

## Primary Gastric Non Malt Lymphoma: Comparison of Two Treatment Modalities and Survival in 44 Patients

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**Abstract:** Modalities of treatment in Primary Gastric Lymphoma (PGL) are still controversial. The purpose of this study is to seek the better treatment modality in terms of survival. Charts of patients diagnosed with PGL, between 1980-2003, were reviewed and divided into 2 groups by modality of treatment: Group A included patients treated by surgery alone or combination therapy including surgery (19 patients) and group B included patients on chemotherapy alone (19 patients). Clinical staging, modality of treatment, background diseases and demographic characteristics were compared. Patients with MALT lymphoma were excluded from the study. Patients in group-B were significantly older than patients in group-A ( $64.5 \pm 8.9$  vs.  $57.4 \pm 13.8$ ,  $p=0.033$ ) and had a shorter duration of symptoms ( $2.8$  months  $\pm 2$  vs.  $5.7$  months  $\pm 7$ ,  $p=0.05$ ). As for modalities of treatment, patients in group-A had better survival than group-B ( $112$  months  $\pm 45$  vs.  $79$  months  $\pm 46$ ,  $p=0.03$ ). Patients in stage 3 and 4, survival in group-A was better than in group-B ( $104$  months  $\pm 77$  vs.  $46$  months  $\pm 58$ ,  $p<0.05$ ). Given the small amount and heterogeneous patients, we found a significant advantage to surgery or combination therapy over chemotherapy alone, especially in advanced clinical stage and survival was significantly higher in this group.

**Key words:** Primary gastric lymphoma, chemotherapy, surgery, comparison, modalities and survival

### INTRODUCTION

Primary gastric lymphoma is the most common extranodal lymphoma, representing 4-20% of the extranodal lymphomas (Aisenberg, 1995). Traditionally, the opted treatment for primary gastric lymphoma has been aggressive surgical resection followed by adjuvant radiotherapy (Biernan, 2003; Al-Akwaa, 2004). Although surgical resection produces excellent results in early staged patients, some investigators have reported that gastric lymphomas can be successfully treated with a combination of chemoradiotherapy (Willich *et al.*, 2000; Choi *et al.*, 2005). Because of its rarity, most of the studies do not have sufficient numbers of patients to allow significant and optimal approach.

We conducted a retrospective study comparing patients who went through surgical gastrectomy alone or combined with chemotherapy and patients treated non-surgically with chemotherapy or radiotherapy, in order to compare the different modalities in terms of survival.

### MATERIALS AND METHODS

All patients with Primary non malt Gastric Lymphoma (PGL) admitted to Golda-Hasharon Campus, Rabin Medical Center, Petah Tikva, Israel, between the years 1980-2003 were included in this retrospective study. Patient's files were reviewed and divided into 2 groups by modality of treatment: Group A included patients treated by surgery alone or combination therapy including surgery (19 patients) and group B included patients on chemotherapy or radiation therapy alone (19 patients). All patients had either symptoms or predominant lesions in the stomach. The diagnosis workup of most patients included blood tests including Lactate Dehydrogenase (LDH), Complete Blood Count (CBC), liver enzymes and electrolytes. Radiologic evaluation including CT and bone marrow biopsy were done as part of the clinical staging procedure that is: Stage 1,2 included patients with Single node, or 2 lymph nodes-on the same side of the diaphragm, stage 3, 4 includes node groups on both

sides of diaphragm or bone marrow involvement. A asymptomatic at any stage and B symptoms: Fever, sweats, weight loss.

Some patients went through endoscopy and biopsy, while others had laparotomy prior to the diagnosis. The PGL was pathologically diagnosed and defined according to the working formulation and later the WHO classification (Harris *et al.*, 1997; NCI, 1982).

Patient's files were reviewed and data was collected concerning histories of hospitalization and follow up clinics, background diseases, patient's origin (where they were born before they immigrated to Israel and according to that were they Ashkenazi or Sephardim Jews), demographic characteristics and survival. Survival was compared from the time of diagnosis in terms of month. Patients who were diagnosed with H. Pylori + Mucosal Associated Lymphoid Tissue (MALT) lymphoma, were excluded from the study along with patients with intestinal or esophageal lymphoma.

**Statistical analysis:** The study was retrospective. Two statistical tests were applied: Chi-square and student T test. We also applied Kaplan-Mayer survival curve.

## RESULTS

Between the years 1980 and 2003, 44 patients were diagnosed with PGL, 4 patients expired before they could receive treatment and 2 patients refused treatment. 38 patients were included in the study. The age of the patients was 32-90 with a mean age of 61. Most patients were born in Eastern Europe (25) (Ashkenazi Jews), only 7 patients were born in Israel, 3 of them were Arabic (Table 1). There was no significant difference between the groups in terms of background diseases.

Table 1: Patient characteristics

Groups	Surgical	Non-surgical	Total
Patients	19	19	38
Females / Males	11 / 8	9 / 10	20 / 18
Age (mean +/-SD)	57 +/-14	64 +/-9	61 +/-12
Early stage (1-2)	11	9	20
Late stage (3-4)	7	9	16
Underlying disease			
a) Cardiovasc	5	7	12
b) Others	4	3	7
c) Healthy	9	8	17
Origin: Ashkenazy*	7	11	18
Sepharadic	6	6	12
Arabs	1	1	2
Israel	4	0	4
	Surg	Non surg	
Early	11	9	20
Late	7	9	16
	18	18	36
10	10	8	8
	0.502335		

\*Ashkenazy-Jews originating from Europe, America and Australia and Sepharadic-Jews originating from the Middle East, Asia and North Africa

The main diagnostic symptom was abdominal pain (87%) followed by loss of appetite (78%) and mild gastrointestinal bleeding (46%). Two patients presented with major bleeding and perforation and died before getting any treatment. Histological examination revealed large cell high grade lymphoma in 68% of patients and the rest (32%) had follicular low-grade lymphoma.

Regarding modality of treatment, 11 were treated by surgery alone, 15 by chemotherapy based on CHOP (cyclophosphamide, adriamycin, vincristin and prednison) for high grade lymphoma and CVP (Cyclophosphamide, Vincristin and Prednison) for low grade lymphoma, 4 by radiation alone and 8 by surgery combined with chemotherapy (CHOP or CVP). Four patients expired before they could receive treatment and 2 did not receive treatment at all (refused). Group A included patients treated by surgery alone or in combination with chemotherapy (19 patients) and all patients that were treated by chemotherapy or radiotherapy with out surgery were in group-B (19 patients). We followed the patient's survival, comparing between group A and group B in terms of modality of treatment, clinical staging, background diseases and other demographic characteristics. Clinical staging before treatment showed 21 patients in stages 1-2 (early stage) and 23 patients in stages 3-4 (late stage). Interestingly, comparing between genders, the percentage of males diagnosed with a late disease (stage 3 and 4) was higher than females (68% vs. 36%,  $p = 0.035$ ) and there was no significant difference in the duration of symptoms.

We also found that patients in group-A were significantly younger than in group-B (average age 64.5 +/-8.9 vs. 57.4 +/-13.8,  $p=0.033$ ). The percent of patients over 55 years of age in group-A is significantly lower than in group-B (53% vs. 89%,  $p=0.012$ ). We have also found that the duration of symptoms in group-A was significantly longer than in group-B (2.8 months +/-2 vs. 5.7 months +/-7,  $p=0.05$ ).

The overall 5-year survival rate was 52%. The 5-year survival of patients with stage 1 and 2 disease was better than patients with stage 3 and 4 disease (71% vs. 34%  $p=0.015$ ) (Fig. 1). In the first year following diagnosis there was no significant difference in mortality between group A and B (21% vs. 23% respectfully,  $p=NS$ ). However, among patients who survived the first year, patients from group-A survived longer than patients from group-B (112 months +/-45 vs. 79 months +/-46,  $p=0.03$ ). Also, among patients in a late stage disease (stages 3 and 4), survival in group-A was significantly better than in group-B (104 months +/-77 vs. 46 months +/-58,  $p<0.05$ ) (Fig. 2). Kaplan-Mayer survival curve has also showed a better overall survival rates in-group A, compared to group B ( $p = 0.03$ ) (Fig. 3).

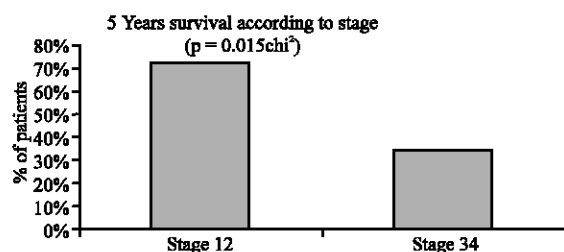


Fig. 1: Survival of patients according to clinical staging

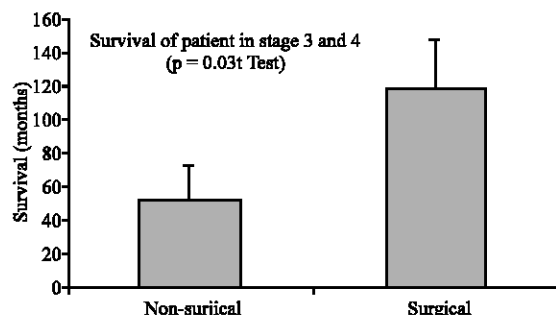


Fig. 2: Overall survival of the two groups in month

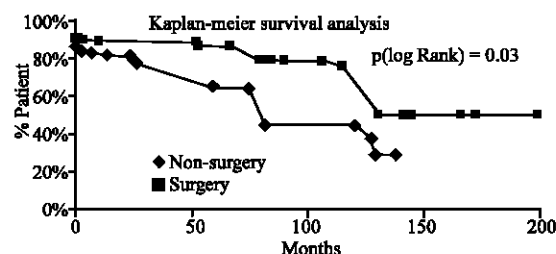


Fig. 3: Kaplan mayer survival curve comparing the two

## DISCUSSION

The gastrointestinal tract is the predominant site of extra nodal Non Hodgkin's lymphoma, although Primary Gastric Lymphoma (PGL) is a relatively rare tumor that constitutes 2-5 % of malignant gastric lesions in the adult population (Ferrucci and Zucca, 2006). The optimal treatment policy for treatment of NHL is still controversial (Dickson *et al.*, 2006) and recently the role of surgery in early stage lymphoma is questionable since the diagnosis is made either by CT scan or gastroscopic biopsy. Some authors proposed combination treatment of surgery followed by chemotherapy or radiotherapy (Gobbi *et al.*, 1990; Binn *et al.*, 2003).

We compared 2 groups: group-A, including patients that underwent surgery with or without chemotherapy and group-B including patients that were treated with out surgical intervention. Although both treatment modalities were not randomized, we think with due caution that a

comparison between both groups is justified. The primary assumption was that most patients treated with surgery would belong to the early years of the study since the imaging process in those years was somehow limited to gastroscopy and abdominal ultrasound, but we did not find any difference in rates of surgery during two decades. However, We have shown that patients selected for non-surgery treatment were significantly older and suffered a longer duration of symptoms prior to diagnosis (although there was no difference in the staging between the groups). These differences can reflect on a selection bias when comparing survival in the 2 groups. Since the study was retrospective without randomization we can only assume that patients were treated according to their original complains and the emergency of its appearance along with their physical condition.

Taking these differences under consideration, we have shown that in the first year following diagnosis, there was about 22% mortality, regardless of treatment modality (surgical vs. non-surgical). This mortality rate can be attributed to the baseline severity of the disease. However, patients that survived the first year benefited more from surgical intervention. Paradoxically, patients with a late stage disease (stage 3 and 4) benefit from surgical intervention. This may be due to bypass of pending obstruction done in surgery and these results are quite unique compared to the literature results (Rigacci *et al.*, 1994). We have also shown, as expected and described before (Ibrahim *et al.*, 2001) that the survival of patients with an early stage disease is much longer than patients with a late stage disease.

An interesting observation is that male patients tend to present with a late stage disease as compared with female patients, while the duration of symptoms between the 2 groups is not significantly different. It was observed, though, that males are 2-3 times more affected than females (Al Akwaa *et al.*, 2004).

It was also observed that most patients were Ashkenazi, meaning that they were from Europe or the former USSR, while the literature reports of higher incidence in the Middle East (Al Akwaa *et al.*, 2004; Willich *et al.*, 2000). While analyzing the origin of patients in Hasharon hospital it was found that the majority of them (60%) were of Sephardim and Arab origin.

## CONCLUSION

In summary we conclude from this retrospective study that surgery combined with chemotherapy seems beneficial to other modalities even in advanced disease. Since the study was retrospective, the possibility of biased treatment modalities exists, but we did not find a

pattern. Prospective randomized trials combined with multi centers study can ascertain and validate these results.

## REFERENCES

- Aisenberg, A.C., 1995. Coherent view of non-Hodgkins lymphoma. *J. Clin. Oncol.*, 13: 2656-2675.
- Al-Akwaa, A.M. and N. Siddiqui, 2004. Al-Mofleh IA: Primary gastric lymphoma. *World J. Gastroentrol.*, 10: 5-10.
- Bierman, P.J., 2003. Gastrointestinal lymphoma. *Curr. Treat Options Oncol.*, 4: 421-30.
- Binn, M., A. Ruskone-Fourmestraux and F. Lepage *et al.*, 2003. Surgical resection plus chemotherapy versus chemotherapy alone: Comparison of two strategies to treat diffuses large B cell gastric lymphoma. *Ann. Oncol.*, 14: 1751-1757.
- Dickson, B.C., S. Serra and R. Chetty, 2006. Primary gastrointestinal tract lymphoma: Diagnosis and management of common neoplasms. *Exp. Rev. Anticanc. Ther.*, 6: 1609-1628.
- Ferrucci, P.F. and E. Zucca, 2006. Primary gastric lymphoma pathogenesis and treatment: What have changed over the past 10 years? *Bjh*, 136: 521-538.
- Gobbi, P., P. Dionigi and F. Babieri *et al.*, 1990. The role of surgery in the multimodal treatment of primary gastric Non Hodgkins lymphomas. *Cancer*, 65: 2528-36.
- Harris, N.L., E.S. Jaffe and J. Diebold *et al.*, 1999. World Health Organization classification of Neoplastic Diseases of the hematopoietic and lymphoid tissues; Report of The Clinical Advisory Committee meeting- Airlie House, Virginia. *J. Clin. Onc.*, 17: 3835-49.
- Ibrahim, E.M., A.A. Ezzat and A.N. El-Weshi *et al.*, 2001. Primary intestinal diffuse large B cell non Hodgkins lymphoma: Clinical features, management and prognosis of 66 patients. *Ann. Oncol.*, 12: 53-58.
- Non Hodgkins Lymphoma Pathologic Classification Project. National Cancer Institute, 1982. Sponsored study of classification of Non Hodgkins Lymphoma: Summary and description of a working formulation for clinical usage. *Cancer*, 49: 2112-35.
- Choi O.H.D IS, J.H. Kim and M.H. Rhu *et al.*, 2005. Management of gastric lymphoma with chemotherapy alone. *Leuk Lymphoma*, 46: 1329-35.
- Rigacci, L., G. Bellesi, R. Alterini and F. Bernardi *et al.*, 1994. Combined surgery and chemotherapy in primary gastric non hodgkins lymphoma: A retrospective study in 66 patients. *Leukemia and Lymphoma*, 14: 483-489.
- Willich, N.A., G. Reimmartz, E.J. Horst, G. Delker and B. Reers *et al.*, 2000. Operative and conservative management of primary gastric lymphoma: Interim results of a German multicenter study. *Int. J. Radiat. Oncol. Biol. Phys.*, 46: 895-901.