



Primary intestinal non-Hodgkin's lymphoma: A clinicopathologic analysis of 81 patients

Guo-Bao Wang, Guo-Liang Xu, Guang-Yu Luo, Hong-Bo Shan, Yin Li, Xiao-Yan Gao, Jian-Jun Li, Rong Zhang

Guo-Bao Wang, Guo-Liang Xu, Guang-Yu Luo, Hong-Bo Shan, Yin Li, Xiao-Yan Gao, Jian-Jun Li, Rong Zhang, Department of Laser Treatment and Endoscopy, Sun Yat-Sen University Cancer Center, Guangzhou 510060, Guangdong Province, China

Guo-Bao Wang, Guo-Liang Xu, State Key Laboratory of Oncology in South China, Guangzhou 510060, Guangdong Province, China

Author contributions: Wang GB designed the study and wrote the manuscript; Xu GL performed statistical analysis; Luo GY and Shan HB analyzed data and edited the manuscript; Li Y, Gao XY and Li JJ acquired and inputted data; Zhang R provided analytical tools and writing assistance.

Correspondence to: Guo-Liang Xu, Professor, Department of Laser Treatment and Endoscopy, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road, Guangzhou 510060, Guangdong Province, China. manuscript_doris@yahoo.cn

Telephone: +86-13751889486 Fax: +86-020-87343272

Received: March 1, 2011 Revised: June 20, 2011

Accepted: June 27, 2011

Published online: November 7, 2011

Abstract

AIM: To analyze the clinicopathologic features and the prognosis of primary intestinal lymphoma.

METHODS: Patients were included in the study based on standard diagnostic criteria for primary gastrointestinal lymphoma, and were treated at Sun Yat-sen University Cancer Centre between 1993 and 2008.

RESULTS: The study comprised 81 adults. The most common site was the ileocaecal region. Twenty-two point two percent patients had low-grade B-cell lymphoma. Fifty-one point nine percent patients had high-grade B-cell lymphoma and 25.9% patients had T-cell lymphoma. Most patients had localized disease. There were more patients and more early stage diseases in the latter period, and the origin sites changed. The majority of patients received the combined treatment, and

about 20% patients only received nonsurgical therapy. The overall survival and event-free survival rates after 5 years were 71.6% and 60.9% respectively. The multivariate analysis revealed that small intestine and ileocaecal region localization, B-cell phenotype, and normal lactate dehydrogenase were independent prognostic factors for better patient survival. Surgery based treatment did not improve the survival rate.

CONCLUSION: Refined stratification of the patients according to the prognostic variables may allow individualized treatment. Conservative treatment may be an optimal therapeutic modality for selected patients.

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Key words: Gastrointestinal lymphoma; Non-Hodgkin's lymphoma; Gastrointestinal oncology; Prognostic factors

Peer reviewer: Markus Raderer, Professor, Department of Internal Medicine I, Division of Oncology, Medical University Vienna, Währinger Gürtel 18-20, Vienna A-1090, Austria

Wang GB, Xu GL, Luo GY, Shan HB, Li Y, Gao XY, Li JJ, Zhang R. Primary intestinal non-Hodgkin's lymphoma: A clinicopathologic analysis of 81 patients. *World J Gastroenterol* 2011; 17(41): 4625-4631 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v17/i41/4625.htm> DOI: <http://dx.doi.org/10.3748/wjg.v17.i41.4625>

INTRODUCTION

In the recent years, the incidence of non-Hodgkin's lymphoma (NHL) has increased worldwide, especially for primary extranodal lymphoma (ENL). Primary gastrointestinal lymphoma (PGIL) is the commonest ENL, which accounts for 30%-45% of ENL. Gastric lymphoma is the most frequent (55%-70%), followed by intestinal lymphoma (20%-35%), and colorectal lymphoma (5%-10%)^[1].

Due to a lack of characteristic symptoms and a low

incidence rate, primary intestinal lymphoma (PIL) is easily misdiagnosed until serious complications occur, such as perforation and ileus. Furthermore, the optimal treatment for PIL remains controversial, and the prognosis is unsatisfactory. Although during the past two decades, the diagnosis and treatment of PGIL has changed tremendously, results from studies of gastric lymphoma are controversial regarding the benefit of surgical resection^[2-4]. However, a large-scale prospective investigation of PIL is difficult due to its low incidence and complicated histologic subtypes.

Numerous retrospective studies report the PGIL in European countries^[5-7], but there were no large-sample studies from Asia in this decade besides Japan^[8]. Our study consisted of 81 Chinese patients with PIL who were diagnosed and treated at Sun Yat-sen University Cancer Centre between 1993 and 2008. It was a single center study, which retrospectively analyzed the clinical features, anatomic and histologic distribution, time trends and the prognosis of the PIL in Chinese patients.

MATERIALS AND METHODS

Patients

This study consisted of 81 adult Chinese patients with PIL who were diagnosed and treated at Sun Yat-sen University Cancer Centre between 1993 and 2008. Patients were included in the study based on standard diagnostic criteria for PGIL; patients had to present gastrointestinal (GI) symptoms or predominant lesions in the GI tract^[9]. The patients who presented with second malignancies, had missing confirmation of histologic subtype, or had no follow-up information were excluded from the study.

The diagnostic workup included: details of the patients' history and physical examination with inspection of Waldeyer's ring, blood cell count, serum chemistry, chest radiographs, abdominal ultrasound, computed tomography (CT) scan of the chest and abdomen, bone marrow aspiration or biopsy, and endoscopy examination with multiple biopsy. Endoscopic ultrasound and positron emission tomography (PET)/CT were carried out when available.

The histologic specimens were obtained by endoscopic biopsy or surgery. These specimens were stained routinely with hematoxylin and eosin. Immunohistochemical staining for CD3 and CD20 was performed on all 81 specimens. In some selected cases, additional staining and polymerase chain reaction-based amplifications of genes for immunoglobulin heavy chain or T-cell receptor gamma chain were done. All slides were reviewed separately by two pathologists and a common consensus was reached in all cases. Histologic classification was done according to WHO criteria^[10].

Patients were then staged according to the Ann Arbor system with modifications^[11].

Treatment and response

The treatment modalities included surgical resection, conservative treatment (chemotherapy and radiotherapy),

and the combined treatment. The main first line chemotherapy were four to six cycles of cyclophosphamide (CHOP) 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² (maximum, 2mg) each on day 1, plus prednisone 100 mg on days 1 to 5) or RCHOP (rituximab 375 mg/m² on day 0, plus CHOP). The regimen of cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate (CODOX-M), alternating with ifosfamide, etoposide and high-dose cytarabine (IVAC), were used for patients with Burkitt's lymphoma^[12].

International Workshop Criteria was used for response evaluation. Therapeutic response after the initial treatment was designated as complete remission (CR), partial remission, stable disease, or progression of disease.

Follow up and statistical analysis

Overall survival (OS) was defined as the time from diagnosis to the date of death for any reason or to the last follow-up. Event-free survival (EFS) was measured from the date of diagnosis to the date that event occurred. Events included disease progression, relapse and patient death for any reason.

The statistical differences were evaluated using the Student's *t*-test, Mann-Whitney *U* test (rank sum test) and the χ^2 test. Survival curves were calculated according to the Kaplan-Meier method, and the value was compared using the log rank test. All variables that influenced the prognosis ($P < 0.10$) were put into a multivariate analysis using the Cox proportional hazards model. Differences were considered significant if the *P*-value was < 0.05 . All statistical analyses were performed using the Statistical Software Package for the Social Sciences version 17.0 (SPSS 17.0).

RESULTS

Patient clinical features

From January 1993 to December 2008, 81 patients with PIL were recruited for the study. The patients had a mean age of 46 years (range, 18-75 years) and comprised of 58 men and 23 women.

The clinical symptoms of PIL were unspecific. Pain was the main diagnostic symptom in most cases (75.3%), followed by hematochezia (25.9%) and diarrhea (16.9%). Palpable mass, constipation and loss of appetite were less common symptoms. Perforation was scarce (7.4%). "B" symptoms occurred in 42.0% patients.

Most patients had localized disease. Sixty-six (81.5%) patients had Stage I ~ II disease and 15 (18.5%) had Stage III ~ IV disease. Most patients (75.3%) received the combined treatment, while about one fifth of patients only received nonsurgical therapy. The clinical features are shown in Table 1.

Sites of origin

The origins of PIL were confirmed by surgery, endoscopy, or CT. They were subdivided as follows: (1) duodenum; (2) jejunum; (3) ileum; (4) ileocaecal region; (5)

Table 1 Clinicopathologic features *n* (%)

Characteristics	Number of patients (<i>n</i> = 81)
Gender	
Male	58 (71.6)
Female	23 (28.4)
Histology	
Low-grade B-cell	18 (22.2)
High-grade B-cell	42 (51.9)
T cell	21 (25.9)
Stage	
I ~ II	66 (81.5)
III ~ IV	15 (18.5)
Treatment	
Surgery alone	3 (3.7)
Nonsurgical	16 (19.8)
Both	61 (75.3)
No	1 (1.2)
Treatment response	
Complete remission	56 (69.1)
Partial remission	7 (8.6)
Stable disease	3 (3.7)
Progression	15 (18.5)

Table 2 Sites of origin *n* (%)

Sites of origin	Number of patients (<i>n</i> = 81)
Duodenum	2 (2.5)
Jejunum	4 (4.9)
Ileum	5 (6.2)
Ileocaecal region	31 (38.3)
Colon	20 (24.7)
Rectum	8 (9.9)
Multiple sites	11 (13.6)

Table 3 Immunohistological phenotypes *n* (%)

Histologic type	Patients		Total (<i>n</i> = 81)
	Male (<i>n</i> = 58)	Female (<i>n</i> = 23)	
B cell	42 (72.4)	18 (78.3)	60 (74.1)
MALT	6 (10.3)	9 (39.1)	15 (18.5)
Follicular lymphoma	3 (5.2)	0 (0.0)	3 (3.7)
Mantle cell lymphoma	3 (5.2)	0 (0.0)	3 (3.7)
DLBCL	27 (46.6)	8 (34.8)	35 (43.2)
Burkitt-like	2 (3.4)	1 (4.3)	3 (3.7)
Burkitt lymphoma	1 (1.7)	0 (0.0)	1 (1.2)
T cell	16 (27.6)	5 (21.7)	21 (25.9)
ETCL	6 (10.3)	1 (4.3)	7 (8.6)
Anaplastic	3 (5.2)	0 (0.0)	3 (3.7)
NK/T	0 (0.0)	1 (4.3)	1 (1.2)
PTCL, NOS	4 (6.9)	1 (4.3)	5 (6.2)
Others	3 (5.2)	2 (8.7)	5 (6.2)

MALT: Marginal zone lymphoma; DLBCL: Diffuse large B-cell lymphoma; ETCL: Enteropathy-type T cell lymphoma; PTCL, NOS: Peripheral T-cell lymphoma, not otherwise specified.

colon; (6) rectum; and (7) multiple sites. The ileocaecal region was defined as involvement of terminal ileum, cecum, appendix and or lower part of ascending colon. The most common site of PIL was the ileocaecal region

(38.3%), followed by the colon (24.7%) and 13.6% small intestine (Table 2).

Histologic subtypes

PIL are heterogeneous diseases. In the current study, B cell NHL and T-cell NHL were both classified into five common subtypes. The B cell subtypes, arranged by order, were: diffuse large B-cell lymphoma (DLBCL) 35 (43.2%), marginal zone B-cell lymphoma 15 (18.5%), Burkitt and Burkitt-like lymphoma 4 (4.9%), follicular lymphoma 3 (3.7%), and mantle cell lymphoma 3 (3.7%). The ranks of the T cell subtypes were: enteropathy-type T cell lymphoma 7 (8.6%), peripheral T-cell lymphoma, not otherwise specified 5 (6.2%), uncertain subtype 5 (6.2%), anaplastic 3 (3.7%), and NK/T 1 (1.2%). All types of intestinal lymphoma showed broadly similar patterns in both sexes, apart from marginal zone lymphoma (MALT) which was predominant in women (9 in 23, 39.1%) (Table 3).

Time trends of intestinal lymphoma

The study was divided into two 8 year periods due to the use of Rituximab after 2000. Twenty-seven (33.3%) patients belonged to Period A, and 54 (66.7%) to Period B. Over these two periods, the average age of patients didn't change (43.9 years *vs* 47.2 years, $P = 0.454$). The sites of origin were different ($P = 0.0469$), whereas the histology differences were not significant ($P = 0.4975$). More patients were in the early stage in period B ($P < 0.0001$), however the treatment and response did not change significantly ($P = 0.686$ *vs* $P = 0.6842$, respectively).

Treatment and prognosis

The follow-up after the diagnosis ranged from 18 to 183 mo (mean, 72 mo). The OS and EFS rates after 5 years were 71.6% and 60.9% respectively. Prognostic factors on univariate analysis were shown in Table 4.

Female patients showed a better OS, but EFS did not different between two groups. The sites of origin were prognostic (Figure 1). EFS in different sites were significantly changed ($P = 0.025$), and OS in the small intestine and ileocaecal region were significantly longer compared with rectum and multiple sites ($P = 0.016$). Histologic subtype was prognostic for EFS and OS ($P = 0.002$ and $P < 0.001$, respectively). B cell phenotype had a better prognosis than T cell phenotype (Figure 2). Patients who had perforation showed a poorer EFS and OS than those did not perforate. In the normal lactate dehydrogenase (LDH) group, EFS and OS were significantly better compared with the elevated LDH group ($P = 0.010$ *vs* $P = 0.034$, respectively) (Figure 3).

We could not detect any significant influence of age, stage, bulky disease, B symptom, treatment or time trend in EFS and OS of the PIL.

Cox multivariate analysis revealed that small intestine and ileocaecal region localization, B-cell phenotype, and normal LDH were independent prognostic factors for better OS and EFS (Table 5).

We also did prognostic analyses for the subgroups of B-cell lymphomas. Kaplan-Meier curves showed the sur-

Table 4 Prognostic factors on univariate analysis¹

Characteristics	n = 81	5-year EFS	P value	5-year OS	P value
Age					
59 or younger	70	56.1	0.939	68.9	0.852
60 or older	11	56.8		68.4	
Gender					
Male	58	56.4	0.843	62.3	0.058
Female	23	56.2		85.6	
Sites of origin					
Small intestine	11	63.6	0.025	80.8	0.219
Ileocaecal region	31	71.0		79.6	
Colon	20	54.5		65.2	
Rectum	8	37.5		50.0	
Multiple sites	11	27.3		46.8	
Histology					
Low-grade B-cell	18	66.3	0.002	87.5	< 0.001
High-grade B-cell	42	71.3		79.2	
T cell	21	23.8		34.8	
Stage					
I ~ II	66	58.8	0.387	69.0	0.727
III ~ IV	15	45.7		71.4	
Bulky disease					
< 8 cm	54	60.6	0.189	70.1	0.837
≥ 8 cm	27	48.1		67.7	
Perforation					
Yes	6	28.6	0.074	25.0	0.024
No	75	58.9		72.5	
B symptom					
Yes	34	55.1	0.768	59.5	0.172
No	47	57.1		75.0	
LDH					
Elevated	25	34.2	0.010	52.2	0.034
Normal	56	65.9		76.9	
Treatment					
Surgery-based	64	54.3	0.668	70.9	0.371
Nonsurgical	16	61.9		60.9	
Radical surgery					
Yes	54	57.7	0.218	70.3	0.599
No	10	40.0		77.8	
Period					
A	27	51.9	0.594	66.7	0.808
B	54	58.8		71.3	

¹Assessed by the log-rank test. EFS: Event-free survival; OS: Overall survival; LDH: Lactate dehydrogenase.

vival of follicular lymphoma was better than MALT and DLBCL, and Burkitt lymphoma was the worst. However, the *P* values were not significant.

Cox multivariate analysis revealed that normal LDH were protective factors for better EFS (*P* = 0.007), and the gender and sites of origin were independent prognostic factors (*P* = 0.037 and *P* = 0.05, respectively). More specifically, females had better OS, and small intestine and ileocaecal region had better prognosis than rectum and multiple sites. We could not detect any significant influence of pathology, age, stage, bulky disease or treatment in B cell PIL (Table 6).

Numbers of T-cell lymphoma were too small for sub-analyses. The small number of patients made it difficult to get an accurate analysis.

DISCUSSION

There are many publications about the epidemiology and

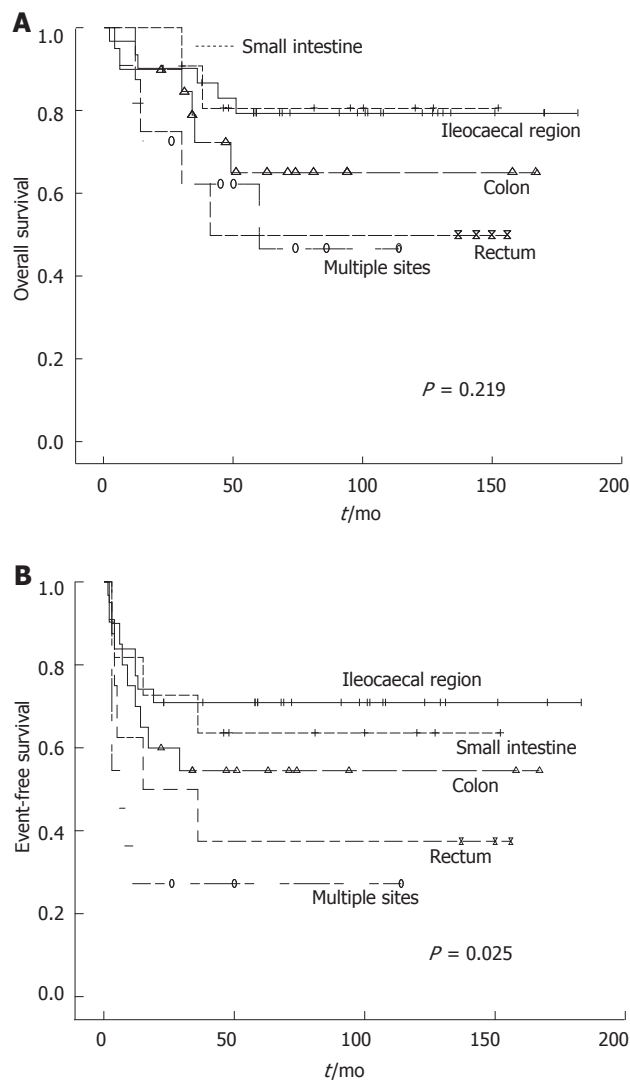


Figure 1 The survival curves stratified by the five groups according to anatomic site of origin. A: Overall survival among five groups (*P* = 0.219). Small intestine and ileocaecal region vs rectum and multiple sites (*P* = 0.016); B: Event-free survival among five groups (*P* = 0.025).

clinical features of PIL. Only a few of the publications recruited more than 80 PIL patients^[1,6,8], however, all of them were published before 2003. Except for a report on PGIL in Chinese patients which recruited 184 intestinal patients in 1995 from Hong Kong^[13], there was no relative large-sample report from mainland China. Due to the differences in living habits and environment effects between Hong Kong and mainland China, it was necessary to analyze the epidemiology and prognosis of PIL in mainland China.

PIL is a male predominant disease, and male:female ratio was 2.5:1. In our series, we found that the age of the patients (median age = 46 and mean age = 46) were younger than the other reports^[5,6,8,13-15].

The ileocaecal region was the most common site, with a frequency of 38.3%. Unlike the other reports^[5,8,13,16], the colorectal involvement was more frequent. The rates of primary sites varied considerably in the other publications, especially noticeable for the rates of the ileocaecal region. The data ranged from 9.5% to 38.3% in our re-

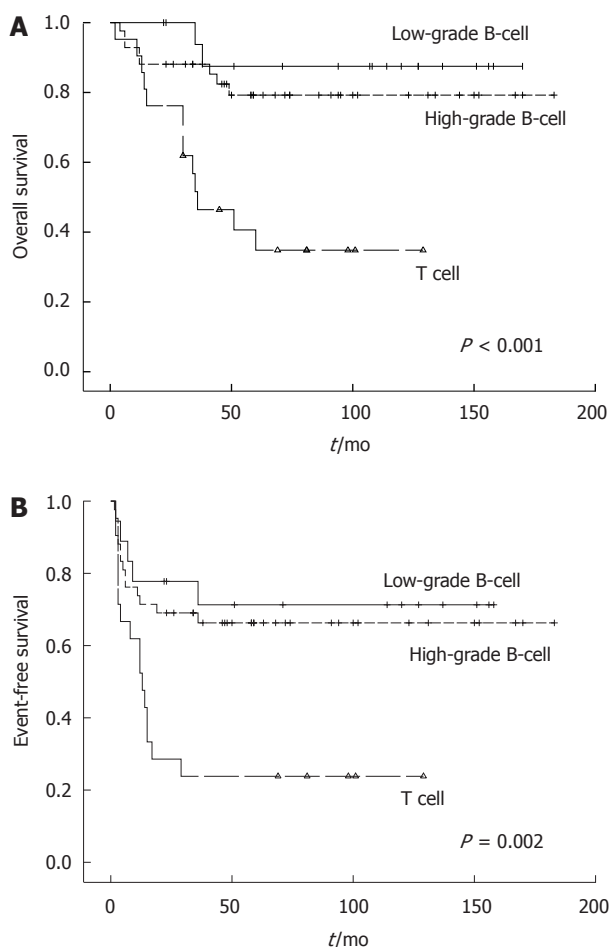


Figure 2 The survival curves stratified by the three histologic subgroups. A: Overall survival among the three groups ($P < 0.001$); B: Event-free survival among the three groups ($P = 0.002$).

port^[16]. We considered that the main reason for the difference was probably the precise definition of the ileocaecal region, which was missing in most reports. We believe it is important to distinguish it as a separate site, because our data show a significantly better prognosis for this region.

High-grade B cell lymphoma was the most common subtype in all the patients. This was followed by T cell lymphoma, which is apparently more than in Europe^[5,6]. In our opinion, the reason for this is due to the higher ratio of T cell lymphoma in the NHL in China than European countries. Two publications reported T cell lymphoma only comprised 5% and 20.6% of the primary intestinal lymphoma in Chinese patients^[17,18]. The difference between the reported series is difficult to interpret. Geographic variations in the prevalence of viral or bacterial infection, celiac disease, diet or other environmental factors may be the cause of the difference. However, the most likely reason may be due to these other studies having too small a sample size.

Our data confirmed the rising trend of PIL over the past 16 years in China, which was similar to reports from the United States^[19] and Europe^[6]. Furthermore, the number of patients with early stages or multiple sites has also increased. Advances in diagnostic procedures have led to an improvement in the accuracy in the diagnosis of lym-

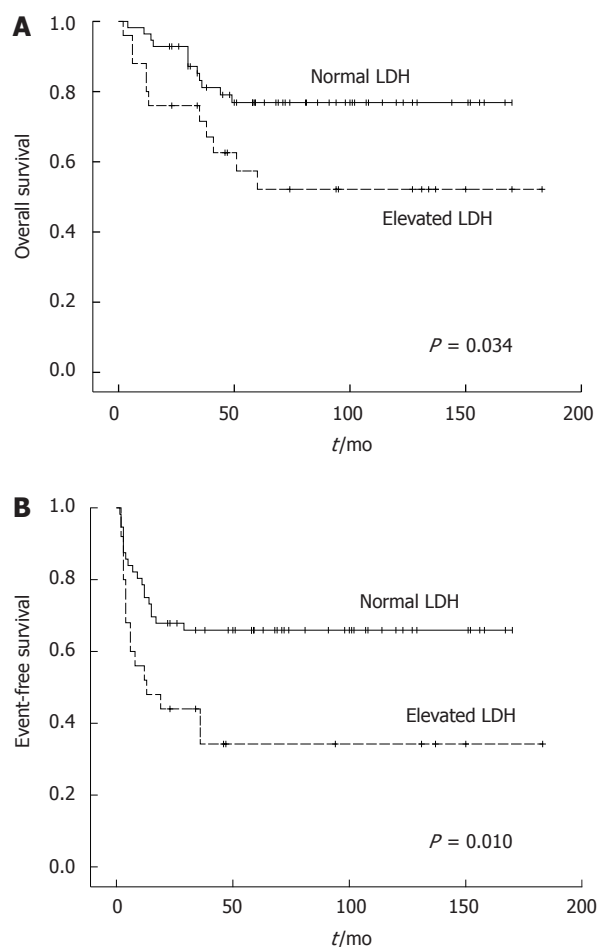


Figure 3 The survival curves stratified by the two groups according to lactate dehydrogenase levels. A: Overall survival between the two groups ($P = 0.034$); B: Event-free survival between the two groups ($P = 0.010$). LDH: Lactate dehydrogenase.

phoma. However, an actual increase in the incidence of intestinal lymphoma should also be considered. Increasing exposure or susceptibility to risk factors, such as *H. pylori* infection, excessive protein or fat in the diet, and environmental pollution also may have contributed to this increase^[6,20].

Most of the patients received combined treatment including surgery and chemotherapy with or without radiotherapy, 69.1% patients reached CR. The OS and EFS rates after 5 years were 71.6% and 60.9%, respectively. This was similar to the other reports^[5,8].

Multivariate analysis revealed that small intestine and ileocaecal region localization, B-cell phenotype, and normal LDH were independent prognostic factors for better OS and EFS. Female gender^[21] and no perforation indicated better OS in univariate analysis, but not significantly in multivariate analysis.

We also did prognostic analyses for the subgroups of B-cell lymphomas. The pathology subtypes of the B-cell lymphomas were not significant prognostic factors. Perhaps the small number of subtypes made it difficult to get an accurate analysis.

Stage and age were prognostic factors in many reports^[2,22-25], and the size of the mass were also mentioned,

Table 5 Prognostic factors assessed by multivariate analysis¹

Variable	Overall survival		Event-free survival	
	Exp(B)	P value	Exp (B)	P value
Pathology (B cell <i>vs</i> T cell)	4.566	0.002	3.833	0.001
LDH (normal 240 U/L)	1.002	0.013	1.003	0.002
Sites of origin	1.370	0.052	1.442	0.010
Gender	2.980	0.089	NE	
Perforation	0.835	0.778	0.625	0.438

¹Assessed by Cox multivariate analysis. LDH: Lactate dehydrogenase.

Table 6 Prognostic factors for the subgroups of B-cell lymphomas¹

Variable	Overall survival		Event-free survival	
	Exp(B)	P value	Exp (B)	P value
Pathology (subtypes of B cell lymphoma)	1.426	0.174	1.141	0.500
LDH (normal 240 U/L)	3.671	0.127	4.663	0.007
Gender	16.328	0.037	0.804	0.716
Sites of origin	1.604	0.050	1.306	0.151

¹Assessed by Cox multivariate analysis. LDH: Lactate dehydrogenase.

but we found no find significant effect. Other factors reported to have contributed to survival included surgical resection and a good performance status^[3].

We found surgery based treatment and radical surgery did not improve the survival rate. This fact raised the question of whether surgery is really necessary. Usually, the diagnostic difficulties, as well as the high rate of initial complications, led to primary resection of PIL in most patients. However, the efficacy of this procedure has not been evaluated so far. Furthermore, we observed complete remissions of PIL in patients receiving only conservative therapy^[8,26,27].

It is clear that there was no benefit from lymph node clearance in lymphoma patients, which makes a case against extended surgical procedures. Surgery is still controversial as first-line therapy in patients with early stages of gastric lymphoma. Our findings indicate that patients with a clear diagnosis, better prognostic factors, and without initial complications should consider the conservative approach so that they may have a better quality of life. However, emergency operation is required when treatment related complications occur, such as perforation, ileus or bleeding.

PIL are heterogeneous diseases. In our point of view, the different prognostic factors and controversial treatment may be caused by the different constitution of these sub-types, ignoring racial and environment factors. Thus, further randomized prospective studies with a large number of patients are essential for this to be established.

ACKNOWLEDGMENTS

We would like to thank Huang YH and Wong JL for technical help and Gao F who provided writing assistance.

COMMENTS

Background

In recent years, the incidence of primary extranodal lymphoma has increased, and gastrointestinal lymphomas are the most frequent subtype. However, the optimal treatment for primary intestinal lymphoma (PIL) remains controversial.

Research frontiers

Numerous retrospective studies reported primary gastrointestinal lymphoma in Europe, but there were no large-sample studies from China. The optimal treatment for PIL remains controversial, and the prognostic data for patients with PIL remain to be elucidated.

Innovations and breakthroughs

This study analyzed the clinical feature, anatomic and histologic distribution, time trends, treatment responses and the prognosis of primary intestinal lymphoma in Chinese patients. The authors found surgery based treatment and radical surgery did not improve the survival rate. The fact raised the question of whether surgery is really necessary. The findings indicate that patients with a clear diagnosis, better prognostic factors, and without initial complications should consider the conservative approach, so that they may have a better quality of life.

Applications

Refined stratification of patients with PIL, according to the prognostic variables, may allow individualized treatment. Conservative treatment may be an optimal therapeutic modality for selected patients.

Terminology

PIL: Primary intestinal lymphoma; marginal zone lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, enteropathy-type T cell lymphoma and peripheral T-cell lymphoma, not otherwise specified *et al* are histologic types of non-Hodgkin's lymphoma.

Peer review

This is an interesting manuscript on primary gastrointestinal-lymphoma in China. The authors analyzed the clinicopathologic features of PIL with special reference to time trends. They determined the prognostic factors for intestinal lymphoma and evaluated the influence of therapeutic modalities on the prognosis. The results showed that conservative treatment might be an optimal therapeutic modality for selected patients with PIL.

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