

Surgical Resection in the Treatment of Primary Gastrointestinal Non-Hodgkin's Lymphoma: Retrospective Study

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Aim. To evaluate the role of surgical resection in the treatment of patients with primary gastrointestinal non-Hodgkin's lymphoma in our institution.

Method. The retrospective study included 79 patients with a histologically confirmed primary gastrointestinal lymphoma, who were diagnosed and treated for the disease in the 1978-1997 period. According to the treatment modality, the patients were divided into surgically treated and surgically non-treated group. Data were analyzed with Fisher's exact test, long-rank test, and Kaplan-Meier method.

Results. The stomach was the primary site of non-Hodgkin's lymphoma in 45 (57%) patients, small intestine in 19 (24%), and colon in 9 (11%) patients. Six patients (8%) had multifocal disease. There were 56 (71%) patients with stages IE and IIE, and 23 (29%) with stages III and IV. Aggressive histology was found in 51 cases (65%), and low grade mucosa-associated lymphoid tissue (MALT) lymphoma in 28 (35%). *Helicobacter pylori* infection was registered in 20 out of 45 patients with gastric lymphoma. Twenty-six (33%) patients underwent surgical resection followed by chemotherapy, 47 (59%) were treated with chemotherapy alone, and 6 (8%) received antibiotics plus chemotherapy. Fifteen patients needed urgent surgical intervention. The overall response rate was 77%. Complete remission was achieved in 54 (68%) patients and partial remission in 7 (9%). Eighteen patients (23%) experienced progressive disease. A 10-year overall survival (OS) was 63% and event-free survival (EFS) was 52% for all patients. Patients with gastric lymphoma had better OS and EFS than patients with primary lymphoma at other sites (65% vs 42%, and 62 vs 28%, respectively) ($p=0.005$). A 10-year EFS rates were 58% and 52% for surgically treated and non-treated group, respectively. There was no significant difference between patients with resected and non-resected tumors ($p=0.855$). Patients with early-stage disease had significantly better OS and PFS than patients with advanced-stage disease ($p=0.048$).

Conclusion. Primary gastrointestinal lymphoma can be successfully treated with chemotherapy alone but surgery remains an important therapeutic option for emergency problems. The main prognostic factors were primary tumor site and extent of the disease.

Key words: gastrointestinal neoplasms; lymphoma; lymphoma, mucosa-associated lymphoid tissue; lymphoma, non-Hodgkin

Primary non-Hodgkin's lymphomas of gastrointestinal tract are the most common extranodal lymphomas, with increasing incidence in recent years (1-5). Although gastrointestinal tract is the most common (40%) extranodal site of primary non-Hodgkin lymphoma, primary gastrointestinal lymphomas are relatively rare tumors accounting for approximately 1-4% of all gastrointestinal malignancies and less than 10% of all lymphomas (6,7). The most frequent primary sites are the stomach (50-60%) and small intestine (20-30%). The esophagus, ileocecal region, colon, and rectum are uncommon sites, accounting for the remaining 20% of gastrointestinal lymphomas

(8-9). Many entities have been recently recognized and included in the Revised European-American Classification of Lymphoid Neoplasms (REAL) and the newest classification of the World Health Organization (WHO) (10-12). Despite their rarity, these tumors form a heterogeneous group in terms of age, geographical, and socioeconomic distribution, as well as their pathological features in different populations (13-16). Approximately 85% of primary gastrointestinal lymphomas are of B-cell type. Histologically they are divided into low grade mucosa-associated lymphoid tissue (MALT) lymphoma, mantle cell lymphoma, and large cell lymphoma. About half of gas-

gastrointestinal lymphomas show histologic pattern of diffuse large B-cell lymphoma and about half of patients have bulky disease (17,18).

The treatment results of gastrointestinal lymphomas are generally better than that of nodal non-Hodgkin's lymphoma, with long-term remission achieved in over 50% cases (19-22). However, the optimal treatment of primary gastrointestinal lymphoma is still not well defined. Surgical resection has been the main treatment method (23-25), but many recent reports advocate medical treatment (26-30). Due to the lack of accurate treatment strategy, gastrointestinal lymphomas remain a challenge to surgeons, medical oncologists, and radiation therapists. The aim of this study was to evaluate influence of surgical resection on the treatment results of patients with primary gastrointestinal lymphomas.

Patients and Methods

Patients

Between January 1979 and December 1998, 79 patients were diagnosed with extranodal non-Hodgkin's lymphoma in gastrointestinal tract. Patients were eligible for the study if they fulfilled Dawson's criteria for the definition of primary gastrointestinal lymphomas (31). The diagnoses of non-Hodgkin's lymphoma had to be reviewed according to the WHO classification. Patients were divided into two groups according to the type of treatment (Table 1). One group included 26 patients who underwent surgical excision of the tumor followed by chemotherapy. The other group consisted of 53 patients treated with chemotherapy alone or in combination with antibiotics. The median age of the patients was 60 years (range 18-86). There were 45 men and 34 women. The most common primary site was stomach (45 patients, 57%), followed by small intestine (19 patients, 25%) and colon (9 patients, 11%). Six (8%) patients had multifocal disease. According to WHO classification (12), high-grade lymphoma was found in 44 patients (56%), whereas low-grade MALT-type lymphoma was found in 28 (35%). In the remaining 7 patients (9%) histologic finding showed mixed cell lymphoma. According to Mushoff's criteria (32), clinical stage IE was found in 44 (56%) patients, stage IIE in 12 (15%), stage III in 14 (18%), and stage IV in 9 patients (11%). Fifty-six patients presented with abdominal pain (71%), 35 (44%) with weight loss, 19 (24%) with palpable mass

Table 1. Characteristics of 79 patients with gastrointestinal lymphomas

Patient characteristics	Total (N=79)	No. of patients treated with	
		surgery + chemotherapy (n=26)	chemotherapy only (n=53)
Median age (years; range)	60 (18-86)	58 (18-76)	60 (26-86)
Sex:			
men	45	12	33
women	34	14	20
Primary site of lymphoma:			
stomach	45	19	26
small intestine	19	4	15
colon	9	2	7
multifocal	6	1	5
Histology of lymphoma ^a :			
indolent	28	8	20
aggressive	44	14	30
mixed	7	4	3
Disease stage:			
IE	44	12	32
IIE	12	6	6
III	14	4	10
IV	9	4	5

^aAccording to the World Health Organization classification: indolent – low grade mucosa-associated lymphoid tissue (MALT) lymphoma; aggressive – large B-cell non-Hodgkin's lymphoma (NHL), mantle cell non-Hodgkin's lymphoma; mixed – large B-cell non-Hodgkin's lymphoma with MALT component.

Table 2. Symptoms and signs of gastrointestinal lymphomas in 79 patients included in the study

Symptoms	Site of lymphoma (No. of patients)				total (N=79) (%)
	stomach (n=45)	small bowel (n=19)	colon (n=9)	multifocal (n=6)	
Abdominal pain	37	11	2	6	56 (71)
Palpable mass	10	1	4	4	19 (24)
Weight loss	18	11	1	5	35 (44)
Diarrhea/ malabsorption	0	7	2	4	13 (16)
Bleeding	11	1	3	2	17 (22)
Ileus	0	7	0	1	8 (10)
Perforation/ peritonitis	3	3	0	1	7 (9)

and 13 (16%) with diarrhea (Table 2). Bleeding occurred in 17 (22%) patients. Abdominal emergency problems needing surgical intervention were registered in 15 (19%) patients (8 cases of ileus and 7 cases of gut perforation with peritonitis).

Diagnostic Procedure

Clinical staging was based on patient medical history, physical examination findings, standard blood tests, bone marrow biopsy, chest X-ray and/or computerized tomography (CT), abdominal CT scan, and radiologic and/or endoscopic examination of gastrointestinal tract. Fifty-three patients underwent esophagogastroscopy, jejunoscopy, or colonoscopy with biopsy. In five patients (1 with gastric, 2 with small bowel, and 2 with colon lymphoma) laparotomy with surgical biopsy was needed because the endoscopic biopsy material was not sufficient for histological diagnosis. Fifteen patients underwent urgent surgical treatment due to acute complications of gut lymphoma. All tissue specimens were reviewed and histologic diagnosis reclassified according to the WHO classification of neoplasms of hematopoietic and lymphoid tissues (12). Clinical stages were determined according to Ann Arbor staging system modified by Musshoff (32).

Treatment

Twenty-six out of 79 (33%) patients underwent surgical resection as part of antitumor treatment, whereas 53 patients (67%) were treated without surgery. The majority of surgically treated patients had gastric lymphoma (19 or 73%); 10 of them underwent total and 9 subtotal gastrectomy. All patients received 6-8 cycles of chemotherapy consisting of cyclophosphamide, doxorubicin (Adriamycin), vincristine, and prednisone (CHOP regimen) (33). Six patients with stage IE gastric low-grade MALT lymphoma and *Helicobacter pylori* infection initially received *H. pylori* eradication therapy consisting of amoxicillin, metronidazole, and omeprazole. Five of them achieved remission but all relapsed within a year and received chemotherapy, as previously mentioned.

Response Criteria

Complete remission was defined as disappearance of measurable tumor and partial remission as more than 50% reduction in the sum of largest perpendicular diameter of measurable tumor. Refractory or progressive disease was defined as transient (<2 months) regression of all measurable lesions by 50% or less or progression during treatment.

Statistical Analysis

Fisher's exact test was used for comparison of patients' characteristics and response rates. Long-rank test was used for survival curves comparison. Survival rates were calculated according to Kaplan-Meier method. The assumed level of significance was 0.05.

Overall survival was measured from the point of inclusion into the study to the time of death due to any cause or loss to follow-up. Event-free survival was defined as the time from entering into the study to the time of relapse, disease progression, death from any cause, or loss to follow-up.

Statistical tests were performed with SPSS for Windows version 10.0 (SPSS Inc, Chicago, IL, USA).

Results

The overall response rate was 77%. Complete remission was achieved in 54 patients (68%) and partial remission in 7 (9%) (Table 3). Eighteen patients (23%) were refractory to treatment or relapsed after transient remission. The 10-year overall survival and disease-free survival for all patients were 63% and 52%, respectively (Fig. 1). Prognostic significance of primary site, surgical resection, histological type, and clinical stage was analyzed.

The response rates for different primary sites were 91% for stomach, 68% for small intestine, 66% for colon, and 17% for multifocal disease, and the 10-year overall survival rates were 65%, 34%, 58%, and 12%, respectively. The differences in the survival rates were significant ($p=0.004$) (Fig. 2). Most patients with multifocal disease were refractory to the treatment (5 out of 6).

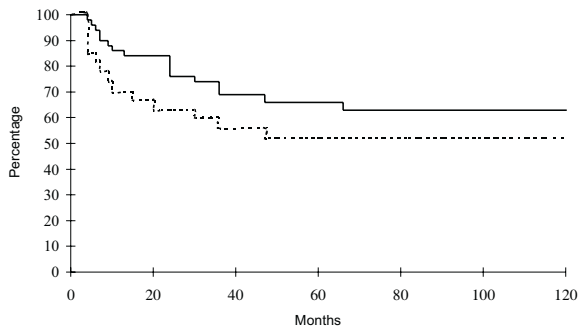


Figure 1. Overall and failure-free survivals of 79 patients with primary gastrointestinal lymphomas. Overall survival – full line; failure-free survival – dashed line.

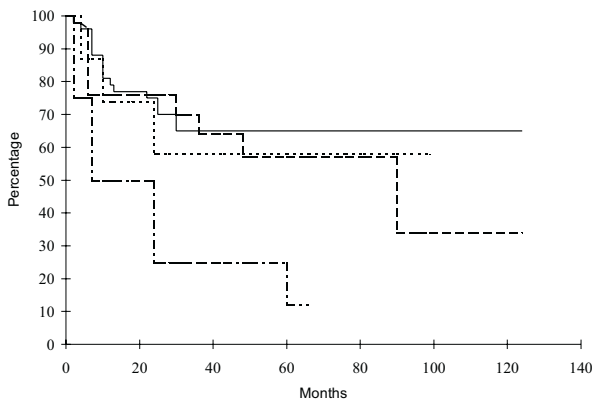


Figure 2. Overall survival of patients with primary gastrointestinal lymphomas according to initial site. Stomach – full line; small intestine – dashed line; colon – dotted line; multifocal disease – dashed/dotted line. Long-rank test, $p=0.004$.

Among surgically treated patients, 20 (77%) out of 26 achieved complete remission, one (4%) achieved partial remission, and 5 (19%) were refractory to the treatment (Table 3). Seventeen (85%) patients with complete remission in surgically treated group had gastric lymphoma. The number of surgically treated patients with bowel lymphoma was too small to draw any statistically relevant conclusion. The 10-year event-free survival rate was 58% in surgically and 52% in non-surgically treated group. There were no significant differences between the two therapy groups (Fig. 3).

Response rates for different histological subgroups were 68% for large B-cell, 84% for low-grade MALT, and 62% for large B-cell with MALT compo-

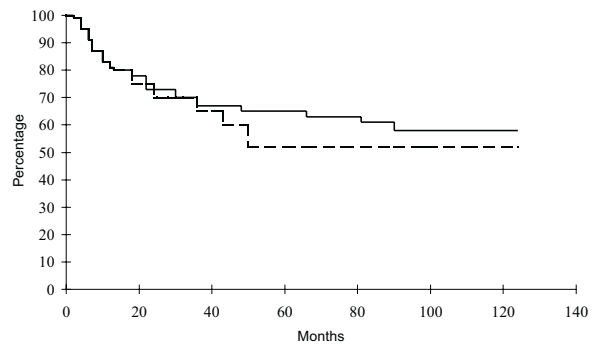


Figure 3. Event-free survival among 79 patients treated with surgical resection plus chemotherapy or with chemotherapy alone. In chemotherapy group, 6 patients had initially received *Helicobacter pylori* eradication antibiotic therapy. Because of refractory disease or relapse, they needed chemotherapy. Surgery + chemotherapy – full line; chemotherapy alone – dashed line. The difference not significant.

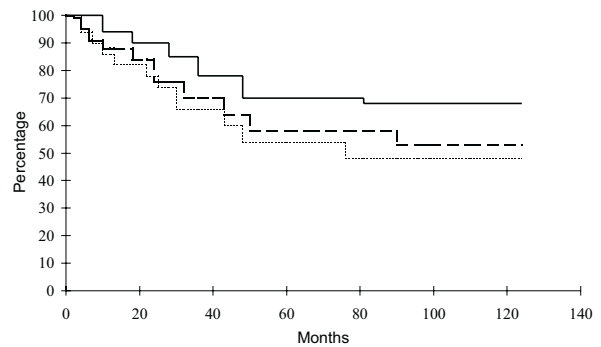


Figure 4. Overall survival of patients with primary gastrointestinal lymphomas according to histology of lymphoma. Low-grade MALT – full line; high grade – dashed line; mixed – dotted line. Long-rank test, $p=0.045$.

Table 3. Treatment results of 79 patients with gastrointestinal lymphoma who underwent surgery and chemotherapy (n = 26) and chemotherapy only (n = 53)

Primary site of lymphoma (No. of patients)	Surgery + chemotherapy			Chemotherapy only		
	complete remission	partial remission	progression	complete remission	partial remission	progression
Stomach (45)	17	0	2	22	2	2
Small intestine (19)	2	1	1	9	1	5
Colon (9)	1	0	1	3	2	2
Multifocal (6)	0	0	1	0	1	4
Total (79)	20 (77%)	1 (4%)	5 (19%)	34 (64%)	6 (11%)	13 (25%)

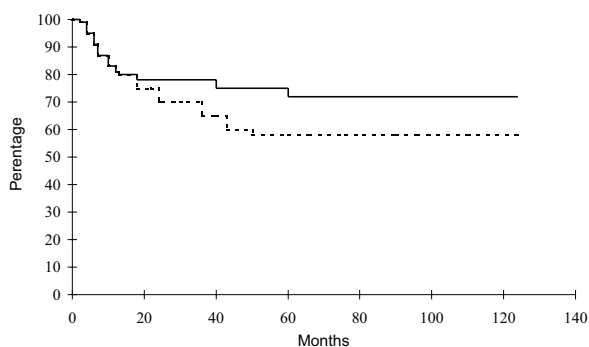


Figure 5. Overall survival of patients with primary gastrointestinal lymphomas according to the extent of disease. Stages I and II – full line; stages III and IV – broken line. Long-rank test, $p=0.048$.

ment lymphoma, and the 10-year survival rates were 53%, 68%, and 48%, respectively (Fig. 4).

The response rate of patients with early stage disease was 84% vs 56% of patients with later stages. Forty-seven (89%) patients with early stage disease achieved complete remission and one (2%) achieved partial remission, whereas among patients with later stage disease 10 (43%) patients achieved complete and 3 (13%) partial remission. The 10-year overall survival rates were 72% and 58%, respectively. The differences were significant ($p=0.050$) (Fig. 5).

Discussion

The optimal treatment for primary gastrointestinal lymphoma is not well defined (21). Randomized prospective therapeutic trials are difficult to perform because these tumors are relatively rare, with diverse histology. Treatment plans may include combinations of surgical resection, radiation therapy, chemotherapy, and antibiotics. Controversy exists regarding the indications and efficacy of surgical resection and the issue whether chemotherapy alone or combined with radiotherapy can replace surgery (21,22,27,35). Surgery is required for making the diagnosis and management of gastrointestinal lymphoma (25,26). Due to improved endoscopic techniques and immunohistochemistry combined with better results of chemoradiotherapy, many authors have recently avoided surgical resection as part of front-line therapy (27-30).

Our results support conservative approach in the treatment of patients with primary gastrointestinal lymphoma. The response rate of over 70% was achieved in both groups of patients, those with resected and non-resected tumors, and the 10-year overall and event-free survival rates for the two groups were not significantly different (64% vs 62%, and 58% vs 52%, respectively). Our results concerning surgical treatment of patients with intestinal lymphoma are inconclusive because the number of surgically treated patients was too small and most of them underwent surgery in emergency conditions. On the other hand, data regarding gastric lymphoma clearly showed that gastrectomy was redundant. Although removal of the tumor may improve response to therapy, the morbidity and mortality associated with total gastrectomy are

too great and results of effective chemotherapy programs without gastrectomy are associated with excellent prognosis. Several reports support this observation. In a recent Austrian study involving 37 patients with localized high-grade B-cell lymphoma who were treated with 3 cycles of CHOP, complete remission was achieved in 86% (34). Danish Lymphoma Study Group obtained similar results: the 5-year survival rate for patients treated with different approaches was 63% and surgery had no influence on survival of patients in early stages (14). In French GELA study patients with aggressive non-Hodgkin's lymphoma in gastrointestinal tract were treated in the same way as patients with nodal lymphoma and achieved the same results without surgical resection (23,24).

For intestinal lymphoma, there is no proof that surgery is unnecessary. The conventional therapy for early stage intestinal lymphoma (stage I) is surgical resection (36-39). Although retrospective studies suggested that surgical extirpation of the primary focus might be sufficient therapy in stage IE disease, 40-60% of patients with regional lymph node invasion (stage IIE) ultimately relapsed when treated solely surgically (38-41). The addition of adjuvant abdominal radiation following surgery achieved good local control and 5-year disease-free survivals ranging from 35-85% (42). However, in half of the patients with stages IE and IIE, the disease recurs outside the radiation treatment field. Additional chemotherapy improves relapse-free survival in patients with gastrointestinal lymphoma (37). In our series, 34% patients with small bowel lymphoma and 58% with colon lymphoma achieved long-term remission.

Our patients with gastric low-grade MALT lymphoma and *H. pylori* infection initially received *H. pylori* eradication therapy. Three of 6 achieved complete and 2 achieved partial remission, whereas one was primary refractory. Surprisingly, all responders relapsed within a year and needed chemotherapy, after which all of them achieved complete durable remission. This is in contrast with many reports of long-term remissions after *H. pylori* eradication and our own experience in the last few years (43-45). From December 2000, 6 out of 8 patients with stage IE gastric MALT lymphoma showed complete regression of tumor after helicobacter eradication therapy with amoxicillin, azithromycin, and omeprazole.

Our long-term outcome analysis suggest that chemotherapy could be successfully used as front-line treatment for advanced and *H. pylori* negative gastric lymphoma. Early stage gastric MALT lymphoma with accompanying *H. pylori* infection should be treated with antibiotics and carefully reassessed. If resection is necessary, subtotal gastrectomy should be preferred. For intestinal lymphoma, surgical resection is indicated in stage I bulky disease and in the case of suspected residual mass after chemotherapy. Life-threatening complications are issue of abdominal emergency and require urgent surgery.

For more accurate assessment of different therapeutic modalities for patients with gastrointestinal

lymphoma, large prospective multicentric randomized trials are needed.

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