. Even though there are no definite differences in the number of complications between those treated by CT ± RT or OP, these facts reflect little concern on complications after surgery. **Conclusion:** In preventing morbidity arising from early or late complications from surgery and promoting quality of life, chemotherapy should be a primary consideration for early stage diffuse large B-cell lymphoma of the stomach.

Key Words: Early gastric lymphoma, diffuse large B-cell, chemotherapy

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INTRODUCTION

Gastric non-Hodgkin's lymphoma accounts for less than 15% of gastric malignancies and 2% of lymphomas, and the stomach is the most common site of extra-nodal involvement in non-Hodgkins's lymphoma.[1-3] Radical surgery has been considered essential for diagnosis and determination of disease stage and for regional tumor control. MALT-type lymphoma is strongly associated with Helicobacter pylori infection, and eradication of H.pylori with antibiotics has replaced radical surgery for the initial treatment of MALT-type lymphoma.[4] For advanced disease, chemotherapy has been the first line of treatment, while in localized disease (stages IE, II1E, and II2E), treatment modalities are controversial. Therefore, we undertook a study to compare the results of treatment modalities in early stage primary gastric diffuse large B-cell lymphoma.

MATERIALS AND METHODS

Patients

We reviewed the records of 43 patients diagnosed between 31 August 1991 and 28 October 2005 with localized gastric diffuse large B-cell lymphoma who were treated at Yonsei Medical Center. Based on Lewin et al,[5] primary gastric lymphoma was defined as disease confined to the stomach or clearly predominant within the stomach and with gastrointestinal symptoms. All cases were histologically proven as diffuse large B-cell lymphoma. Cases of MALT-type lymphoma were excluded.

Staging & response criteria

Staging procedures included physical examination, complete blood cell count with differential count, blood chemistry, chest x-ray, upper gastrointestinal endoscopy with biopsy, and computed tomography of the chest, abdomen, and pelvis. Positron emission tomography was used on recently diagnosed patients for staging evaluation. Some patients with stage I cancer who received surgical treatment did not undergo bone marrow aspiration and biopsy. Stage was assessed using the Musshoff modification of Ann Arbor system. Stage IE disease was defined as disease confined to stomach only. Stage IIE was defined as disease extending into the abdomen with involvement of local (perigastric) lymph nodes (IIE_1) or even distant (mesenteric, paraortic) lymph nodes (IIE_2). Response evaluation was defined according to World Health Organization criteria. A complete response or remission was defined as the complete disappearance of all measurable lesions for at least 4 weeks. A partial response or response was defined as greater than or equal to a 50% reduction in the size of all measurable lesions for at least 4 weeks with no appearance of new lesions. A progressive disease was defined as at least a 25% increase lesion size. Stable disease was defined as a disease that met neither partial response nor progressive disease criteria.

Statistical analysis

Overall survival was calculated using the date of diagnosis to January 8, 2006 or death, whichever occurred first. For those undergoing chemotherapy or chemotherapy plus radiotherapy, disease-free survival was calculated as the time from the documented date of complete response to the first relapse or last follow up date, whichever occurred first. For those undergoing surgery or surgery plus chemotherapy, disease-free survival was calculated as the time from the date of surgery to the date of relapse or the last follow up, whichever came first. Survival rate was estimated by the Kaplan-Meier method, and differences were evaluated using the Log-rank test.

RESULTS

Patient characteristics

Patient characteristics and clinical features are summarized in Table 1. There were 21 cases (48.8%) of stage IE disease, 14 cases (32.6%) of

Table 1. Patient Characteristics

		CT ± RT	OP	OP + CT	Total
No. of cases (%)		11 (25)	17 (41)	15 (34)	43
Age, mean (yrs)		52.9	53.4	52.7	52.9
Range		41 - 71	17 - 74	36 - 72	17 - 74
Sex	M	5	7	8	20
	F	6	10	7	23
Stage	IE	3	13	5	21
	IIE_1	4	3	7	14
	IIE_2	4	1	3	8
Total gastrectomy		-	1	11	12
Subtotal gastrectomy		-	16	4	20
B symptoms		1	1	0	2

CT ± RT, chemotherapy ± radiotherapy; RT, radiotherapy; OP, operation.
A patient who refused treatment was excluded.

Table 2. Chemotherapy Regimens

Tx group	Regimen	No.
CT ± RT	R-CHOP	4
	CHOP	3
	ProMACE/CytaBOM	2
OP + CT	CHOP	5
	R-CHOP	1
	CHOP + Etoposide	1
	CEOP	1
	BACOP	2
	VACOP	3
	BACOP + ProMACE/CytaBOM	1
	R-VACOP	1

CHOP, Cyclophosphamide 750 mg/m^2 at D1, doxorubicin 50 mg/m^2 at D1, vincristine 1.4 mg/m^2 at D1, prednisolone 100 mg at D1 to D5; R-CHOP, Rituximab 375 mg/m^2 at D1, added to CHOP; ProMACE/CytaBOM, Prednisolone 60 mg/m^2 at D1 to D14, doxorubicin 25 mg/m^2 at D1, cyclophosphamide, etoposide 120 mg/m^2 at D1, cytarabine 300 mg/m^2 at D8, bleomycin 5 U/m^2 at D8, vincristine 1.4 mg/m^2 at D8, methotrexate 120 mg/m^2 at D8, leucovorin 25 mg/m^2 by P.O. 6 times per day on methotrexate administration; BACOP, Bleomycin 5 U/m^2 at D15 & D12, doxorubicin 25 mg/m^2 at D1 & D8, cyclophosphamide 650 mg/m^2 at D1 & D8, vincristine 1.4 mg/m^2 at D1 & D8, prednisolone 60 mg/m^2 on D1 to D14; CAVOP, Cyclophosphamide 550 mg/m^2 on D1, doxorubicin 35 mg/m^2 on D1, etoposide 100 mg/m^2 on D1, vincristine 1.2 mg/m^2 on D1, prednisolone 50 mg/m^2 on D1 to D10; R-CAVOP, Rituximab 375 mg/m^2 on D1 added to CAVOP.

stage IIE_1 disease, and 8 cases (18.6%) of stage IIE_2 disease. Two cases had B symptoms (4.7%). Chemotherapy or chemotherapy plus radiotherapy (CT ± RT) was used in eleven cases as the first line treatment; 3 of these patients underwent adjuvant radiotherapy. Seventeen cases underwent surgery alone (OP) as a first line therapy, and 15 cases underwent surgery plus chemotherapy (OP + CT).

Chemotherapy regimens used in the study are summarized in Table 2. A majority of the patients received the CHOP regimen with or without Rituximab. In those treated by OP, one case had a total gastrectomy, and 16 cases had a subtotal gastrectomy. In those treated by OP + CT, 11 cases had a total gastrectomy, and 4 had a subtotal gastrectomy. One case in those treated by OP + CT underwent an emergency operation due to panperitonitis from perforation; the rest in this group underwent surgery with curative intent.

Response to treatment

The results of each treatment modality are shown in the Table 3 and Fig. 1 and 2. Within the first 3 - 6 cycles of chemotherapy, seven patients treated by CT ± RT completely responded, and 3 partially responded (complete response rate, 63.6%; overall response rate, 90.9%). One partial responder achieved complete response after the second line chemotherapy. The other two partial responders refused further treatment but remained alive at the conclusion of this study. One patient discontinued treatment after only 1 cycle of chemotherapy and died 1 year after chemotherapy. The complete response and overall response rates were both 100% in those treated by OP and in those treated by OP + CT. One patient treated by CT ± RT relapsed, as did 4 patients treated by OP and 1 patient treated by OP + CT. One patient (9.1%) treated by CT ± RT died, as did 3 (17.6%) treated by OP and 1 (6.7%) treated by OP + CT. In all, there were a total of 5 (11.6%) deaths, and

Table 3. Complete Response, Overall Survival, and Disease Free Survival in Patients with Different Treatment Modalities

	No.	CR (%)	RR (%)	Relapse (n)	Death (n)	OS (%)		*p*	DFS s (%)		*p*
						3-year	5-year		3-year	5-year	
Total	43	93.0	97.7	5	5	91.4	91.4		100	93.8	
CT ± RT	11	63.6	90.9	1	1	89.0	85.7		100	100	
OP	17	100	100	4	3	87.5	87.5	0.76	87.5	77.8	0.99
OP + CT	15	100	100	1	1	100	100		100	100	

CR, complete response; RR, response rate; OS, overall survival; DFS, disease-free survival; CT ± RT, chemotherapy group and chemotherapy followed by radiotherapy group; OP, surgery alone group; OP + CT, surgery followed by chemotherapy group.

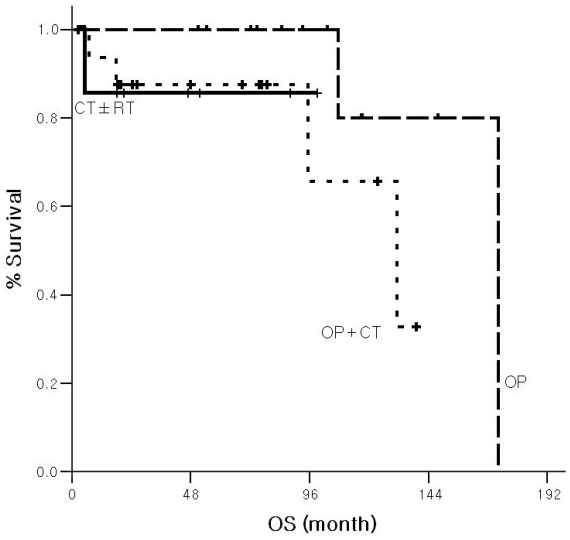

Fig. 1. Overall survival.

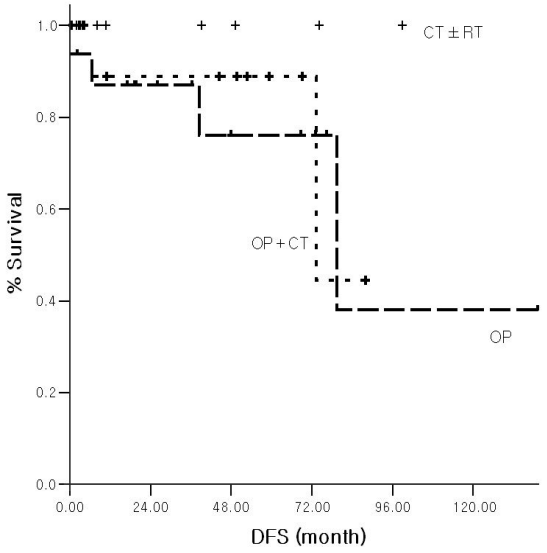

Fig. 2. Disease free survival.

all died as a result of disease progression.

The overall survival rate for all 43 cases was 91.4% at both the 3- and 5-year time points. Disease free survival was 100% at 3 years and 93.8% at 5 years. The 3-year overall survival rate of those treated by CT ± RT was 85.7%. It was 87.5% for those treated by OP and 100% for those treated by OP + CT. The 5-year overall survival rate was the same as the 3-year overall survival rate in all groups ($p = 0.76$). The 3-year disease free survival rate was 100% in those treated by CT ± RT and by OP + CT, and it was 87.5% in those treated by OP. The 5-year disease free survival rate was 100% in those treated by CT ± RT, 77.8% in those treated by OP, and 100% in those treated by OP + CT ($p = 0.99$).

Complications

Table 4 lists complications that arose in each group. Two cases experienced sepsis during the neutropenic period but fully recovered with antibiotics and G-CSF (Granulocyte-Colony Stimulating Factor). One case treated by CT had upper gastrointestinal bleeding during chemotherapy and was successfully treated by endoscopy. Two cases treated by OP suffered malabsorption after gastrectomy, and 1 case presented with frequent reflux of bile. Among those treated by OP + CT, 2 cases had malabsorption, and 1 case had

Table 4. Complications of Treatment

Treatment	Complication	No.
CT ± RT	Sepsis due to neutropenia	2
	Upper gastrointestinal bleeding	1
OP	Malabsorption	2
	Bile regurgitation	1
OP + CT	Malabsorption	2

panperitonitis due to cancer perforation before diagnosis. Among the 4 cases treated by OP and the 6 cases treated by OP + CT who underwent gastrectomy and who had regular follow-ups to measure serum vitamin B_{12} and folic acid levels, there was found none of them (4 cases total gastrectomy, 6 cases subtotal gastrectomy).

DISCUSSION

Studies have long supported surgery as the first line of treatment for patients with localized gastric lymphoma.[6,7] The rationale for surgery as a first-line treatment included the fact that patients who underwent surgery had a better prognosis than those who did not. Also, surgery might reduce the chance of perforation or gastrointestinal bleeding during chemotherapy. Finally, surgery allowed exact staging of patients. Maor et al. reviewed 79 cases of primary gastric non-Hodgkin's lymphoma (stages IE and IIE) and compared the survivors in each treatment group. Even though there were few cases, their data suggested a reassessment of surgery as the first-line treatment. Laparotomy and resection associated with substantial mortality and morbidity, and accurate staging by laparotomy seldom changed treatment. Specifically, there were 5 perioperative deaths among 31 patients (16%) who underwent surgery, while there were no complications among the 35 patients treated by chemotherapy. CHOP-Bleo (cyclophosphamide, vincristine, doxorubicin, prednisolone, bleomycin) chemotherapy alternated with local radiotherapy can achieve local tumor control and obviates the need for resection. Thus, Maor et al. recommended that surgical resection be reserved for tumors that do not respond to initial chemotherapy or for cases with complications.[8]

According to Avilés et al., 28 cases were treated with a regimen of CHOP-Bleo alternating with CMED (cyclo-phosphamide, methotrexate, etoposide and dexamethasone), and 24 cases received the same regimen after surgery. The complete remission rate for chemotherapy was 92.9% (26 cases). There was no significant difference between the two groups.[9]

Liu et al. advocated systemic chemotherapy alone after comparing the treatment outcome of surgery plus chemotherapy (21 cases) versus chemotherapy alone (38 cases) for early gastric diffuse large-cell lymphoma. The complete response rate in those treated by chemotherapy was 80.6%, and the overall response rate was 83.3%. The 5-year overall survival rate and relapse-free survival rate were 72.6% and 86.0%, respectively, in those treated by chemotherapy alone, while they were 77.8% and 77.9%, respectively, in those treated by surgery plus chemotherapy ($p = 0.40$, overall survival; $p = 0.94$, relapse-free survival).[10]

Avilés et al. conducted another controlled clinical trial for 589 cases of primary early stage diffuse large cell gastric lymphoma. In their study, 10-year overall survival rates were 54% for surgery, 53% for surgery plus radiotherapy, 91% for surgery plus chemotherapy, and 96% for chemotherapy ($p < 0.001$). Event-free survival rates at 10 years were 27% for surgery, 23% for surgery plus radiotherapy, 82% for surgery plus chemotherapy, and 92% for chemotherapy.[11] Treatments that included chemotherapy resulted in better survival than surgery.

Furthermore, in another Korean multi-center study, Kang et al. reviewed 130 cases of primary aggressive B-cell lymphoma of the stomach. Complete response rates were 80% for chemotherapy. Three-year failure-free survival rates were 78% for chemotherapy and 84% for surgery plus chemotherapy ($p = 0.1735$). Three-year overall survival rates were 86% for chemotherapy and 88% for surgery plus chemotherapy ($p = 0.441$). Our data and the abovementioned reports strongly suggest that surgery gives no additional advantage to the survival and prevention of relapse.[12]

In a recent randomized multi-center study supporting stomach-preserving treatment for gastric lymphoma,[13] the overall survival rate was 86.6% for surgical management and 87.0% for stomach-preservation 42 months after treatment. The event-free survival rates were 83.9% for surgical management and 84.5% for stomach preservation, which is not significantly different.

Due to treatments for complications, perioperative mortality was 1.5 - 16%.[8,14] However, Gobbi et al reviewed 682 cases and redefined perioperative mortality as 7.2% (49 cases).[15] Anastomosis leakage was observed in 1.5 - 5% of the cases,[10,14] and gastrointestinal bleeding from the remnant stomach or from the anastomosis site was observed in 1.5 - 10% of the cases.[10,14] The most common late post-surgical complications were 'dumping syndrome' (6.4%) and malabsorption (5.5%).[11] In contrast to those treated by surgery, the most common complication following chemotherapy was neutropenia (8.5 - 71%), accompanied by sepsis in 5.6% of the cases.[16,17] Gastrointestinal bleeding was reported in 3 - 5.6% of the cases,[10,16] and perforation occurred in 5% of the cases.[10] In Gobbi's report, 5 of 188 patients (2.7%), who underwent stomach-preservation treatment, died of gastrointestinal bleeding or perforation.[15]

In the current study, there was no perioperative or chemotherapy-related mortality, markedly different from previously reported studies. In contrast to Gobbi's report of chemotherapy-related fatal complications, such as gastrointestinal bleeding and perforation, we observed no perforations and only 1 case (9%) of bleeding, which was successfully controlled. Neutropenia and sepsis were observed more frequently here than in other Korean studies. Surgery-related malabsorption was observed here more frequently than in Aviles' study, whereas anastomosis leakage and bleeding were not seen here.

Total gastrectomy removes IF-producing cells and leads to cobalamin deficiency in about 5 years (range, 2 - 10 years). After subtotal gastrectomy, less than 1% of patients show frank cobalamin deficiency, but 25 - 50% have depressed cobalamin levels.[18] The importance of cobalamin deficiency from gastrectomy has been emphasized because of occasional non-reversible neurological deficits. In a Korean report of 59 cases with total gastrectomy, 41 cases (69.5%) developed B_{12} deficiency 4 years after surgery. Neurologic deficit occurred in 9 cases (15.3%) in a median time of 33.4 months.[19] Hines et al. and Khalid et al. reported cobalamin deficiency in only 10 - 20% of patients 8 years after partial gastrectomy. Up to 6% of these cobalamin-deficient patients developed manifestations of cobalamin deficiency with megaloblastic anemia.[20,21] In our study, 4 cases who were treated by total gastrectomy and 6 cases treated by subtotal gastrectomy were followed up for longer than 5 years (maximal 9.6 years follow up for total gastrectomy, 7.5 years for subtotal gastrectomy). There was no reported occurrence of vitamin B_{12} deficiency or megaloblastic anemia in our study, which inevitably arises from total or subtotal gastrectomy.

In conclusion, to prevent morbidities arising from early or late surgical complication and to promote quality of life, chemotherapy should be considered a primary choice in early stage diffuse large B-cell lymphoma of the stomach. Also, further studies are needed to determine whether the best chemotherapy regimen involves radiation.

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