Clinicopathologic Characteristics and Therapeutic Outcomes of Primary Gastrointestinal Non-Hodgkin's Lymphomas: 10 Years of Experience from a Single Center in Eastern Anatolia

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Key Words

Gastrointestinal non-Hodgkin's lymphoma • Prognostic factors • Clinicopathologic features • Survival

Abstract

Objective: The objective of this retrospective study was to report the clinicopathological data and the treatment outcomes in patients with primary gastrointestinal non-Hodgkin's lymphoma. **Patients and Methods:** We carried out a retrospective analysis of 41 patients (22 females, 18 males, median age 58 and range 18–90 years) who presented to our department with histopathological diagnosis of primary gastrointestinal non-Hodgkin's lymphoma between 1995 and 2004. **Results:** The stomach was the most common extranodal site and was seen in 25 of 41 (61%) patients. At presentation 28 (68.3%) patients had gastrointestinal symptoms while 27 (65.9%) had B symptoms. The range of follow-up was 2–84 months with a median of 9 months. The overall survival rate was 3 years for 25 (61.2%) patients. The 3-year overall survival rate was better in patients with early-stage disease (stages I and II₁) who were treated with surgery plus chemotherapy and/or radiation therapy than in those treated with chemotherapy alone (91.6 vs. 50%, $p < 0.05$).

The disease had a significant impact on both the progression-free survival and overall survival rates. **Conclusion:** Our data showed that surgical resection prior to postoperative chemotherapy was a better option for patients with early-stage disease with better patient survival.

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Introduction

The gastrointestinal tract is the predominant extranodal site of non-Hodgkin's lymphoma (NHL). Primary gastrointestinal non-Hodgkin's lymphoma (GI-NHL) accounts for 4–20% of all NHL cases or 30–45% of all extranodal NHL cases [1]. It has been suggested that the incidence of primary GI-NHL increased over the past two decades [2, 3]. In Turkey and Middle Eastern countries, primary extranodal lymphomas constitute more than 25% of all NHLs. The incidence of primary GI-NHL in Eastern countries seems to be higher than in Western countries [4]. High-grade histopathologic types of gastric lymphoma are more common in Turkey and Middle Eastern countries than in Western countries [4, 5].

Table 1. Characteristics of 41 patients with GI-NHL

Patient characteristics	Patients	
	n	%
Age, years	41	
≥60	19	46.3
<60	22	53.7
Gender		
Female	22	46.3
Male	19	53.7
Main symptoms		
Gastrointestinal symptoms ¹	28	68.3
Hemorrhage	4	9.8
Perforation	2	4.9
Ileus	5	12.2
Diarrhea	1	2.4
Jaundice	1	2.4
B symptoms		
Present	27	65.9
Not present	14	34.1
Site of disease		
Stomach	25	61
Small bowel	11	26.8
Large bowel	3	7.3
Multiple site	2	4.9
Endoscopic/surgical findings		
Vegetating mass	12	29.3
Ulceration	6	14.6
Ulcerovegetating mass	22	53.7
Polyposis	1	2.4
Bulky disease (≥10 cm)	7	17.1
Histopathologic grade		
High-grade B-cell lymphoma		
Diffuse large B-cell	24	58.5
Low-grade B-cell lymphoma		
Marginal zone lymphoma (MALT)	11	26.9
Follicular	1	2.4
Mantle cell	1	2.4
T-cell lymphoma	4	9.8
WHO performance status		
0	25	61.1
1	12	29.2
2	3	7.3
3	1	2.4
4	0	0
Histopathology		
T cell	4	9.8
B cell	37	90.2
Lugano staging		
Stage I	6	14.6
Stage II1	8	19.5
Stage II2	5	12.2
Stage IIE	9	22
Stage IV	13	31.7
MALT = Mucosa-associated lymphoid tissue.		
¹ Nausea, vomiting and/or abdominal pain.		

More than half of primary GI-NHLs arise in the stomach and this is frequently followed by the small intestine [1]. The predominant symptoms are epigastric pain, dyspepsia, nausea and vomiting. Upper or lower gastrointestinal bleeding (hematemesis or melena) occurs at the outset in 20–30% of cases, while ileus and perforation are quite rare [6, 7].

The management of nodal NHL is well established, but much debate and controversy still remains regarding the optimal regimen in GI-NHL, particularly in gastric lymphomas. Surgery, radiation therapy and chemotherapy have been used alone or in combination [8]. The efficacy of surgery in adequately controlling tumors, especially gastric lymphomas, has been demonstrated in some studies [9, 10]. It was pointed out that surgery alone or surgery combined with chemotherapy and/or radiotherapy may increase survival rates, and that a conservative treatment approach using radiotherapy and/or chemotherapy as the initial treatment modality without primary resection may preserve the stomach. In several studies, multiple alternative chemotherapy regimens have also been introduced in the management of advanced stages of lymphoma (stages II₂, IIE, and IV), and modern techniques of radiotherapy have been proven to be quite effective in its treatment [11, 12]. No benefit from surgery was reported from these controlled clinical trials in current publications [13, 14].

Most of the studies published so far were retrospective. Only a few of them were prospective controlled randomized trials and the sample sizes of these reports were too small to achieve adequate statistical power [7, 15]. The objective of this study was to assess the clinicopathologic characteristics and therapeutic outcomes of primary GI-NHL.

Patients and Methods

Patients

This retrospective study was based on a review of medical records from patients with primary GI-NHL diagnosed at Turgut Ozal Medical Center, Department of Hematology, between January 1995 and December 2004. This review included clinical features, histopathological classification, site of involvement, efficacy of different treatment modalities and prognostic factors for improved survival. All subjects fulfilled the diagnostic criteria for primary GI-NHL as defined by Lewin et al. [16]. Fifty medical charts were reviewed, and 41 patients were included in the study. Nine patients were ineligible because of insufficient data (table 1). Treatment modalities were compared with age, gender, histopathological grade, B- or T-cell lineage, stage, and location of disease.

Histologic Classification

All histologic materials were obtained by endoscopic biopsy and surgery. These tissue specimens were stained routinely with hematoxylin and eosin (H&E). Immunohistochemical staining for CD3 and CD20 was performed on all 41 specimens. In some selected cases, additional staining was done using antibodies CD5, CD10, CD23, CD30, CD56, cyclin D1, *bcl-2*, *bcl-6*, *c-myc*, p53, Ki-67, immunoglobulin light chains (κ , λ), or β 1. All H&E and immunohistochemical slides were reviewed separately by 2 observers and a common consensus was reached in all cases. All patients were reviewed and classified histopathologically using the WHO classification [17] of low-grade B-cell lymphomas [marginal zone B-cell lymphoma of MALT type (MALT lymphoma), follicular lymphoma, and mantle cell lymphoma], high-grade B-cell lymphomas (diffuse large B-cell lymphoma), and T-cell lymphoma.

Staging and Diagnostic Procedures

All patients were staged according to the Lugano International Conference classification (I, II₁, II₂, IIE, and IV), which was submitted as a modified version of the Ann Arbor criteria for GI-NHL [18]. All patients underwent staging procedures that included chest radiograms, abdominal ultrasonography, computed tomography of the chest and abdomen, radiographic studies of the duodenum and small intestine, upper gastrointestinal endoscopy, and bone marrow biopsy. The macroscopic type of lymphoma was either vegetating mass, ulceration, ulcerovegetating mass, polypoid or bulky disease (≥ 10 cm). This typing was determined based on the resected specimens or endoscopic findings. Response criteria and end points were reported according to published guidelines [19]. Patients were examined at 3-monthly intervals for the first year and 6-monthly thereafter.

Treatment

An initial surgical treatment decision, in which the hematologist and/or the radiation oncologist were not involved, was made according to the surgeon's preference. Initial surgery was performed in 19 patients: 8 patients underwent total or subtotal gastrectomy, 4 had Roux-en-Y anastomosis (a choledochojejunostomy performed for biliary bypass), 5 had tumor resection, and 2 had debulking surgery. Of these patients, 12 received chemotherapy, 6 were treated with chemotherapy plus radiotherapy (3,600 cGy total abdominal $\pm$ 600 cGy boost radiotherapy to tumor bed), and 1 with chemotherapy plus palliative surgery. Twelve patients received chemotherapy alone while 5 received chemotherapy plus radiotherapy, and 5 patients with poor performance status received only supportive care.

If there was any evidence of residual disease on physical examination or on imaging studies, and/or the presence of close or microscopically positive surgical margins or lymph nodes greater than 1 cm in size, additional cycles of chemotherapy were administered. Even if additional chemotherapy was not wholly successful in controlling the disease, radiotherapy was used. Finally, if there was no response to adjuvant treatment after surgery, second-line chemotherapy was administered.

Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) and other anthracycline-containing regimens were the most frequently used regimens in 36 of the 41 patients (table 2). In general, patients were treated with 6–8 cycles of the classical lymphoma regimen (CHOP-like regimens). For treating pa-

Table 2. Treatment modalities of all patients

Treatment modalities	Patients	
	n	%
Surgery + chemotherapy	12	29.3
Surgery + chemotherapy + radiotherapy	6	14.6
Chemotherapy + palliative surgery	1	2.4
Chemotherapy + radiotherapy	5	12.2
Chemotherapy alone	12	29.3
Supportive care only	5	12.2
Total	41	100

tients with early-stage disease, if the involved field radiotherapy was deemed necessary as a part of pretreatment in advance, a total of 4 cycles of chemotherapy were administered.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Program for Social Sciences, version 15.0, Chicago, Ill., USA). Overall survival (OS) and progression-free survival (PFS) rates were calculated with the life table Kaplan-Meier method, starting from the date of diagnosis to the date of death or last follow-up visit. The statistical significance of observed differences was assessed using the log-rank test. The prognostic value of different variables for the outcome was assessed by univariate and multivariate analysis using the Cox regression model. The level of statistical significance was defined as $p < 0.05$.

Results

Primary GI-NHL accounted for 9.7% of all lymphomas. Of the 41 patients with histopathological diagnosis of primary GI-NHL, 19 were males and 22 females with a median age of 58 years (range 18–90). Patients with intestinal involvement were younger as compared with patients with gastric involvement (median age 49 vs. 60 years). Stomach, small intestine, large intestine, and synchronized multiple gastrointestinal site involvement (ileocecal region was considered as small intestinal involvement) occurred in 25 (61%), 11 (26.8%), 3 (7.3%), and 2 (4.9%) patients, respectively. According to the Lugano staging system, 6 patients (14.6%) were stage I, 8 (19.5%) stage II₁, 5 (12.2%) stage II₂, 9 (22%) stage IIE, and 13 (31.7%) stage IV disease. According to the WHO performance status, 25 patients (61.1%) were 0, 12 patients (29.2%) 1, 3 patients (7.3%) 2, and 1 patient (2.4%) 3 (table 1).

Fig. 1. OS of all primary GI-NHL patients.

Fig. 2. Effect of histopathological grades on PFS in low-grade, high-grade and T-cell primary GI-NHL.

Initial presenting symptoms were: upper gastrointestinal symptoms (nausea, vomiting and/or abdominal pain: $n = 28$; jaundice: $n = 1$; diarrhea: $n = 1$), and emergency admission: $n = 11$ (patients with perforation: $n = 2$; with gastrointestinal bleeding: $n = 4$; with ileus: $n = 5$). In 41 patients, who were diagnosed endoscopically or surgically, a tumoral mass was detected. But 6 patients presented with solely gastric ulcerations. This finding shows that biopsy is often required in gastric ulcerations in order to confirm the diagnosis of lymphoma. At the time of diagnosis, 27 (65.9%) patients had B symptoms (table 1).

Endoscopic and/or Surgical Findings

Endoscopic and surgical findings obtained from the 41 registries were gastric ulcerations: $n = 6$ (14.6%), vegetating masses: $n = 12$ (29.3%), ulcero-vegetating masses: $n = 22$ (53.7%), multiple polyposis: $n = 1$ (2.4%), and bulky disease (>10 cm): $n = 7$ (17%, table 1).

Histopathology

Based on the WHO classification, high-grade and advanced-stage disease was relatively common: 24 patients (58.5%) had diffuse large B-cell lymphoma. Low-grade B-cell lymphoma was less common: MALT: $n = 11$ (26.9%); follicular lymphoma: $n = 1$ (2.4%); mantle cell: $n = 1$ (2.4%), and T-cell disease: $n = 4$ (9.8%). Based on our working formulation, 5 (12.2%) patients had low-grade,

33 (80.5%) intermediate-grade, and 3 (7.3%) high-grade disease. Immunohistochemically 4 (9.8%) patients had neoplastic cells that were positive for the T-cell markers (table 1).

Survival Analysis

In the median follow-up of 9 months (range 2–84 months), 6 of 41 patients died. Febrile neutropenia was the cause of death in 1 (which was chemotherapy-induced in an advanced stage), hemorrhagia in another (secondary to thrombocytopenia which was chemotherapy-related in an early stage), and the remaining 4 died due to disease progression (all of whom had advanced-stage disease). Five patients with only supportive care were not included in prognostic factor analysis. The 3-year OS rate was 61.2% in all patients (fig. 1). The 3-year OS rates were 78, 65, and 42% among patients with low, intermediate, and high grade, respectively (fig. 2): 82, 63, and 29% among those with stage I–II₁, stage II₂–III_E, and stage IV disease, respectively (fig. 3). The 3-year PFS rates were 68, 49, and 30% among patients with low-grade, high-grade and T-cell lymphoma ($p = 0.022$), respectively (fig. 2), and 71, 52, and 26% among those with stage I–II₁, stage II₂–III_E, and stage IV disease, respectively ($p = 0.018$, fig. 3).

Univariate analysis of the influence of age, gender, B symptoms, stage and histopathologic grade of disease, and T-cell marker positivity on patient survival showed

Fig. 3. PFS of early- and advanced-stage primary GI-NHL.

Fig. 4. Effect of the presence of B symptoms on PFS.

Table 3. Cox multivariate analysis for OS

Parameters	Odds ratio	95% CI	p value
Sex	1.0357	0.39–2.95	NS
Localization	1.3987	0.57–3.12	NS
Stage	2.1285	1.12–4.83	0.02
Grade	1.8824	0.71–4.21	NS
Age (<60 or ≥60 years)	0.7841	0.27–1.96	NS
Surgery	1.0274	0.36–1.94	NS
B symptom positivity	1.7432	0.59–5.12	NS

Table 4. Cox multivariate analysis for PSF

Parameters	Odds ratio	95% CI	p value
Sex	1.1245	0.41–2.62	NS
Localization	0.7621	0.28–2.12	NS
Stage	1.7538	1.06–3.75	0.04
Grade	1.3676	0.54–3.42	NS
Age (<60 or ≥60 years)	0.9430	0.36–2.01	NS
Surgery	1.1743	0.47–2.28	NS
B symptom positivity	2.2953	0.91–5.83	0.04

that advanced stage, high-grade histopathology, and the presence of B symptoms, which negatively affected the PFS rate ($p < 0.05$, fig. 2–4), were the statistically significant factors. However, Cox regression multivariate analysis revealed that only advanced stage correlated with OS rate ($p = 0.02$, table 3). According to Cox regression multivariate analysis, advanced stage significantly and negatively affected PFS ($p = 0.04$), also the presence of B symptoms affected PFS to a significant extent ($p = 0.04$, table 4).

The 3-year OS rate was better in stage I and II₁ patients who were treated with surgery plus chemotherapy ($\pm$ radiotherapy) than in those treated with chemotherapy alone ($p = 0.036$, fig. 5). In the early stage, surgery plus chemotherapy achieved significantly better results than chemotherapy alone in terms of higher overall response

rate (complete response + partial response, 100 vs. 58.3%), 3-year PFS (83.3 vs. 41.6%) and 3-year OS rates (91.6 vs. 50%). In the advanced stage, there was no difference in the 3-year PFS (25 vs. 33.3%), 3-year OS (41.6 vs. 50%) and overall response (33.3 vs. 41.6%) rates between the two groups. In advanced-stage disease, surgical resection seemed to be a disadvantage, but it was not found to be statistically significant ($p = 0.6$).

Effect of Surgery on Survival

The analysis of the effect of surgery in patients with completely resectable early-stage (stages I and II₁) and unresectable advanced-stage (stages II₂, IIE, and IV) disease showed no difference in OS and PFS of patients based on histopathological and clinical variables (grade, age, and B symptoms).

Fig. 5. Effect of surgery on OS in early-stage primary GI-NHL.

Discussion

Primary GI-NHL typically presents with nonspecific signs and symptoms attributable to the site of involvement, extent and histologic subtype of the disease, and the performance status of the patient. Gastrointestinal localizations are the most common sites of primary extranodal lymphoma as in our study (table 5). The previously reported predominant symptoms of epigastric pain, dyspepsia, nausea and vomiting, anorexia and very frequent weight loss were also observed in our study where 68.3% of patients presented with gastrointestinal symptoms such as abdominal pain, nausea and vomiting. Eastern countries have a higher incidence of primary GI-NHL than Western countries [4, 5, 20]. Geographic variations in the prevalence of environmental factors may be the cause of this difference. However, the incidence of primary GI-NHL in the US [3], Europe [21] and Turkey [4] has increased over the past two decades. Advances in diagnostic procedures may have led to an improvement in

the accuracy in the diagnosis of lymphoma. Increasing exposure or susceptibility to risk factors, such as ultra-violet light, chemicals, and excessive protein or fat in the diet, also may have contributed to this increase [20]. With regard to gender distribution, in contrast to previous reports [1, 5, 7, 8], there was a slight female predominance in our series (with a female:male ratio of 1.15:1). This difference may support the hypothesis that gender-specific, constitutional or behavioral factors can play a role in the development of GI-NHL.

Advanced stages of gastric lymphoma are more prevalent in Turkey, Middle Eastern and Far Eastern countries than in Western countries. Compared with Western reports of 10–31%, 53.7% of our patients had disseminated disease at the time of diagnosis (stages II₂E–IV), which is similar to eastern data (52%) [2–5]. Poor prognostic factors were more frequent in our patients than in Western countries.

Optimal management of primary GI-NHLs remains controversial. Surgery, radiotherapy and chemotherapy have been used either alone or in combination. Currently, the most controversial issue in the treatment of primary GI-NHLs is to determine whether or not the surgical treatment approach is necessary as the primary treatment modality. In patients with completely resectable early-stage disease, surgery has more of an advantage but could delay the use of chemotherapy, could be associated with some morbidity, and may also have a mortality rate of up to 10% [22]. Furthermore, it has also been suggested that surgery does not have a significant influence on OS and PFS rates. Currently, several series have reported that surgery is not indicated unless complications such as perforation, hemorrhage or obstruction occur, which cannot be managed conservatively [8]. Avilés et al. [13, 14] reported on the role of surgery in high-grade MALT, low-grade MALT and diffuse large B-cell gastric lymphomas. No benefit from surgery was found from these controlled clinical trials. Primary chemotherapy or radiotherapy is currently recommended in cases of localized or advanced disease [1, 7, 23]. In our series, 2 deaths were due to surgical complications (one due to intra-abdominal infection and the other due to hemorrhage). Although it was stated that surgery has the advantage of total tumor removal and limits the risk of hemorrhage and perforation, this was not supported by the analysis of our patients.

In a randomized study on gastric NHL, results after chemotherapy or surgery plus chemotherapy (91% survival rate at 10 years) were significantly superior to results after surgery alone (54% survival rate at 10 years) or surgery plus radiotherapy (53% survival rate at 10 years) [22].

Table 5. Sites of origin in primary GI-NHL in the literature

Author	Nation	Patients	Anatomic sites of origin, n (%)			
			gastric	intestinal	combined	others
Radaszkiewicz et al. [25]	Austria	372	258 (69)	71 (19)	8 (2.2) ^a	35 (9.4) ^b
d'Amore et al. [1]	Denmark	306	175 (57)	109 (36)	22 (7.2)	–
Liang et al. [26]	Hong Kong	425	238 (56)	184 (43)	ND	3 (0.8) ^c
Gurney et al. [21] ^d	United Kingdom	1,047	463 (44)	440 (42)	ND	144 (14) ^b
Koch et al. [7]	Germany	371	277 (75)	70 (19)	24 (6.5)	–
Nakamura et al. [20]	Japan	455	342 (75)	96 (21)	17 (3.7)	–
Current study (2008)	Turkey	41	25 (61)	14 (34.1)	2 (4.9)	–

ND = Not described. ^a Cases involving multiple gastrointestinal tract organs. ^b Unspecified. ^c Cases with primary esophageal lymphoma. ^d Registry data without prognostic analysis.

However, other investigators showed no difference in survival rates after chemotherapy alone versus surgery plus chemotherapy [8, 23]. In our series, surgery in combination with chemotherapy (3-year OS rates, 91.6%) was significantly superior to chemotherapy alone (3-year OS rates, 50%) in the treatment of early-stage disease ($p = 0.03$). In the early stage, among the patients treated with surgery plus chemotherapy (83.3%), 3-year PFS rate was statistically significantly higher than among those who received chemotherapy (41.6%) alone ($p = 0.06$). In the early stage, among the patients treated with surgery plus chemotherapy (100%), the OS rate was statistically significantly higher than the rates among those who received chemotherapy (58.3%) alone ($p = 0.01$). However, surgery had no advantage in terms of 3-year OS rates for patients with advanced-stage disease (41.6 vs. 50%, $p = 0.11$). In the advanced stage, there was no significant difference in 3-year PFS rates between the two groups (25 vs. 33.3%). There was no significant difference in the overall response rates between the two groups (33.3 vs. 41.6%). However, we should mention that the number of patients was too low to come to a conclusion.

Primary gastric lymphomas are most commonly of B-cell lineage, while primary gastric T-cell lymphomas are extremely rare and have a poor prognosis [24]. Our findings are consistent with the results of previous research. The median follow-up time, however, was too short (only 9 months). This is a major disadvantage, when survival or prognostic factor analysis are performed. It is noteworthy that among the 41 patients of the study, only 6 died, 2 from complications and 4 from disease progression. Among those 4 patients (9.8%) who succumbed to disease, 3 had T-cell NHL. Therefore, any survival esti-

mates and comparisons were based on events caused by complications or T-cell NHL and only one event was attributed to disease progression in a patient with B-cell NHL. If the follow-up period had been longer, probably more events would have occurred due to B-NHL progression.

The results of our study showed that the stage of the disease was the most important prognostic factor affecting clinical outcome. Patients with early-stage disease had significantly longer 3-year PFS and 3-year OS rates than patients with advanced stage-disease ($p < 0.05$, tables 3, 4). Our results were similar to those observed in the studies by Koch et al. [7] and Eser et al. [5].

Conclusion

Surgical resection followed by postoperative chemotherapy may be a viable option for patients with early-stage disease which may lead to improved patient survival but since the number of patients in our study was small, our result should be interpreted with caution. Further randomized prospective studies with larger sample size should be carried out to clarify the optimal management of primary gastrointestinal lymphoma.

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