

Clinicopathologic study of Primary Gastric Lymphoma and its Outcome: NCI Experience

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ABSTRACT

Background: The stomach is the most common site of extra nodal lymphoma, In Western countries 60% of primary gastrointestinal lymphomas affect the stomach which is considered to be the most common site of extra-nodal lymphomas, with high incidence of non- Hodgkin's type, mostly of mucosa-associated lymphoid tissue (MALT) lymphoma. **Objective:** To review the demographic, clinicopathological features, management and outcome of primary gastric lymphoma (PGL). **Patients and Methods:** A total number of 115 patients diagnosed with primary gastric lymphoma in the National Cancer Institute in Cairo, between January 2008 and December 2014 were included. **Results:** The study, included 52 females (45.2%) and 63 males (54.8%). Epigastric pain and dyspepsia were the most common presenting symptoms. Ulcerative tumor type was the most common morphology in 56 patients (48.7%). Chemotherapy and radiotherapy were the main line of treatment in 94 cases (81.7%) and 21 cases (18.3%) treated with surgery, chemotherapy and radiotherapy. Local recurrence, bleeding and obstruction were the most common complications. The mean overall survival in patients treated with chemo-radiotherapy was 63.75 months. Overall survival at 1 year, 2 years and 5 years were 86.2%, 81.9% and 51.9% respectively. The mean overall survival in Patients treated with surgery was 85.37 months with overall survival at 1 year, 2 years and 5 years were 95.2%, 95.2% and 79.5% respectively. **Conclusion:** Treatment for primary gastric lymphomas is still controversial. Surgical intervention versus systemic treatment must be based on the characteristics of each individual patient.

Key words: Gastrectomy, Extra nodal Lymphoma, Mucosa-associated lymphoid tissue (MALT) Lymphoma.

INTRODUCTION

The gastrointestinal tract is the predominant site of extra nodal lymphoma involvement. Primary lymphomas of the gastrointestinal tract are rare, while secondary gastrointestinal involvement is relatively common. Despite their rarity, primary lymphomas of the gastrointestinal tract are important since their evaluation, diagnosis, management and prognosis are distinct from that of lymphoma at other sites and other cancers of the gastrointestinal tract. [1,2,3]

Primary gastric lymphoma mainly consists of marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type (MALT lymphoma) and diffuse large B-cell lymphoma (DLBCL). [4]

Primary gastric lymphoma should be limited to the stomach with or without its draining lymph nodes, with or without direct spread to adjacent organs with no palpable peripheral lymphadenopathy, without any abnormalities in chest X-ray, white blood cell count and bone marrow

aspirates^[5]. Several risk factors such as human immunodeficiency virus (HIV), Helicobacter pylori infection, celiac disease, inflammatory bowel disease, and immuno-suppression after solid organ transplantation have been identified for gastrointestinal tract lymphoma. [6]

In this study, we reviewed demographic, clinical characteristics, clinical presentation and diagnostic work up of patients with primary gastrointestinal tract lymphoma who were referred to our center. We also evaluated their outcome after therapy and Current Controversy in Treatment of Primary Gastric Lymphoma and to study prognosis of primary gastric lymphoma in the form of overall survival and disease free survival.

PATIENTS AND METHODS

This retrospective study included 115 patients with primary gastric lymphoma attending the National Cancer Institute between January 2008 and December 2014, 94 cases (81.7%) treated

with chemotherapy and radiotherapy, 21 cases (18.3) treated with surgery, chemotherapy and radiotherapy. Data was collected from the patients' medical records with minimum follow up period of 6 months from the date of surgery and histopathological features was obtained from the pathology department.

Diagnosis of the patients was established clinically, by patient medical history and complete physical examination. Laboratory investigations included complete blood count, serum biochemistry, bone marrow aspiration and biopsy. Chest X-ray, computed tomography (CT) of the chest, abdomen and pelvis, were done as well as upper gastrointestinal endoscopy and biopsy.

All pathology blocks and slides were reviewed by pathologist.

Moreover, immunohistochemically studies were performed to determine the subtype of non-Hodgkin's lymphoma.

RESULTS

Between January 2008 and December 2014, 115 patients were diagnosed with PGL 63male (54.8%) and 52 female (45.2%), 94 cases (81.7%), were treated with chemotherapy and radiotherapy and 21 cases (18.3%) were treated with surgery, chemotherapy and radiotherapy. The median age at diagnosis was 56 years ranging from (35 to 75 years) Epigastric pain and dyspepsia were the most common presenting symptoms (table 1).

Table (1): presenting symptoms of PGL

| <i>Symptoms</i> | <i>Count (No.)</i> | <i>Frequency (%)</i> |
|----------------------|------------------------|--------------------------|
| Epigastric pain | 53 | 46 |
| Dyspepsia | 40 | 34.8 |
| Hematemesis | 26 | 22.6 |
| Accidental discovery | 6 | 5.2 |
| Epigastric mass | 5 | 4.3 |
| Anemia | 28 | 24.3 |
| Cachexia | 6 | 5.2 |

Diagnosis of the gastric lymphoma was established by endoscopic biopsy 99 patients (86%) and or by surgical specimen pathological analysis 18 patients (15.6%), the ulcerative tumor type was the most common type in 56 patients (48.7%)

Table (2): Pathological tumor types:

| <i>Tumor type</i> | <i>No</i> | <i>%</i> |
|-------------------|-----------|----------|
| Diffuse | 17 | 14.7 |
| Ulcerative | 56 | 48.7 |
| Fun gating mass | 3 | 2.6 |
| Mass | 27 | 23.5 |
| Mural thickening | 11 | 9.6 |
| Malt mucosa | 1 | 0.9 |

Of all patients, 21(18.3%) patients underwent surgery, 9 patients(7.8%) had partial gastrectomy, and 4 patients had total gastrectomy (3.5%), 8 patients (7%) had biopsy only and only 6 patients (5.2%) had lymph node dissection with gastrectomy.

Local recurrence occurred in 38(33%) patients. Recurrences were mostly after treatment with definitive chemoradiotherapy without surgery in 34 (29.5%). Four recurrences (3.5%) occurred after surgery, one after partial gastrectomy and three after surgical biopsy, other complications like bleeding, obstruction occurred in 4(3.5%) patients and leakage occurred in 10(8.7%) patients.

Mean overall survival (OAS) in patients treated with chemo-radiotherapy was 63.75 months with overall survival at 1 year, 2 years and 5 years were 86.2%, 81.9% and 51.9% respectively, in patients treated also with surgery mean overall survival was 85.37 months with OAS at 1 year, 2 years and 5 years were 95.2%, 95.2% and 79.5% respectively. Overall survival was significant between two groups with p-value 0.015.

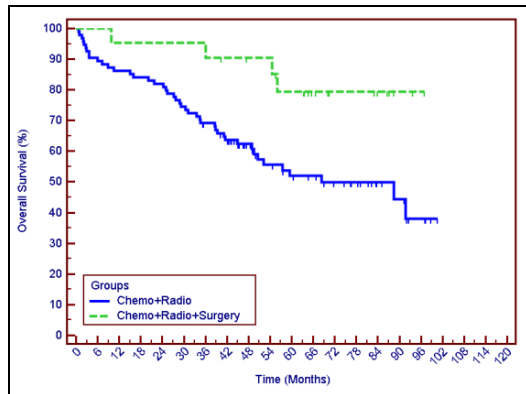


Fig. (1): Kaplan- Meier survival curve for overall survival.

Mean DFS in patients treated with chemo-radiotherapy was 65.72 months and 1 year, 1 years, 5 years DFS was 88.8%, 78.1% and 62.4% respectively

In patients treated also with surgery mean DFS was 79.12 months and 1 year ,2 years ,5 years DFS was 81.0%.DFS was significant between two groups with p-value 0.0126.

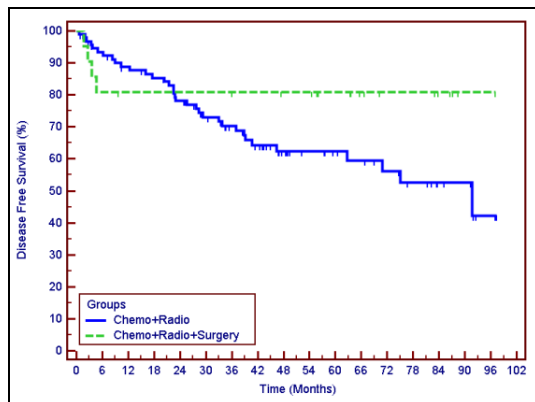


Fig. (2): Kaplan-Meier survival curve for disease free survival

DISCUSSION

PGL account for 2-8% of all gastric malignancies with an increasing ratio of gastric lymphoma against other gastric tumors in last two decades which may be due to improvement of diagnostic procedures.^[7] Several risk factors like *Helicobacter pylori* infection, immunosuppression

after solid organ transplantation, human immunodeficiency virus (HIV) were involved.^[6]

According to a COX regression analysis for the factors which affected OAS of our patients we found that age and surgery were the only two significant factors to OAS with p-value <0.001-0.028 respectively. Younger patients do far better than older patients with same stage of disease due less comorbidities and better performance status. Patients aged <60 years in our study had longer OAS with p-value (0.002). Also, Li X et al found that age was a significant factor between patients who underwent surgery and patients who did not have surgery. Age was younger in those undergoing surgery.^[8]

The most common presentation in our study was epigastric pain which accounted for 46 % of the involved patients followed by dyspepsia (40%). In agreement with Psyri et al who describes that epigastric pain and discomfort (83%), anorexia and weight loss (41%), and postprandial vomiting (28%) were the most common presenting signs and symptoms.^[9]

We found that abdominal ultrasound or computerd tomography has no significant value in diagnosing PGL but computerd tomography has important value in detecting lymphoma outside stomach (chest or liver). New promising techniques like Perfusion CT and MRI can also help the monitoring, and assessment of the response, PET-CT imaging and new PET tracers like 18F-fluoro-thymidine may significantly benefit the overall management of lymphomas.^[10]

In our study diagnosing the gastric lymphoma mainly by endoscopic biopsy and in few cases, it was diagnosed postoperatively after surgery, Rotary et al showed that positive diagnosis was established by histopathological and immunohistochemically examination of the gastric biopsy fragments, obtained by upper gastrointestinal endoscopy, or of the gastric resection samples. Ulcerative tumor type was the most type in in our study (48.7%) in agreement with the published studies 37.5% were ulcerative tumor.^[11]

Local recurrence had occurred in 33% of all patients, mostly in patients treated only by chemo-radiotherapy without surgery. Many complications may occur either from the tumor or its management, bleeding, obstruction occurred in 3.5% patients or leakage occurred in 8.7% mainly. In the literature, incidence of these

complications range from 0 to 25%. The prognosis of these complications is very poor with an almost 100% mortality so, in several studies, upfront surgical interference prevented these serious complications.^[12,13]

In our study, we found that mean OAS in patients treated with chemo-radiotherapy was 63.75 months with OAS at 1 year, 2 years and 5 years were 86.2%, 81.9% and 51.9% respectively. And patients treated also with surgery was 85.37 months with OAS at 1 year, 2 years and 5 years were 95.2%, 95.2% and 79.5% respectively.

Regarding mean DFS in patients treated with chemo-radiotherapy was 65.72 months and 1 year, 1 years, 5 years DFS was 88.8%, 78.1% and 62.4% respectively and In patients treated also with surgery mean DFS was 79.12 months and 1 year, 2 years, 5 years DFS was 81.0%. DFS was significant between two groups with p-value 0.0126, which agree with several studies that defend the surgical role in management of PGL for the following reasons: relieving symptoms and improving survival by excision of the tumor; correct histological diagnosis and accurate staging of the disease; as well as it prevents severe complications such as bleeding or perforation.

At the present time, surgical resection of the tumor is the most rational approach to the management of gastric lymphoma provided that no contraindications to surgery such as disease spread (unrespectable para-aortic nodes, liver involvement, free nodules in the abdomen) or general contraindications to surgery. A review of the literature shows that there are no differences of survival between total and partial gastrectomy^[14].

A french prospective, randomized, metacentric study confirms that subtotal gastrectomy is preferable to total gastrectomy as an incomplete resection status did not influence survival, relapse, or disease-free survival because all patients received adjuvant chemotherapy.

Also, accurate lymphadenectomy of draining nodes and resection of Large tumors (>5cm) plays an important in curative resection and in correct staging^[15].

Those researchers who advocated surgery either with or without chemotherapy focused on the accurate staging of the tumor and the association of this treatment with less hemorrhage or perforation of the stomach.

With the advent of endoscopic ultrasound, laparotomy biopsy is no longer warranted^[16,17]. We also consider surgery alone will be sufficient to cure PGL in low risk stage IE disease, and it will be a good alternative primary treatment for those patients who are fragile and prone to develop CHOP related complications.

Since systemic chemotherapy has been the treatment of choice for most nodal and extra nodal lymphomas, many series suggest that also in primary gastric lymphoma, chemo and/or radiotherapy can replace surgery as primary treatment. Treatment based only on chemotherapy or radiotherapy has been described^[13,18,19]. It is very difficult to evaluate and compare the efficacy of these therapies because there are no prospective controlled studies.

Infrequency of the disease and small number of cases for each single study^[13,20] put limitations in our retrospective study.

A need for a prospective randomized trial with large number of patients is needed for better assessment of different modalities of treatment of PGL.

CONCLUSION

Treatment for primary gastric lymphomas is still controversial. The choice between surgery and chemo-radiotherapy must be based on the characteristics of each individual patient (histological type, stage, age and co-morbidities).

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