# INTRODUCTION

Non-Hodgkin lymphoma (NHL) is primarily a disorder of lymph nodes. However, it is well recognized that NHL may arise from extra-nodal sites ***(Swerdlow, 2008).*** Certain extra nodal sites lack endogenous lymphoid tissue, which leaves incompletely resolved questions about the cell of origin of lymphomas that arise in these sites ***(American Cancer Society, 2013)***. Estimated new cases and deaths from NHL in United States in 2018 are; 74,680 and 19,910 respectively ***(American Cancer Society, 2018)***. Extra nodal lymphomas constitute 20-40% from all NHL ***(American Cancer Society, 2018).***

During the past two decades, primary extra nodal non-Hodgkin's lymphoma (PENHL) had increased more rapidly than nodal lymphomas ***(Chua et al., 2009)***. Multiple factors including AIDS, immune suppressive drugs, viral infection; e.g.,: Epstein-Barr virus, pesticides and solvents might explain the increased incidence of PENHL. The greatest increases have been observed for lymphomas of central nervous system, gastro intestinal tract, skin and eye ***(Swerdlow et al., 2008).***

In the gastrointestinal tract alone, for example, *Helicobacter pylori* infection, celiac disease, *Campylobacter jejuni* infection, a variety of immunodeficiency syndromes, and possibly inflammatory bowel disease predispose an individual to the development of different types of lymphoma;

lymphomagenesis, therefore, appears to be related to chronic antigenic stimulation, inadequate immune regulation, or a combination of these factors ***(Zullo et al., 2009, 2010; Nakamura et al., 2012).***

***Dawson and his colleagues (1961)*** reported that for diagnosis of PENHL a patient had to present with main disease manifestation in an extra nodal site with or without regional lymph node involvement, with no liver or spleen involvement ***(Dawson et al., 1961).*** Later, these criteria were changed to allow for contagious involvement of organs including liver, spleen and distal nodal disease, provided that the extra nodal lesion was the presenting site and constituted the predominant disease bulk ***(Richard et al., 2000).***

Non Hodgkin's lymphoma of the GIT is the most common extra nodal site at presentation, accounts for up to 30-40% of PENHL, While NHL of the head and neck constitutes 10-20%. Distinct sites within this area include: Waldeyer's ring, the salivary glands, nasal cavity, paranasal sinuses, thyroid gland and orbital lymphomas ***(Pileri et al., 2014).*** Other frequent and clinically important site includes skin ,accounting for approximately 10-14% of all PENHL ***(Willemze et al., 2005).***

Primary bone lymphomas constitute 5% while breast lymphomas constitute 2% of PENHL. Primary CNS lymphoma is rare (accounting for 2-4% of all PENHL), other rare sites

include spinal extra dural lymphomas, lung and genitourinary tract ***(Zucca, 2008).***

Many different types of lymphoma of B-cell, T-cell, and natural killer (NK)-cell lineage can arise in extranodal sites. Marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) can arise in any of a large number of anatomic sites. Diffuse large B-cell lymphoma is the most common type of extranodal lymphoma overall ***(Swerdlow et al., 2008).***

The behavior of lymphomas of the same pathologic type sometimes differs, depending on the site of origin. For example, patients with gastric marginal zone lymphomas of mucosa-associated lymphoid tissue appear to have a higher disease-free survival rate than those with marginal zone lymphomas that arise in other sites. Marginal zone lymphomas may show different patterns of spread, depending on the site of origin ***(Fischbach et al., 2011).***

Diffuse large B-cell lymphomas may show remarkably divergent behavior, depending on the site of origin. Primary diffuse large B-cell lymphoma of bone has an excellent prognosis with optimal therapy; however, when it relapses, it has a tendency to spread to other bones ***(Lima et al., 2008)***. Diffuse large B-cell lymphoma that is primary in the CNS has a poor prognosis, even with aggressive therapy, but in most cases it remains confined to the CNS ***(Kluin et al., 2008)***. Primary

testicular diffuse large B-cell often behaves aggressively; it has a tendency to develop widespread disease, with preferential spread to the opposite testis and the CNS ***(Zucca et al., 2008)***. Even when the histologic features are similar, differences may exist in the immunophenotype and in underlying genetic abnormalities; these differences may be responsible for site-specific differences in the prognosis ***(Friedberg et al., 2008).***

Therapeutic options of extra nodal lymphoma include: surgery, radiotherapy, single and combined chemotherapy, antibacterial and antiviral agents, immune modulation, monoclonal antibodies, discontinuation of immune suppressive drugs, bone marrow transplantation and anti sense oligonucleotides ***(NCCN, 2017).***

For adequate treatment of PENHL, therapy should be tailored to the individual patients taking into consideration the primary site of origin, the histologic subtype of lymphoma and the natural history of the disease ***(NCI, 2018)***.

# AIM OF THE WORK

**The aim of the work is to:**

Review demographic data and the clinico-epidemiological characteristics of primary extra nodal lymphoma, review all treatment lines delivered (both local and systemic treatments), assess treatment results (disease free survival, overall survival and treatment side effects) in all patients presented to Ain Shams Clinical Oncology Department (ASCOD) from January 2009 to December 2013.

# GASTROINTESTINAL NON-HODGKIN'S LYMPHOMA (GI-NHL)

Gastrointestinal non-Hodgkin's lymphoma is the most frequent primary extranodal localization accounting for 30-40% of all extranodal sites and constitutes about 3% of gastrointestinal cancers. A number of definitions have been used to identify patients with primary GI-NHL. In general, those patients should have disease predominantly confined to the alimentary tract, with clinical features suggestive of gastric or intestinal pathology ***(Ghrimire et al., 2015).***

A number of risk factors for gastrointestinal non-Hodgkin's lymphoma (**GI-NHL**) have been determined such as *Helicobacter pylori* (**H.pylori**) infection ***(Sonnenberg et al., 2013; Pereira, 2014)***, immunosuppression after solid-organ transplantation, celiac disease, inflammatory bowel disease and human immunodeficiency virus (**HIV**) infection ***(Paniz et al., 2013; Butnaru et al., 2015).***

**Histological classification of gastrointestinal lymphomas** ***(Rohatiner et al., 1994; Ruskone et al., 2003)***

**B-cell**

- Diffuse large B-cell type (**DLC**)
- Mucosa-associated lymphoid tissue (**MALT**) type (extranodal marginal-zone lymphoma):
  - Low grade
  - High grade with or without low grade component

- Immunoproliferative small intestinal disease (**IPSID**):
  - Low grade
  - High grade with or without a low grade component
- Lymphomatous polyposis (mantle cell lymphoma).
- Burkitt's lymphoma and Burkitt-like
- Other types of low or high grade lymphoma corresponding to lymph node equivalents.

**T-cell**

- Enteropathy associated T-cell lymphoma (**EATCL**).
- Other types not associated with enteropathy.

**Primary Gastric Lymphoma**

Gastric lymphoma is the most frequent stomach malignancy after adenocarcinoma. Primary gastric NHL accounts for 50-60% of all gastrointestinal lymphomas and therefore, considered the most common site of extranodal lymphomas ***(Ghirmire et al., 2015).***

## ***Clinical presentation***

The median age at diagnosis is 55 years old with slight male predominance 1.3:1. Patients usually present with epigastric pain, nausea, vomiting, loss of appetite and B-symptoms. Weight loss is common, although this is more often a

consequence of the localization of the primary lymphoma rather than a constitutional symptom of the disease. Few patients may present with bleeding and perforation. Bone marrow involvement is rare while Waldeyer's ring involvement is a common presentation in gastric lymphoma ***(Psyrri et al., 2015).***

## ***Histopathology***

According to REAL classification, pathological entities encounted in primary gastric lymphoma include mucosa associated lymphoid tissue (MALT) type in 44% of the cases followed by high grade diffuse large B-cell type in 36%, high grade with low grade component in 18% and less commonly mantle cell lymphoma, lymphoblastic or Burkitt's lymphoma as well as low grade non MALT-type ***(Watanabe et al., 2012).***

## ***Diagnostic work-up***

It includes: complete blood count (**CBC**), erythrocyte sedimentation rate (**ESR**), LDH, routine blood chemistries and bone marrow aspiration. Other investigations include: plain X-ray chest,barium studies, computes tomography (**CT**) scans of abdomen and pelvis as well as endoscopic ultrasonography (**US**) examination to assess depth of penetration. Endoscopic biopsy provides adequate material to make diagnosis of gastric lymphoma. Multiple endoscopic biopsies are highly recommended because multifactorial disease is present in 80% of cases and microscopic lymphoma foci can be present at sites distant from the main tumor ***(Vetro et al., 2015).***

## Staging

The modification of Ann Arbor classification suggested by Musshoff has been used for many years ***(George et al., 2004)***. The recent international workshop recommended the following classification:

**Table (1):** Modified Blackledge staging system for gastrointestinal lymphomas (Lugano staging system for gastrointestinal NHL ***(Rohatiner et al., 1994; Psyrri et al., 2015)***

| | |
|---|---|
| **Stage I** | **Tumor confined to gastrointestinal tract without serosal penetration:**<br>Single primary site.<br>Multiple non contiguous lesions. |
| **Stage II** | **Tumor extending into abdomen from primary site:**<br>Nodal involvement;<br>$II_1$ local (gastric / mesenteric)<br>$II_2$ distant (para-aortic / paracaval) |
| **Stage IIE** | **Penetration of serosa to involve adjacent structures:**<br>Enumerate actual site of involvement, eg; stage IIE pancreas, stage IIE large intestine, and stage IIE post abdominal wall.<br>Perforation / peritonitis |
| **Stage IV** | Disseminated extranodal involvement or gastrointestinal tract lesion with supradiaphragmatic nodal involvement. |

N.B: there is no stage III for this disease.

## Prognostic factors

Prognostic factors that have been reported as indicating a poor prognosis are old age, advanced stage, involvement of

para aortic LNs, bulky tumor, serosal penetration, T-cell versus B-cell type and histologic grade ***(Li et al., 2014).***

## ***Treatment***

The optimal treatment of gastric lymphoma is still a controversial issue. Surgery, radiotherapy and chemotherapy have been used alone or in a various combinations. Treatment strategy usually depends on histologic grading of the disease and the stage of the disease ***(NCI, 2015).***

### Treatment of high grade gastric lymphoma

Gastric lymphoma is a multicentric disease and clear resection margin is not necessarily a guarantee for radical resection and total gastrectomy for complete excision is eventually needed ***(Aviles et al., 2004).***

Surgery usually has a mortality rate of 10%, it causes long term morbidity due to loss of function and delays the use of chemotherapy or radiotherapy ***(Arnold et al., 2015)***. Some publications have suggested that using primary chemotherapy and radiation alone without surgery can be curative and produce outcomes similar to that obtained with surgery and adjuvant treatment ***(Maor et al., 2004).***

The treatment recommendations for stage I patients four cycles **CHOP** (cyclophosphamide 750 mg/m$^2$, doxorubicin 50 mg/m$^2$, vincristine 1.4 mg/m$^2$ and on day one plus prednisone 100 mg from day 1 to 5). Followed by extended field

radiotherapy (**EFRT**): total abdominal irradiation 30 Gy + 10 Gy boost on the tumor residue. For stage II patients six cycles **CHOP** and additional involved field (**IF**) external beam radiotherapy 40 Gy. For stage (IIE-IV) locally advanced or disseminated high grade lymphoma patients combination chemotherapy is the standard treatment of choice ***(Koch et al., 2001).***

## Gastric (MALT) Lymphoma

The group of MALT (mucosa-associated lymphoid tissue) lymphomas comprises a number of low grade extranodal B-cell lymphomas that share similar clinical, pathologic, immunologic and molecular features ***(Janusz et al., 2012).***

The development of gastric MALT lymphoma in response to infection with *H.pylori* is well established. The microorganism can be found in the gastric mucosa of nearly all the patients and most of the patients having the serologic evidence of prior H.pylori infection. Chronic gastritis caused by H.pylori provides the immunologic stimulus for T-cell dependant B-cell proliferation. Genetic alterations and clonal expansion occur which results in B-cell growth that is no longer dependant on the presence of H.pylori ***(Janusz et al., 2012).***

### ***Clinical presentation***

Gastric MALT lymphoma is an indolent disease with marked tendency to remain localized for several years,85% of

the cases present in stage I and stage II with a ten-year survival of 90%. It usually occurs in patients over 40 years of age but can occur at any age. Sex incidence is equal. The presenting symptoms are usually those of non-specific dyspepsia which suggestive of gastritis or peptic ulcer than a neoplastic lesion ***(Sara et al., 2014).***

## ***Treatment of low grade gastric MALT lymphoma***

There is increasing evidence indicating that eradication of H.pylori using appropriate antibiotics can be effectively employed as the sole initial treatment in low grade gastric MALT lymphoma. Subsequent studies have shown that eradication of H.pylori may induce regression of the lymphoma in approximately 75% of cases ***(Sara et al., 2014).***

**The recommended anti-helicobacter therapy is:**

**First line treatment**

| | | | |
|---|---|---|---|
| Omeprazole | 20 mg | Bid for | 10 days |
| Amoxicillin | 1000 mg | Bid for | 10 days |
| Clarithromycin | 500 mg | Bid for | 10 days |

**Second line treatment**

| | | | |
|---|---|---|---|
| Omeprazole | 20 mg | Bid for | 7 days |
| Metronidazole | 400 mg | Bid for | 7 days |
| Clarithromycin | 500 mg | Bid for | 7 days |

The expected rates of eradication of H.pylori are over 90%, and although eradication may occur within a month of the completion of drug therapy, complete histologic response usually taked up to 18 months. Strict follow up is needed to define the long term effectiveness of this treatment ***(Grgov et al., 2015).***

Clinically, it would be extremely useful to identify those cases of gastric MALT lymphoma that do not respond to eradication of H.pylori. Studies that used endoscopic ultrasound have suggested that if the tumor had invaded beyond the submucosa, it will not respond. More recently, by using reverse transcriptase polymerase chain reaction, it has been shown that cases positive for t (11;18) (q21;q21) with nuclear expression of BCL 10 protein fail to respond to H.pylori eradication. Moreover, the frequency of both t (11;18) (q21;q21) and nuclear BCL 10 proteins expression was found to be significantly higher in tumors that show dissemination to local lymph nodes or distal sites (78% and 93% respectively) than those confined to the stomach (10% and 38% respectively). These findings suggested that both t (11; 18) (q21; q21) and nuclear expression of BCL 10 are associated with more advanced MALT lymphoma ***(Grgov et al., 2015).***

Locoregional irradiation therapy is the treatment of choice for patients with gastric MALT lymphoma refractory to antibiotics ***(Grgov et al., 2015).***

Another alternative approach to the management of antibiotic refractory gastric lymphoma is the use of single agent chlorambucil or cyclophosphamide alone or combined-modality therapy as in localized high grade lymphomas. ***Martinelli et al. (2002),*** reported the high degree of activity of the monoclonal anti-CD20 antibody rituximab in treatment of relapsed or refractory gastric MALT lymphoma.

## Primary Intestinal NHL

Primary intestinal NHL is the third most common intestinal neoplasm after adenocarcinoma and carcinoid tumours. Primary small bowel lymphoma is more common than large bowel or rectal lymphoma. It accounts for 20% -40% of primary gastrointestinal lymphomas, distinct histological presentations include MALT lymphoma, diffuse large cell lymphoma, enteropathy-associated T-cell lymphoma **(EATCL),** mantle cell lymphoma **(MCL),** follicular cell lymphoma, and immunoproliferative small intestinal disease **(IPSID).**

## Enteropathy-associated T-cell lymphoma (EATCL)

Approximately 10% to 25% of primary intestinal small bowel lymphoma have a T-cell immunophenotype. The most frequent symptoms at presentation are weight loss, abdominal pain, maldigestion, diarrhea, bowel Obstruction, and loss of responsiveness to gluten-restricted diet. Most patients are in their sixth or seventh decade. The disease is more common in

Europe and relatively rare in North America ***(Grgov et al., 2015)***

T-cell lymphoma of the small bowel are the most common complication of celiac disease. Patients with celiac disease have a 200- fold increased risk of developing intestinal lymphoma. It has been suggested that adult onset celiac disease is itself a form of low-grade lymphoma. The relation between refractory sprue and intestinal lymphoma has been also proposed by ***Cellierc and Colleogues (2000),*** they suggested that refractory sprue may be the missing link between celiac disease and EATCL.

## Western-type primary small intestinal lymphoma (PSIL)

Patients with Western-type small intestinal lymphoma frequently present with non-specific abdominal pain and partial small bowel obstruction. They may have an abdominal mass, occult bleeding, anemia, and/or perforation. Most of the Western-type PSIL are of B-cell origin, intermediate or high grade and co-express CD20 antigen. Only 20% of small intestinal lymphomas are of MALT type. Similar to the gastric MALT disease, an association between intestinal MALT and *H. pylori* infection has been established. Ann Arbor staging system has been modified by ***Alebert et al. (2004),*** to account for contiguous (stage II1) or non-contiguous (stage II2) involvement of abdominal lymph nodes.