

# Primary Non-Hodgkin Lymphoma of the Stomach: Clinicopathological Characteristics and Prognostic Factors in Iranian Patients

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## Abstract

**Background:** Primary Gastric Lymphoma (PGL) is an uncommon malignancy with various histological subtypes and treatment outcomes. The aim of this study was to investigate the potential prognostic factors and clinicopathological characteristics of Iranian patients with PGL.

**Methods:** The clinicopathological characteristics of 60 patients with PGL were retrospectively reviewed from 2001 to 2012. The patients underwent various combinations of chemotherapy, radiotherapy, and surgery. We evaluated multiple potential prognostic factors and their associations with patient survival rate.

**Results:** According to the results, Diffuse Large B-cell Lymphoma (DLBCL) and Mucosa-Associated Lymphoid Tissue (MALT) were two predominant histological subtypes. The majority of cases were diagnosed with stage I tumor in the distal part of the stomach. The 5-year disease-free survival (DFS) and overall survival (OS) rates were 60% and 70%, respectively. It was revealed that poor World Health Organization (WHO) performance status, presence of B symptoms, and International Prognostic Index (IPI) score  $\geq 3$  were significantly associated with decreased patient survival.

**Conclusion:** Most of the patients with PGL in early stage have a favorable prognosis.

**Keywords:** Non-Hodgkin lymphoma; stomach; prognostic factor; overall survival rate

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## Introduction

Although stomach is the most common site of extranodal non-Hodgkin's lymphomas, overall incidence rate of these lymphomas is low, accounting for less than 5% of gastric malignancies [1-3]. According to World Health Organization (WHO) classification, Diffuse Large B-cell Lymphoma (DLBCL) and Mucosa-Associated Lymphoid Tissue (MALT) are the two main histological subtypes of the disease with different clinical and pathological features and treatments [4]. Advances in immunohistochemical staining and imaging have precluded surgical intervention as a primary diagnostic and staging tool. Non-specific abdominal symptoms (such as: abdominal discomfort, nausea vomiting, and weight loss) lead to delayed establishment of diagnosis. They are

frequently diagnosed by endoscopy presented from minimal mucosal changes to large ulcerated polypoid mass. Radiological investigations may suggest a diagnosis but they are not specific and usually more useful in staging [1, 5]. Several staging systems have been developed to differentiate localized from systemic form of the disease, which is necessary for treatment planning and prognostic significance [6-8]. Moreover, there have been many controversies concerning the role of surgery in patients' health outcomes [9-11]. Despite the increased knowledge about this type of tumor, there is no consensus in the optimal mode of treatment [12, 13]. General prognosis of this disease depends on various tumor- and host-related factors including patient's age and performance status, histological subtype, grade of lymphoma, and disease stage [14, 15]. Aim of the present study was to analyze the

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**Table 1.** Tumor distribution according to histological subtypes.

Histology	Number (%)
DLBCL	38 (63.3)
MALT lymphoma	14 (23.3)
T-cell lymphoma	2 (3.3)
SLL	3(5)
Mantel cell lymphoma	3 (5)

DLBCL: diffuse large B-cell lymphoma; SLL: small lymphocytic lymphoma

clinicopathological features, prognostic factors, and treatment outcomes of Primary Gastric Lymphoma (PGL) in patients referring to two oncology hospitals in Northeast of Iran.

**Materials and Methods**

This retrospective study was carried out in the oncology departments of Omid and Imam Reza hospitals in Mashhad (Northeast of Iran) over an 11-year period, from 2001 to 2012. Patients with primary presentations of gastrointestinal symptoms and predominant gastric lesions were recruited with respect to the definition presented by Levin et al. Finally, sixty consecutive patients with histopathological diagnosis of PGL were included.

The patients and tumor characteristics including age, sex, performance status, tumor stage, histology, grade, B symptoms, lactate dehydrogenase (LDH) level, International Prognostic Index (IPI) score, and treatment modality were obtained from the medical records. The potential relationships between these variables and survival rate were evaluated.

Ann Arbor staging and WHO system were used for initial staging and performance status determination, respectively. Disease-free survival (DFS) rate was calculated as the interval between

the time of histological diagnosis and the date of relapse, or disease progression, or the last follow-up. Overall Survival (OS) rate was defined as the interval between the initial diagnosis and death or the last follow-up. Kaplan-Meier method was applied for survival analysis, and a p-value less than 0.05 was considered statistically significant.

**Results**

**Clinical characteristics**

60 patients with PGL were included in the study. The median age at diagnosis was 52 years (age range: 28-82 years) with a 2:1 male-to-female ratio. Epigastric pain (51, 85%) and weight loss (45, 75%) were the most common patient complaints in diagnosis, and B symptoms were observed in 25% of the patients. Tumor distribution according to histological subtypes shows in table 1. Imaging and clinical findings revealed 43 (71%) and 15 (25%) subjects who presented with stage I and II disease, respectively; also, 1 (2%) patient was diagnosed with stage III disease and 1 (2%) patient had stage IV disease. According to the endoscopic reports, antrum (41%) and body of the stomach (37%) were the most frequent tumor locations. Also, the performance status score was 0 or 1 in 90% of the patients and 2 and 3 in 8% and 2% of the subjects. LDH level was within the normal range in 47 (78%) patients, while it was higher than normal in 13 (22%) subjects.

**Treatment outcomes**

25 (42%) patients underwent surgical intervention, and followed by chemotherapy and/or radiotherapy. Overall, 17 (68%) and 7 (28%) patients underwent total and partial gastrectomies. Also, gastrojejunostomy was performed as palliative care in one patient with gastric outlet obstruction.

51 (85%) patients received chemotherapy with or without radiotherapy, and three (6%) patients

**Table 2.** Various treatment modalities according to histological subtypes.

Treatment modality	DLBCL	MALT lymphoma	T-cell lymphoma	SLL	Mantel cell lymphoma
SUR +CT	13	3		1	1
CT alone	4				
SUR+CT+RT	6	6	1	2	2
SUR+RT		2	1		
CT+RT	15				
RT alone	0	3	0	0	0
Total					

DLBCL: diffuse large B-cell lymphoma; SLL: small lymphocytic lymphoma; Sur: surgery; CT: chemotherapy; RT: radiotherapy

**Table 3.** Analysis of potential prognostic factors for overall survival.

	Patients	5-year OS (%)	p-value
<b>Age</b>			
≤60 years	46	75.2	0.67
>60 year	14	63.6	
<b>Gender</b>			
Male	41	69.1	0.84
Female	19	68.5	
<b>Histology</b>			
DLBC	38	62	0.43
MALT	14	75.4	
Others	8	96.8	
<b>Ann Arbor stage</b>			
I	43	77.3	0.06
II	15	71.5	
III	1	100	
IV	1	00.0	
<b>WHO performance score</b>			
0-1	54	78.5	0.034
2	5	50.6	
3	1	00.0	
<b>Grade</b>			
High	40	65.6	0.96
Low	20	78.3	
<b>B symptoms</b>			
No	45	80.7	0.040
Yes	15	46.3	
<b>LDH level</b>			
Normal	47	66.8	0.73
Elevated	13	70.4	
<b>IPI score</b>			
0-2	49	79.8	<0.001
≥3	11	23.4	
<b>Treatment modality</b>			
Surgery	25	63.1	0.61
Without surgery	35	80.5	

received radiotherapy alone. Table 2 shows various treatment modalities according to the histological subtype. Chemotherapy consisted of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Radiotherapy was performed with Cobalt-60 or 6 MV Linear accelerator (Linac), with a median dose of 42.5 GY (range: 30-50.4 GY).

## Survival and Prognostic Factors

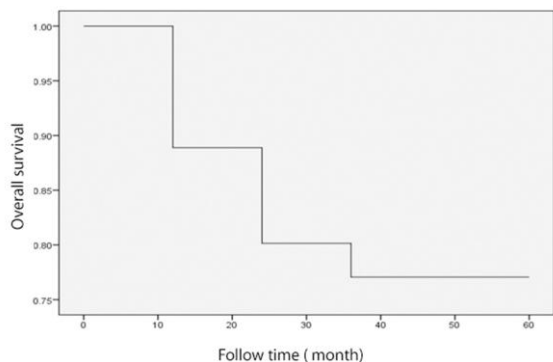
The median follow-up duration was 63 months (range: 3-146 months). The 5-year disease-free survival (DFS) and overall survival (OS) rates were 60% and 70%, respectively (Figures 1). In univariate analysis among all potential prognostic factors, WHO performance status ( $p<0.03$ ), B symptoms ( $p=0.04$ ), and IPI score ( $p<0.001$ ) were statistically significant differences in terms of survival rate (Table 3). However in the multivariate analysis only IPI score was significantly related to the survival.

## Discussion

According to the results of the current study that was conducted in two referral oncology centers in Northeast of Iran, 5-year OS and DFS rates were 70% and 60% in patients with PGL, respectively. Our findings showed that 0-2 IPI scores, good WHO performance status, and absence of B symptoms were the most significant prognostic factors for obtaining better clinical outcomes.

The incidence of gastrointestinal lymphoma (including PGL) has increased over the last decades [16]. PGL is a heterogeneous malignancy with different histological subtypes including low grade-MALT and high grade DLBC lymphomas [4, 17]. In our study, DLBC was the most common histological subtype that followed by MALT; the obtained result was similar to the findings of two studies conducted in North and South of Iran and different western studies [18-21].

Some studies reported improved survival rate for MALT compared to DLBC [22, 23]. In this study, although an improvement was observed in the survival rate of patients with MALT, but it was not statistically significant. The relative small number of patients with MALT histology may affect the analysis, leading to undetected significance. In the present study, the median age of the patients was 52 years, similar to previously conducted research (range 50 - 60 years) [2-5]. In fact, age more than 60 years has been reported as one of the prognostic factors in some studies; however, we found no relationship between age and survival rate in this study [14, 15]. Grade of lymphoma is considered an important tumor characteristic, which affects both prognosis and treatment outcomes. According to previous researches, there is a significant association between low-grade MALT and H pylori infection; therefore, antibiotic therapy is the primary mode of treatment in this histological subtype. Radiotherapy



**Figure 1.** It shows overall survival among 60 patients with primary gastric lymphoma.

is indicated for patients who are unresponsive to antibiotics or experience recurrence after the first remission [22-24]. In this study, all patients with MALT were unresponsive to medical therapy and were referred to the hospitals for oncologic treatments. On the other hand, chemotherapy is an option for patients with high histological grades.

This study did not show a relationship between histological grade and survival rate. In addition, in some studies, LDH level was considered a tumor-related prognostic factor, and its level greater than the upper limit of the normal range implied poor prognosis [14, 15]. However, in some studies similar to the current research, abnormal LDH level was not a prognostic factor [25]. Night sweating, unexplained fever and weight loss are regarded as B symptoms, which affect patient survival rate [14, 26, 27]. In our study, presence of B symptoms adversely affected the prognosis (p-value=0.04). Moreover, according to Ann Arbor staging system for lymphoma, patients are categorized into four categories [28]. In the current study, most of the patients (58, 96%) were categorized in stage I or II disease, and disease stage was not shown as a significant prognostic factor. International Prognostic Index (IPI) is currently the most important clinical predictive system for patients with lymphoma. This clinical system composes of five highly determinant factors including age >60 years, elevated serum LDH level, poor performance status, advanced disease stage, and involvement of multiple extranodal sites. The modified IPI comprises all the mentioned factors, except the last one, and the patients' scores vary from 0 to 4 [29]. In this analysis, we found a significant association between modified IPI and patient survival rate (p-value<0.001). At present, there is no consensus on

the treatment of gastric lymphoma [30-31]. Traditionally, surgical resection was regarded as the main treatment plan. However, the necessity of aggressive resection is being questioned in the era of effective chemotherapy regimens, with or without radiation [32, 33]. In this study, 42% of patients underwent surgical interventions, without any significant impact on the survival rate. The most popular chemotherapy regimen in PGL is CHOP [34, 35]. Rituximab, a monoclonal antibody against CD20, is a novel agent, and its effects on gastric lymphoma have not been conclusively reported. Some studies showed a significant improvement in survival rate by using rituximab [36-38]; however, none of the patients received rituximab in the present study.

## Conclusion

PGL as a heterogeneous disease is associated with various health outcomes and depends on multiple potential prognostic factors. However, most of the patients in this study present it in early stage and has a favorable prognosis.

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## Conflict of Interest

The authors declare no conflicts of interest in this study.

## Authors' Contribution

Sare Hosseini designed and wrote the article. Parvaneh Dehghan collected the data and analyzed them and both authors read and approved the final manuscript.

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