

The Role of D2 Gastrectomy for the Treatment of Primary Gastric Lymphoma: 9-Year Experience at Ramathibodi Hospital

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Abstract

Background: Primary gastric lymphoma (PGL) is a relatively rare disease. Several reports have discussed the therapeutic benefit of various treatment strategies for PGL. The role of surgery in the management of localized PGL remains controversial. However, few studies have been based on patients accurately staged by systematic lymph node dissection.

Objective: The aim of this study was to evaluate the therapeutic efficacy of D2 gastrectomy with curative intent for PGL. This is the first report of the result of D2 gastrectomy for PGL in Thai patients.

Materials and Methods: We retrospectively reviewed the clinicopathologic features, surgical outcome, morbidity and mortality in 12 patients with PGL who underwent D2 gastrectomy with curative intent during the period between May 1995 and October 2003.

Results: Diffuse large cell lymphomas in this homogenous group of patients were all localized diseases (stage I, III1 or IIE). Endoscopic biopsies revealed malignant lymphoma in only 6 patients (50%). Total gastrectomy and subtotal gastrectomy was each performed in 6 patients. Five patients underwent D2 gastrectomy alone, whereas seven patients received postoperative adjuvant chemotherapy. The morbidity rate was 25% and there was no operative death. The median follow-up time was 60.4 months (ranged 24-103 months). At the last follow-up period of at least 2 years after surgery, all patients were still alive. Ten patients (83.3%) were alive without disease and 2 patients (16.7%) were alive with disease relapse.

Conclusion: The results suggest that surgery remains the appropriate frontline therapy for localized PGL.

INTRODUCTION

Primary gastric lymphoma (PGL) is defined as an extranodal lymphoma arising in the stomach.¹ Secondary gastric lymphoma indicates involvement of the stomach as a part of a diffuse or disseminated lymphoma arising elsewhere.¹ Stomach is the most common site of secondary involvement in the

dissemination of nodal lymphoma.¹⁻⁴ Tertiary gastric lymphoma is recurrent lymphoma involving the stomach after treatment of a nodal lymphoma and is uncommon.¹ Over 95% of PGL are non-Hodgkin's lymphoma and over 90% of PGL are β -cell lymphoma.^{1,5}

GI tract is the most common (30-50%) extranodal site of non-Hodgkin's lymphoma and the stomach is the most frequently involved site (50-75%).^{1-3,5-11}

Although the stomach is the most common site of extranodal non-Hodgkin's lymphoma, PGL remains relatively rare malignancy and represents approximately 1% to 11% of all gastric malignancies.^{1,3,5-6,8,12-17} However, the incidence appears to be rising.^{13,17-21} The survival data have shown that the prognosis of PGL is much better compared to nodal lymphoma as well as gastric carcinoma.^{8,14} The best treatment for localized PGL remains controversial. Classical treatment of PGL has been surgical resection with or without chemotherapy.^{1-2,4,9-13,15-17,21-37} However, some authors have reported that PGL can be successfully treated with chemotherapy or radiation therapy or combination of both modalities without surgery.^{8,19,38-44} All modalities can be effective under certain conditions, and each modality is associated with specific treatment-related complications. Due to the lack of established treatment strategy, PGL remains a challenge to surgeons, hematologists and radiation therapists. The controversy is due to the relative rarity of the disease and the consequent difficulty in accumulating a substantial number of patients within a single institution for making comparisons between therapeutic protocols. Most reports of PGL involve non-homogeneous retrospective analysis of a limited number of patients treated by different methods including different histologic classification, stagings and treatments. Randomized prospective clinical trials are difficult to perform because the tumors are relatively rare, with diverse histology and wide range of stage distribution and there are several possible treatment combinations.

In our institution, consensus on the optimal treatment of PGL has not been reached, and the choice of treatment modality is mainly dependent on the expertise of the primary responsible specialist. The goal for definitive therapy is to achieve maximal survival with minimal morbidity at the lowest cost to the patient and health care system.

The purpose of this study was to retrospectively analyze the role of D2 gastrectomy with curative intent on survival, morbidity and mortality of patients with PGL. This is the first report of the results of D2 gastrectomy for PGL in Thai patients.

PATIENTS & METHODS

Patients

To allow a follow-up period of at least 24 months

for this analysis, only PGL whose date of surgical treatment was no later than October 2003 were selected for this study. Between May 1995 and October 2003, 12 patients with histologically confirmed PGL underwent D2 gastrectomy with curative intent at the Department of Surgery, Faculty of Medicine, Rama-thibodi Hospital, Mahidol University. Medical records of these patients were retrospectively reviewed. Demographic information, clinical data, surgical notes and pathological reports were analyzed in each patient. PGL was defined according to the criteria proposed by Dawson et al⁴⁵ in 1961 (Table 1). Investigations were carried out to ensure that the gastric lesion was not a part of, or had not developed into, a systemic lymphoma. Using the WHO classification, the pathologists diagnosed diffused large cell lymphoma in all patients.⁴⁶ Patients were staged according to the modified Ann Arbor classification recommended at 5th International Conference on Malignant Lymphoma (Lugano, 1993).⁴⁷ A summary of the Lugano classification is shown in Table 2.

The macroscopic patterns were classified as

Table 1 Dawson criteria for primary GI tract Lymphoma

- 1. Lymphoma was definitely histologic diagnosis.
- 2. The tumor mainly involved the GI tract with or without nodal involvement
- 3. No palpable superficial lymphadenopathy
- 4. Chest X-ray showed no obvious enlargement of the mediastinal nodes
- 5. WBC count and differential count were within normal limit
- 6. The spleen and liver are free of tumor

Table 2 International Workshop (Lugano) staging system for PGL

Stage I	- tumor confined to the stomach (single or multiple foci)
Stage II	- tumor extending into abdomen (nodal involvement) - II1 - local nodes - II2 - distant abdominal nodes (para-aortic, para-caval nodes)
Stage IIE	- tumor invasion to adjacent organs or structure e.g., IIE (pancreas), IIE (colon), IIE (abdominal wall)
Stage IV	- disseminated extranodal involvement or supra diaphragmatic nodal involvement

Note: No stage III disease, supra-diaphragmatic nodal involvement being included within stage IV

exophytic (polypoid), ulcerative and infiltrative (gastritis-like) type. The principal treatment plan for PGL of this study consists of surgical resection of the stomach (either subtotal or total gastrectomy) with D2 lymph node dissection, followed by systemic chemotherapy for patients with nodal involvement.

Surgical Technique

All patients underwent D2 gastrectomy with curative intent by one surgeon (CE). The technique of D2 gastrectomy for gastric adenocarcinoma was used. The detailed technique was described elsewhere by the authors.⁴⁸⁻⁵⁰ Extent of gastric resection was determined by tumor location. Generally, when the tumor was located in the lower third of the stomach, a subtotal gastrectomy was performed. In others, a total gastrectomy was performed. Pancreas-preserving total gastrectomy was performed according to the Maruyama techniques.⁵¹ Splenectomy was performed routinely in all cases of total gastrectomy to facilitate complete removal of the splenic hilar nodes (gr 10). Distal pancreatectomy was performed, only when necessary, in cases of direct tumor extension to the pancreas. Para-aortic lymph node dissection (gr 16b1) was also performed routinely for accurate staging of stage II2 disease. Peritoneal washing cytology was performed routinely and immediately after the abdomen was opened.

Surgery was considered potentially curative (UICC-R0) or resection with curative intent when there was no gross residual tumor after surgery and resection margins were free of cancer cells histologically.

RESULTS

During a 6-year period from May 1995 to October 2003, 12 patients with PGL underwent D2 gastrectomy with curative intent. The clinicopathologic features, staging and surgical outcome are presented in Table 3-4.

Age and sex

Patient population consisted of 2 males and 10 females. The median age was 65 years (ranged 33-70 years).

Clinical presentation

The most common presenting symptom was

epigastric pain in 66.7%, followed by weight loss in 50%, nausea/vomiting in 33.3% and UGI hemorrhage in 8.3%.

Pathology

The most frequent location of tumor was the lower third of the stomach (50%), followed by involvement of both the lower and middle part of the stomach (33.3%) and both the middle and upper part of the stomach (16.7%). No multiple foci of tumor were detected on histologic examination in all patients.

The predominant macroscopic appearance of the tumor was ulcerative in 58.3%, followed by infiltrative in 41.7%.

Pretherapeutic endoscopic biopsies revealed the presence of malignant lymphoma in only 50%. In another 25% of patients, endoscopic biopsies revealed poorly differentiated carcinoma. In the remaining 25% of the patient, the diagnosis was inconclusive.

The histologic examination of the surgical specimen showed diffuse large cell lymphoma in all patients.

In only one of 12 patients (8.3%), disease was limited to the stomach, but in 11 of 12 patients (91.7%), regional nodes were involved. Nodal involvement was found in 2/3 patients (66%) whose tumor limited to the muscularis propria. All patients (9/9) with tumor invasion to serosa presented with nodal metastasis. There were no patients with positive para-aortic nodes. According to the Lugano staging classification, the most frequent was stage III1 disease in 10/12 patients (83.4%), followed by stage I disease in 1/12 patients (8.3%) and stage IIE (pancreas) in 1/12 patients (8.3%). Peritoneal washing cytology was negative in all patients.

An average number of 37 lymph nodes (ranged 28-50) were examined in the subtotal gastrectomy group and 46 lymph nodes (ranged 34-60) in the total gastrectomy group. The average number of metastatic nodes was 6 (ranged 0-28) in the subtotal gastrectomy group and 8 (ranged 0-28) in the total gastrectomy group.

Treatment outcome

Subtotal gastrectomy was performed in half of the patients (50%). Combined resection (pancreas) was performed in one case. Perioperative blood transfusion was required in only 2 patients (16.7%). Seven patients

Table 3 Clinicopathologic features of primary gastric lymphoma (n = 12)

Pts.	Gender	Age	Location of tumor	Gross finding	Endoscopic Biopsy	Pathology	Cytology	Depth of tumor	LN ratio
1	F	66	Lower+Middle	Infiltrative	ML	ML,DLC	Negative	Serosa	2/45
2	M	62	Lower	Ulcerative	Poorly diff	ML,DLC	Negative	Serosa	2/34
3	F	38	Middle +Upper	Infiltrative	Poorly diff	ML,DLC	Negative	Serosa	28/60
4	F	78	Lower	Ulcerative	ML	ML,DLC	Negative	Serosa	2/28
5	F	47	Lower	Ulcerative	ML	ML,DLC	Negative	Serosa	2/39
6	F	67	Lower	Ulcerative	ML vs Poorly diff	ML,DLC	Negative	Serosa	7/43
7	M	79	Lower+Middle	Ulcerative	Poorly diff vs Inflammation	ML,DLC	Negative	Serosa	2/41
8	F	63	Middle+Upper	Infiltrative	ML	ML,DLC	Negative	Serosa	14/57
9	F	33	Lower+Middle	Infiltrative	ML	ML,DLC	Negative	Muscle	0/38
10	F	70	Lower	Ulcerative	ML vs Poorly diff	ML,DLC	Negative	Muscle	1/28
11	F	65	Lower+Middle	Infiltrative	ML	ML,DLC	Negative	Serosa	2/34
12	F	61	Lower	Ulcerative	Poorly diff	ML,DLC	Negative	Muscle	20/50

Note: ML = malignant lymphoma
DLC = diffuse large cell type
Poorly diff = poorly differentiated carcinoma

Table 4 Staging and treatment outcome of primary gastric lymphoma (n=12)

Pts.	Extragastric metastasis	Stage	Surgical treatment	Postoperative adjuvant chemotherapy	Status	Follow-up (month)
1	No	II1	Total gastrectomy with D2 LND + splenectomy + liver biopsy	Yes	Alive, free from disease	57
2	No	II1	Subtotal gastrectomy with D2 LND with BII	No (denied)	Alive, free from disease	86
3	No	II E	Total gastrectomy with D2 LND + splenectomy +distal pancreatectomy	Yes	Alive with recurrence	24
4	No	II1	Subtotal gastrectomy with D2 LND with BII	No (intolerate)	Alive, free from disease	48
5	No	II1	Subtotal gastrectomy with D2 LND with BII	Yes	Alive, free from disease	54
6	No	II1	Subtotal gastrectomy with D2 LND with BII	Yes	Alive, free from disease	103
7	No	II1	Total gastrectomy with D2 LND + splenectomy	No (denied)	Alive, free from disease	94
8	No	II1	Total gastrectomy with D2 LND + splenectomy + liver biopsy	Yes	Alive, free from disease	77
9	No	I	Total gastrectomy with D2 LND + splenectomy + liver biopsy	No	Alive, free from disease	55
10	No	II1	Subtotal gastrectomy with D2 LND with BII	No (intolerate)	Alive with recurrence	50
11	No	II1	Total gastrectomy with D2 LND + splenectomy + liver biopsy	Yes	Alive, free from disease	41
12	No	II1	Subtotal gastrectomy with D2 LND with BI	Yes	Alive, free from disease	36

Note: LND = lymph node dissection.

Table 5 Summary of clinicopathological data of primary gastric lymphoma (n = 12)

Variables	Number (%)
Gender	
Male:Female	2:10 (16.7% vs 83.3%)
Age (years)	
Mean (sd)	63 (+11)
Median (range)	65 (33-79)
Location of tumor	
Lower third	6 (50%)
Lower + middle	4 (33.3%)
Middle + Upper	2 (16.7%)
Gross findings	
Ulcerative	7 (58.3%)
Infiltrative	5 (41.7%)
Endoscopic biopsy	
Malignant lymphoma	5 (50%)
Poorly differentiated carcinoma	3 (23.5%)
Malignant lymphoma vs Poorly diff carcinoma	2 (16.7%)
Inflammation vs Poorly diff carcinoma	1 (8.3%)
Pathology	
Malignant lymphoma, diffuse large cell	12 (100%)
Peritoneal washing cytology	
Positive	0
Negative	12 (100%)
Depth of tumor	
Muscularis propria	3 (25%)
Serosa	9 (75%)
Nodal involvement	
Yes	11 (91.7%)
No	1 (8.3%)
Adjacent organ invasion	
Yes (pancreas)	1 (8.3%)
No	11 (91.7%)
Lymph node examined (median)	
Subtotal gastrectomy	37 (28-50)
Total gastrectomy	46 (34-60)
Lymph node metastasis (median)	
Subtotal gastrectomy	6 (1-20)
Total gastrectomy	8 (0-28)
Staging	
I 1 (8.3%)	
II 10 (83.4%)	
III 1 (8.3%)	

Table 6 Treatment and outcome data of primary gastric lymphoma (n = 12)

Variables	Number (%)
Perioperative blood transfusion	
Yes	2 (16.7%)
No	10 (83.3%)
Surgical treatment	
Subtotal gastrectomy	6 (50%)
Total gastrectomy	6 (50%)
Postoperative adjuvant chemotherapy	
Yes	7 (58.3%)
No	5 (41.7%)
Time to detection of recurrence (months)	
Median (range)	30 (18-42)
Length of follow-up (months)	
Median (range)	60.4 (24-103)
Status at final follow-up	
Alive with disease	2 (16.7%)
Alive, free from disease	10 (83.3%)

Table 7 Postoperative morbidity, reoperation and hospital mortality data (n = 12)

	Number (%)
Post operative morbidity	3 (25%)
Wound infection	2
Duodenal stump leak	1
Reoperation	0
Hospital mortality	0

patients were still alive. Two patients (16.7%) were alive with relapse and 10 patients (83.3%) remained free from disease. Regarding the two patients with relapse (No 3+10), the average time to relapse was 30 months (ranged 18-42).

Morbidity and Mortality

Morbidity, re-operation and mortality data are presented in Table 7. There was no operative mortality in this series. Postoperative complications developed in 3/12 patients (25%), consisting of wound infection in 2 patients and duodenal stump leakage in 1 patient. No reoperation was required.

(58.3%) received postoperative adjuvant chemotherapy administered by the hematologists.

Survival

The median follow-up period was 60.4 months (ranged 24-103). All patients were observed for a minimum of two years. At the last follow-up, all

DISCUSSION

The clinical manifestations of PGL are similar to that of gastric adenocarcinoma and are non-specific.

The most common presenting symptom is epigastric pain, followed by weight loss, nausea/vomiting and bleeding.^{1,12,16,17,22,23,25,27,39} These findings are similar to other reports. "B" symptoms (weight loss, fever, night sweats) are uncommon and presented in about 11-12% of patients.^{5,7,39,52} Weight loss was usually not considered a "B" symptoms but as a consequence of pain and loss of appetite in PGL.

Establishing an endoscopic diagnosis of PGL is often difficult due to variable macroscopic appearance. This may range from polypoid, ulcerative and infiltrative (gastritis-like) lesion. There was no existing pathognomonic endoscopic picture for PGL. The correct diagnosis was made preoperatively by endoscopic biopsies in only 50% of patients in this study. In recent series, successful endoscopic diagnosis was made in 38-92% of the patients.^{13,17,22,23,25,29,39,53} It is often difficult to distinguish lymphoma from poorly differentiated carcinoma. The endoscopic diagnosis may require multiple biopsies, repeated biopsies and the usage of large forceps for deep biopsies to reach suspicious submucosal lesions.^{1,3}

In addition, preoperative staging in PGL was often inaccurate. The preoperative stage was reported to be correct in 42%, understaged in 8%, and overstaged in 19%.²⁵ Even with the use of endoscopic ultrasonography, accurate preoperative staging is often impossible.^{11,27}

Most of the PGL (approximately 80-89%) were in stage I or II disease (localized).^{29,54} Approximately 45% to 50% of PGL are diffuse large cell lymphoma.^{25,29} This study presented a rather homogeneous group of PGL patients. All patients had localized diffuse large cell lymphoma (stage I, II1 and IIE disease). D2 gastrectomy with curative intent was performed in all patients.

Treatment strategies in nodal non-Hodgkin's lymphoma are well established, but there still remains much debate and controversy regarding the optimal approach in PGL. Surgery, chemotherapy, and radiation therapy have been used alone or in various combinations. The goal of the treatment is to achieve maximal survival with minimal morbidity at the lowest cost to the patients and the health care systems.²⁵ Today there are two major therapeutic approaches to the localized PGL, primary surgery with or without additional therapy,^{1,2,4,9-13,15-17,21-37} or primary chemotherapy with or without radiation therapy which may

vary among institutions and specialties.^{8,19,38-44} Several authors reported that surgery alone was sufficient in the treatment of localized PGL.^{9,11,17,21,25,34,37,55} Surgical resection followed by chemotherapy have been commonly and widely used in many centers.^{8,24,28-29,56-60} Some authors suggested that surgery might not be an essential procedure for treatment of patients with early PGL,^{8,19,38-44} that surgical resection could be reserved for tumor that failed to respond to initial chemotherapy and/or radiation therapy, and to treat complications.^{41,52,61}

However, definite conclusions were difficult to draw because most studies were retrospective and concerned short series of patients. Moreover, most enrolled patients presented with different stages of diseases, different sites of GI tract and different histopathologic classifications.

Based on a questionnaire mailed to leading institutes with interest in the management of PGL, de Jong et al. in 1999⁶² concluded that hematological-oriented groups preferred conservative treatment, in contrast to gastroenterology-oriented groups which chose a surgical approach.

Brands et al. in 1997⁵³ reviewed 178 papers and analyzed 3,157 patients with PGL. Over half of the publications recommended resection alone. Surgery alone or in combination with adjuvant therapy was used in 81%. Only 15% thought that chemotherapy or radiation therapy or combination was adequate. Complications rates were reported to range from 0-56% (mean 9%) after radiation therapy and from 0-80% after chemotherapy (mean 30%).

PGLs are usually regarded as a localized disease that can be cured by surgery. In addition, D2 gastrectomy is a common procedure for gastric cancer in our institution and is associated with a low morbidity and no mortality. Under these circumstances, we support the concept of "surgery first".

Advantages claimed for surgery in PGL include the followings. 1) It allows not only a correct histological diagnosis but also an accurate stage of the disease. 2) Removing of the lesion, relief of symptom and improving survival were achieved. This is the main reason supporting surgical resection in PGL. The 5-year survival rate for stage I disease was 75-100%, for stage II disease was 40-80%.^{1,7,9,12,16,21,22,29,33,53} Many authors reported that factor most strongly associated with better prognosis was curative resection.^{29,33,36,57}

3) In addition, surgical resection prevents severe complications such as bleeding and perforation secondary to chemotherapy or radiation therapy. Many authors reported perforation rate of 0.7-20% and bleeding rate of 2.2-80% from radiation therapy or chemotherapy.^{4,24,27,39,41} Independently from the incidence, the results of the treatment for these complications were very poor with a mortality rate near 100%.^{16,27} Furthermore, induction of secondary malignancies, such as acute non-lymphocytic leukemia⁶³ and urinary bladder cancer⁶⁴ has been documented.

The incidence of treatment-related death secondary to chemotherapy was reported to be 1-10%, depending on the aggressiveness of the regimen.^{19,21}

The survival rate in this study cannot be calculated as all patients are still alive during the follow-up period between 2-9 years after surgery. The study showed a very good surgical outcome with the morbidity rate of 25%, with no re-operation and no mortality. This remarkable results have to be compared with 0-10% postoperative mortality in other series^{6,9,13,21-23,25,26,53} and the rates of mortality related to chemotherapy of about 1-10% reported in previous studies.^{19,21,38}

The philosophy in the management of PGL has been to attempt curative resection when the disease is localized and the patients are in acceptable surgical risk. The advantage of D2 gastrectomy must be balanced carefully against the toxicity of chemotherapy and/or radiation therapy. The D2 gastrectomy should not add significantly to the morbidity and mortality associated with the procedures. The safety of D2 gastrectomy in the author's experience has been reported in the surgical therapy for gastric adenocarcinoma. The author recommended adjuvant chemotherapy for patients with PGL with lymph node involvement (stage II disease). Adjuvant chemotherapy for patients with stage I at high risk of recurrence, as high-grade lymphoma or large tumor (>5 cm), is still controversial. The author did not use adjuvant radiation therapy because local tumor control was sufficient with D2 gastrectomy alone. The role of radiation therapy is only for local treatment.

D2 gastrectomy might be beneficial for patients with PGL for many reasons. Firstly, the incidence of nodal metastases was high.²¹ The incidence of nodal metastasis was 21% in mucosal or submucosal lesion, 73% in muscularis propria or subserosal lesion and 80% in serosal lesion.²⁸ Secondly, PGL is not commonly

associated with peritoneal dissemination,²¹ i.e. with no positive cytology in this series. PGL is a highly curable disease. As opposed to other lymphoma, PGL has a pattern of metastasis similar to that of gastric adenocarcinoma. Local extension to adjacent organs and regional lymph node metastasis tend to precede distant metastasis. A relatively slow growing tumor and late occurring systemic metastasis lead to the possibility of radical resection of these PGL.¹³ Thirdly, accurate staging is essential when selecting patients for chemotherapy. Regional lymph nodes and para-aortic nodes cannot be visualized by noninvasive method and D2 gastrectomy is the only means to achieve this.

CONCLUSION

PGL is a highly curable disease. Patients with localized disease (stage I, III and IIE) had an excellent prognosis providing that local control of disease was achieved. The results of this study confirm that curative surgical resection is still the mainstay of treatment of PGL. D2 gastrectomy has the advantages of an accurate diagnosis, exact staging and also the possibility of cure of disease. D2 gastrectomy followed by adjuvant chemotherapy in selected patients is an appropriate strategy for PGL in patients on whom this procedure can be safely performed. However, prospective multicenter controlled trial will be required to confirm the validity of this approach.

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