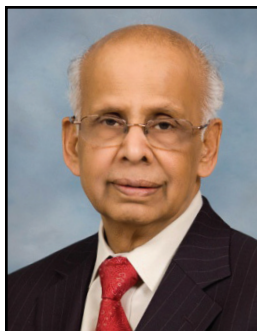


C.S. Pitchumoni, MD, Series Editor

# Epidemiological Spectrum of Gastrointestinal Lymphoma



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## INTRODUCTION AND DEFINITION

Lymphomas of the gastrointestinal (GI) tract can be primary or secondary. Primary GI lymphomas (PGIL) originate from the GI tract and are relatively uncommon, accounting for 1 to 4% of the malignant tumors of the GI tract. The more common secondary lymphomas involve the GI tract as a result of extra intestinal involvement. GI tract is the most common site of extra nodal involvement in lymphomas.<sup>1</sup> The diagnosis of PGIL can often be missed by initial endoscopic or radiological examination, and hence a high index of suspicion may be needed for diagnosis.<sup>2</sup> This may be contributing to underreporting of the prevalence.

Lymphomas of the GI tract may be of the B-cell or T cell type. One of the definitions of PGIL, somewhat arbitrary, is summarized in Table 1.<sup>3</sup> According to another definition,<sup>1</sup> PGIL are any of those where patients exhibit GI symptoms and/or the lymphoma is confined

to the GI tract, or is clearly predominant within portion of the GI tract. The majority of GI lymphomas are non-Hodgkin's Lymphoma (NHL). Hodgkin's lymphoma of the GI tract, although reported, are rare.<sup>4,5,6</sup> The specific subtypes of NHL which involve the GI tract primarily versus secondarily have not been clearly studied.<sup>7</sup>

Epidemiology of GI lymphomas differs substantially in different geographical regions of the world. Most population based studies have been done in Asian and European patients, with very few studies from North American cohorts.<sup>7</sup> Also, a huge difference exists in the prevalence and epidemiology of GI lymphomas in different anatomical regions of the GI tract.<sup>8</sup> The aim of this review is to provide data on the complex epidemiology of GI lymphoma as part of the present series on cancers of the GI tract.

## CLASSIFICATION AND STAGING OF GI LYMPHOMA

GI lymphomas can be broadly classified as B-cell lymphomas, which is the major type (about 90%) or T cell lymphomas.<sup>9</sup> There are many popular staging systems in use. The original classification of GI

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**Table 1. Defining Features of Primary GI Lymphomas**<sup>3</sup>

Absence of palpable superficial lymphadenopathy at the time of first patient encounter
No mediastinal lymph-nodes enlargement on chest X-ray
Normal total and differential white cell count
During laprotomy, bowel is the main organ resected. The lymph nodes in the immediate vicinity of the resected bowel are the only lymph nodes that are affected grossly
No liver and spleen involvement

lymphomas was proposed by Isaacson et al.<sup>10</sup> (Table 2). The most recent WHO classification of GI lymphomas, widely followed world over<sup>11</sup> is summarized in Table 3. Another widely utilized staging system is the Ann-Arbor staging system,<sup>12</sup> modified by Musshoff et al. for the GI tract<sup>13</sup> (Table 4).

A more specific staging system for GI lymphomas has been developed by the European Gastro Intestinal Lymphoma Study Group (EGILS).<sup>14</sup> This system is better than the Ann Arbor system since it is specifically designed for the GI tract and allows for better staging of local tumor infiltration and nodal involvement based on Endoscopic Ultrasound, a recent diagnostic modality (Table 5).

### GEOGRAPHICAL DISTRIBUTION PATTERN OF GI LYMPHOMAS

The variable anatomical distribution of GI lymphomas in different geographical regions is primarily attributable to the difference in the prevalence of risk factors. Another reason could be that in some studies, simultaneous involvement of various GI sites is not reported separately.<sup>1,15</sup> It is not clear as to why this separate reporting has not been done. It could be either because it was not diagnosed in the first place or it was reported as primary gastric or primary intestinal lymphoma.

Trends from several large population based studies are discussed below.

#### United States

The following distribution has been observed for primary GI NHL.<sup>7,16</sup> from the United states (see

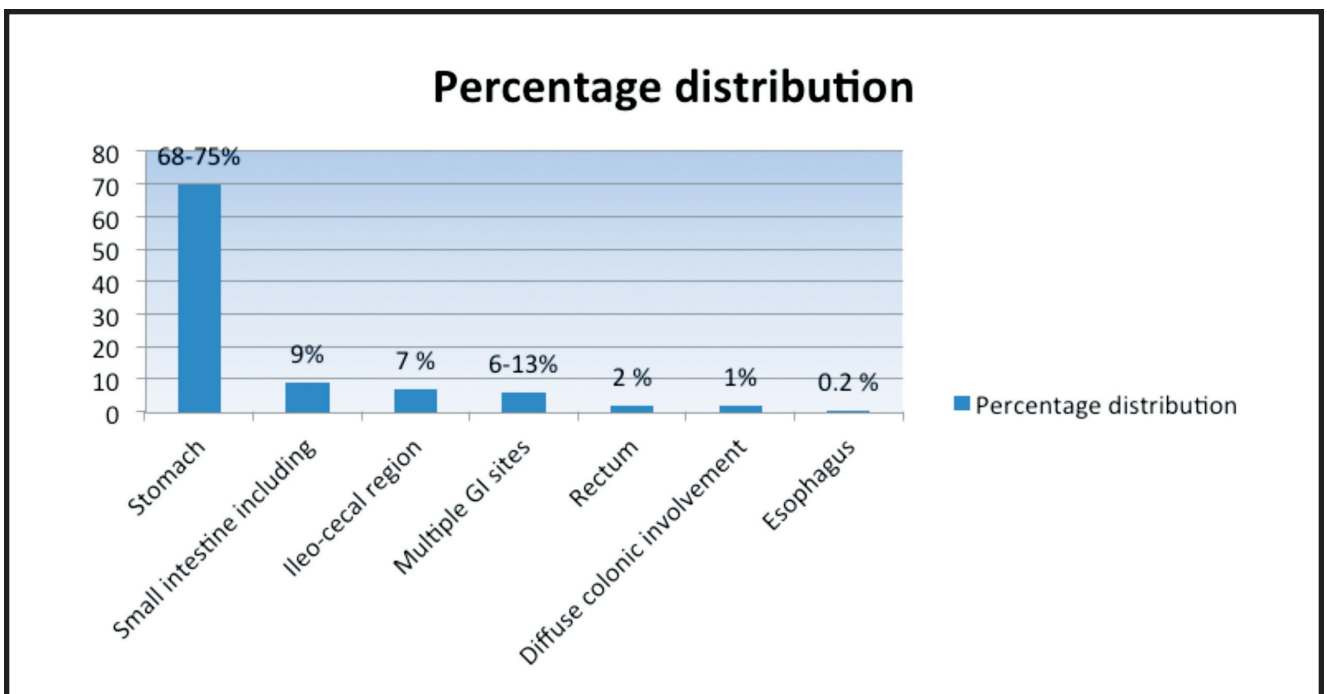
**Figure 1. Anatomical Distribution of GI Lymphoma in Western European Population**<sup>17</sup>

Figure 2). The pattern of prevalence is as follows:

The stomach is the most frequent single site involved in 44% of the cases. If lymphomas of small and large intestine are combined together, intestinal lymphomas account for more cases than gastric lymphoma, in contrast to Western European data where the stomach is the single most common site and is even more frequently involved than the small and large intestine combined.<sup>17</sup> The difference is interesting as prevalence of various risk factors for gastric lymphomas are almost identical in Western Europe and the United States. Overall the most common lymphomas are gastric MALT lymphoma and diffuse large B-cell lymphomas (DLBCLs). DLBCLs are the most common type of lymphoma noted in the intestine (33%). Mantle cell lymphoma (22%) and follicular lymphoma (21%) are the next most frequent types of lymphomas in the intestine. Burkitt’s lymphoma accounts for 9% of all intestinal lymphomas and is mostly confined to the intestines.

The incidence of gastric lymphoma is 3.8 per 1,000,000 person-years (PY), that of small intestinal lymphoma is 0.4 per 1,000,000 PY and that of colorectal lymphoma is 0.6 per 1,000,000 PY.<sup>16</sup> Amongst all the anatomical locations, the only site where the incidence of lymphoma has declined over time is the stomach, most likely due to the widespread diagnosis and

treatment for *Helicobacter Pylori* (*H. Pylori*),<sup>18</sup> an etiological factor for gastric lymphoma.

Male predominance is noted in intestinal MALT lymphoma (male: female ratio of 5:1), intestinal DLBCL (male: female ratio 1.7:1) and intestinal Burkitt’s lymphoma (male: female ratio 1:0). In the other lymphoma subtypes, there is no major sex difference. DLBCLs, MALT lymphomas, Follicular lymphomas are mainly seen in the sixth and seventh decade (median age 68 years), whereas the median age for Burkitt’s lymphoma is 41 years.<sup>7</sup>

**Western Europe**

The following anatomical distribution has been observed in large population based, retrospective, epidemiological studies from Greece and Germany for primary GI NHL<sup>17,19,20</sup> (see Table 6 and Figure 1). The stomach is noted to be the most frequent site, followed by small intestine including duodenum. In the stomach, about 40% of the lymphomas are low grade MALT type. The prevalence of non-MALT type NHL (mantle cell lymphoma) and Burkitt’s lymphoma/lymphoblastic lymphoma are noted to be 1.4% and 3.2% respectively.

In the small intestine, almost all of the NHL are germinal-center lymphoma originating from the germinal center. Only T cell type NHL and not Burkitt’s lymphoma are noted in the ileocecal region. The

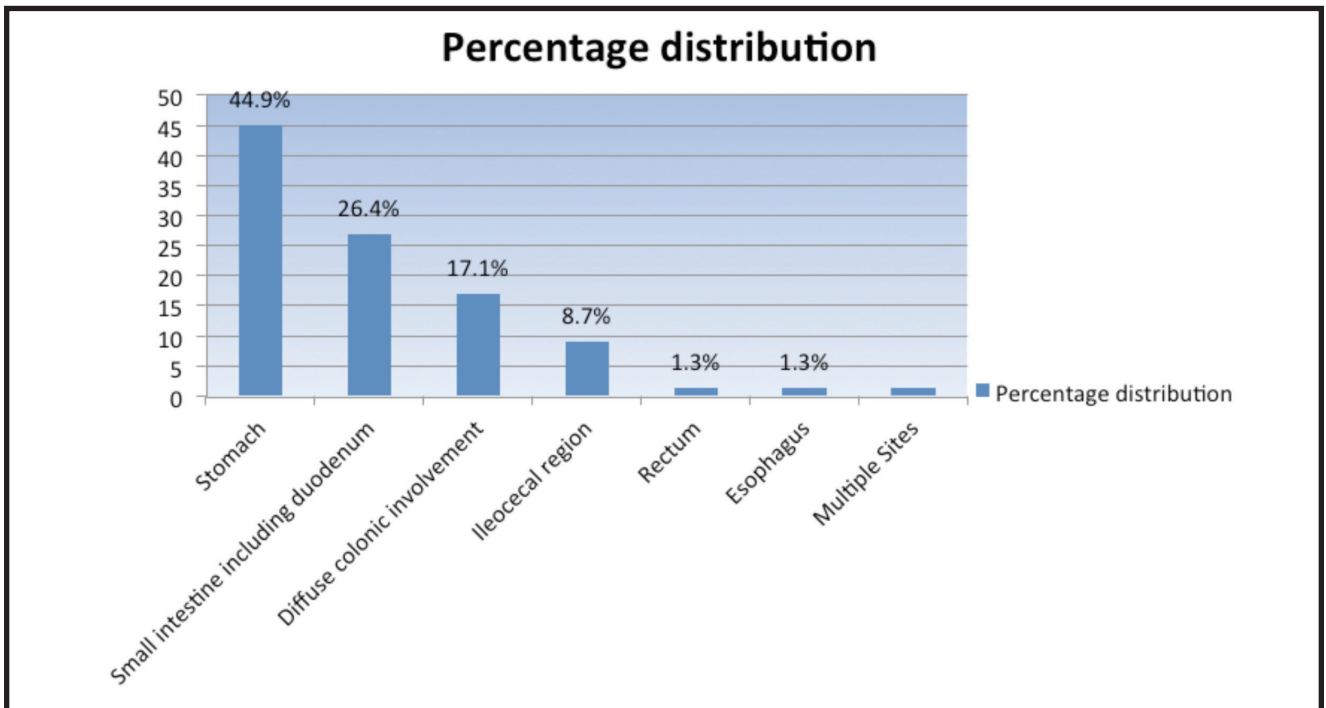


Figure 2. Anatomical distribution of GI Lymphoma in the United States<sup>7,16</sup>

prevalence of MALT lymphoma in the small intestine is rare (3.1%). Results from some of the major Western European population based studies are summarized in Table 6.

As in the United States, a male preponderance is observed for gastric lymphoma (male: female 1.1:1), small intestinal lymphoma (male: female ratio 1.9:1) and ileocecal lymphoma (male: female ratio 2.7:1). The median age for gastric lymphoma is 61.<sup>2</sup> and for small intestinal lymphoma it is 62.<sup>3</sup>

### Middle East and Mediterranean Basin

Some studies from Middle eastern countries report that the small intestine is the most common site for primary GI lymphoma.<sup>21, 22</sup> However, in other studies the pattern is found to be similar to that in western countries and stomach is found to be the most common site.<sup>23,24,25 26</sup> DLBCL, the predominant histological variant in patients with NHL of the stomach, is the most common type of lymphoma noted in most of the recent studies. This is similar to the trend in western countries, however the relative percentage of DLBCL in the Middle Eastern population is slightly higher than in the west. This could very well be the beginning of a change in the epidemiological trend of the GI lymphomas in the Middle East. The high prevalence of gastric NHL could be due to the effect of environmental factors, specifically the increasing prevalence of *Helicobacter pylori* infection in the Middle Eastern countries. However, this is contrary to the observations from western countries where the prevalence of *H. Pylori* is decreasing.

In Saudi Arabia, the mean age of GI lymphomas is 55 years (range 40-60 years). The overall male: female ratio is 1.2:1, the ratio being 2:1 for small intestine, 1:0 for large intestine and 1:1 for stomach.<sup>25</sup> This is by and large similar to the epidemiological trend seen in the West

### Indian Subcontinent

The largest single center study from the Indian state of Tamil Nadu included 336 patients with primary GI lymphoma. The anatomical pattern of distribution was found to be similar to that in Western studies and the following pattern is observed.<sup>27</sup> (Figure 3).

The most common site is stomach followed by small intestine and large intestine. DLBCL is the most common subtype of lymphoma like in the west with an overall prevalence of 66.27%, followed by Burkitt's

**Table 2. Classification of GI Lymphoma by Isaacson et al.<sup>10</sup>**

Marginal Zone MALT* lymphoma
Diffuse Large B-cell lymphoma
Mantle Cell lymphoma
Burkitt's lymphoma
Follicular lymphoma
Intestinal T cell lymphoma

\* Abbreviation: MALT - mucosa associated lymphoid tissue

lymphoma (10.48%) and MALT lymphoma (10.12%). A few cases of immunoproliferative disease of the small intestine (IPSID) are also noted, which are rare in western countries but the prevalence is less than that seen in the Middle East

Male predominance is observed (male: female ratio 3.93:1) and the mean age at diagnosis is 45 years (range 3-88 years). The mean age is slightly lower than that noted in Western studies, likely due to a higher number of cases seen in pediatric age group. The prevalence of EATL is much lower than that seen in the western studies likely due to a low rate of diagnoses of celiac disease in India. Major population based studies are not available from Northern India.

### China

The findings from recent population based studies from Zhejiang and Tianjin provinces are depicted in Figure 4.<sup>28,29,30</sup>

As seen in Figure 4, the stomach is the most common site involved, followed by the ileocecal region. The prevalence of PGIL is higher in the ileocecal region in China as compared to the West and India. The reason for this relatively higher prevalence in ileocecal region is not clear from these studies. The majority of the cases (182 out of 216) are B-cell lymphomas.

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As in the West and India, a male predominance is noted (male: female ratio 1.27:1) and the median age at diagnosis is 56.9 years (range 8-89 years).

## EPIDEMIOLOGY BASED ON ANATOMICAL LOCATION OF GI LYMPHOMA

### Esophageal Lymphomas

Esophageal involvement is rare with Esophageal lymphoma accounting for approximately 1% of all PGIL. The available literature is meager in the form of case reports.<sup>31</sup> Esophageal extension of a primary mediastinal or gastric lymphoma is common. Primary esophageal lymphoma more often involves the distal esophagus.<sup>32</sup>

### Gastric Lymphomas

Gastric lymphoma, the most common anatomical type of GI lymphoma, accounts for about 68 to 75 % of all PGIL.<sup>17,19</sup> Primary gastric lymphoma constitutes about 3 % of all gastric cancers and accounts for 10% of all lymphomas.<sup>20</sup> In the GI tract, lymphoid tissue is only present in the tonsils and Peyer's patches in terminal ileum. The normal gastric mucosa lacks structured lymphatic tissues (lymphatic follicles). However, in response to inflammatory processes, lymphoid tissue appears in the gastric mucosa, called mucosa associated lymphoid tissue (MALT), a term first coined by Isaacson et al.<sup>33</sup>

Incidence of gastric lymphoma is higher in males compared to females. The peak age of incidence is between 50 and 60 years.

A majority of the gastric lymphomas are of the low-grade MALT type (40%), with non-MALT type NHL (mantle -cell lymphoma) and Burkitt's lymphoma being very rare (1.4% and 3.2% respectively).<sup>17</sup> MALT lymphoma, Mantle cell lymphoma and Burkitt's lymphoma are discussed separately in detail.

Diffuse large B-cell lymphoma (DLBCL) comprises 40-70% of all gastric lymphoma and is the most common B-cell NHL overall.<sup>17,19</sup> Stomach is the most common location for GI DLBCL, but it can also occur rarely in rectum, colon or terminal ileum. The origin of DLBCL is not clear however it could arise as a transformation of MALT lymphoma. Median age of diagnosis is in the fifth decade with male predominance. No risk factors except immunodeficiency (congenital immunodeficiency, organ transplant, HIV infection)

**Table 3. WHO Classification of GI Lymphomas<sup>11</sup>**

<b>B phenotype</b>
Low-grade B-cell lymphoma of the MALT* type: <ul style="list-style-type: none"> <li>- of the Western type (focalized)</li> <li>- of the Mediterranean type (extensive): IPSID* (essentially alpha-chain diseases)</li> </ul>
High-grade B-cell lymphoma of the MALT* type with or without low degree of lagnancy including: <ul style="list-style-type: none"> <li>- centroblastic</li> <li>- immunoblastic</li> <li>- large anaplastic cells</li> </ul>
Centrocytic lymphoma = lymphomatous polyposis
Burkitt or Burkitt-type lymphoma
Other types (equivalent to lymph node lymphomas) <ul style="list-style-type: none"> <li>Follicular</li> </ul>
<b>T phenotype</b>
T cell (EATL*) associated with enteropathy
T lymphomas not associated with enteropathy

\* Abbreviations:

MALT - mucosa associated lymphoid tissue

IPSID - immunoproliferative disease of the small intestine

EATL - enteropathy associated T cell lymphoma

have been identified for DLBCL. The prevalence of H. Pylori infection in patients with DLBCL is 35%, but majority of the DLBCL are associated with MALT lymphoma implying that it arises from MALT lymphoma transformation.<sup>34</sup>

### Small Intestinal and Colorectal Lymphomas

Small intestinal lymphomas account for about 23-26% of all GI lymphomas in the West. After stomach, small bowel is the second most common location for all GI

lymphomas. The epidemiology of small intestinal lymphomas is interesting because it differs depending on the geographical region.<sup>23,25</sup>

There are three main types of small intestinal lymphomas:

- Immunoproliferative small intestinal disease (IPSID) also called Mediterranean lymphoma, Seligman disease or alpha heavy chain disease.
- Enteropathy associated T cell lymphoma (EATL) associated with celiac disease.
- Non IPSID lymphomas, for example: Mantle cell, Burkitt's lymphoma, follicular lymphoma

According to some studies, small intestinal lymphomas are the most common GI lymphomas in the Middle East accounting for nearly 75 % of all GI lymphomas.<sup>25</sup> However, other studies show that the distribution is similar to that seen in Western population and stomach is the most common site.<sup>23</sup> Most common type of small intestinal lymphoma in Middle Eastern population is IPSID. Risk factors are summarized in table.<sup>7,21</sup>

The overall incidence of EATL is rare but EATL is associated with celiac disease and is the most common type of small intestinal lymphoma in the West. Per a

study from Netherlands, the overall crude incidence is 0.1 per 100,000. The peak incidence is in the seventh decade, with the proximal small intestine being the most common location.<sup>35</sup> Although the incidence of uncomplicated celiac disease is about 2 times higher in women compared to men, the incidence of EATL is higher in men as compared to women.<sup>36</sup>

Colorectal lymphomas are very uncommon, comprising about 3% of all GI lymphomas and about 0.3 % of all colorectal malignancies. Literature about their epidemiology is limited however the incidence is higher in males as compared to females.

### Primary Pancreatic Lymphomas (PPL)

PPLs are extremely infrequent. The most commonly accepted diagnostic criteria for the diagnosis of PPL are as follows.<sup>37</sup>

1. Mass involving the pancreas with or without loco-regional lymph nodes
2. No superficial/mediastinal lymphadenopathy
3. No hepatic or splenic involvement
4. Normal peripheral leukocyte count

In a series of 12 cases of PPL,<sup>38</sup> median age at diagnosis was found to be 65.5 years and 91.7% of the

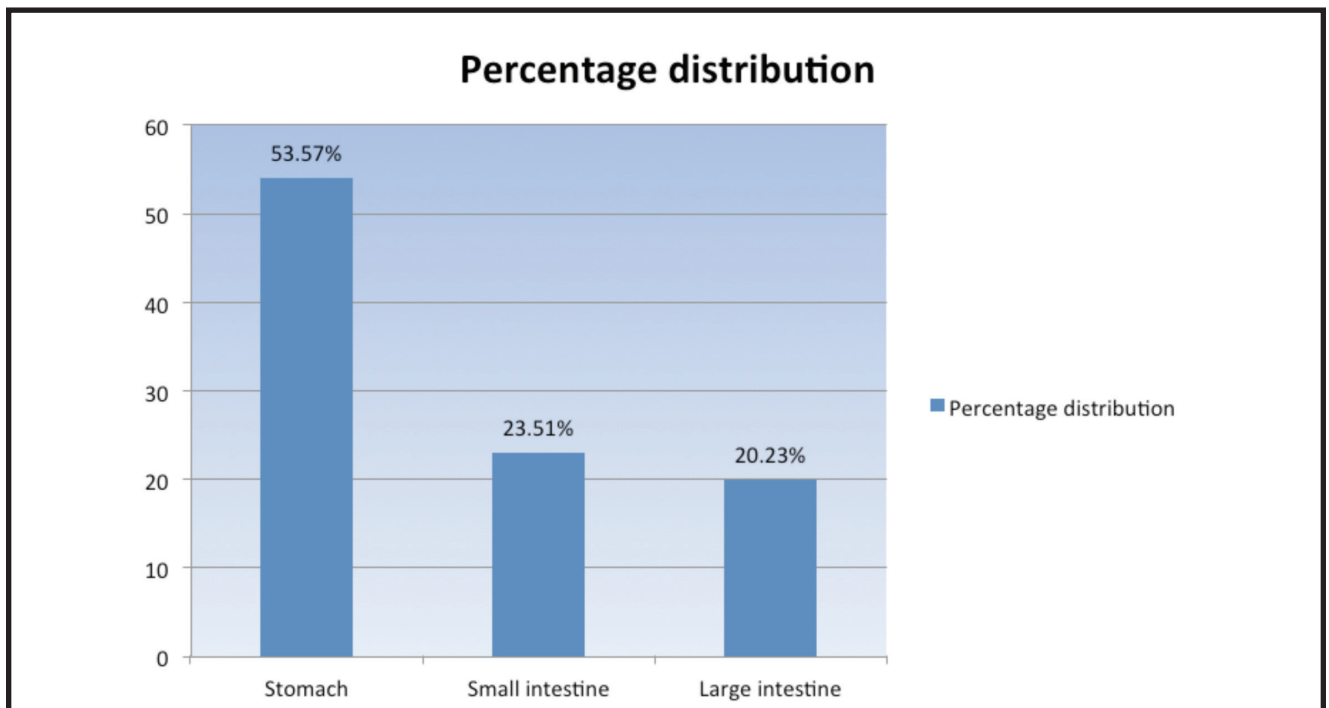


Figure 3. Anatomical Distribution of GI Lymphoma in an Indian Cohort <sup>27</sup>

patients were Caucasian and 58.3% were male. Only one patient had a diagnosis of HIV prior to the diagnosis of PPL. The majority of cases involved the head of the pancreas (83.4%).

## GI LYMPHOMA ASSOCIATED WITH SPECIFIC DISORDERS

### Helicobacter Pylori (H. Pylori) Infection and Mucosa Associated Lymphoid Tissue (MALT) Lymphoma

Gastric MALT lymphomas have a close association with H. Pylori infection, with 90-95% of the MALT

lymphoma patients having evidence of H. Pylori infection currently or in the past.<sup>39</sup> Although the incidence of H. Pylori infection is different in different parts of the world, the global prevalence of H. Pylori is estimated to be as high as 50%.<sup>40</sup> The overall incidence of Gastric lymphoma, however, is very rare, accounting for up to 2-8% of all gastric cancers. The median age at presentation is 61 years and there is no sex preponderance.<sup>17</sup>

Even amongst the developed countries there are regions where the prevalence of MALT lymphoma is higher than average.<sup>41</sup> For example, in north-eastern Italy, the frequency of primary gastric lymphoma was

**Table 4. Ann Arbor Staging System Modified by Musshoff for GI Lymphomas** <sup>12,13</sup>

TX extension not specified	
T0 no lymphoma	
T1m mucosa involvement	
T1sm submucosa involvement	
T2 involvement of the muscularis propria or subserosa	
T3 serosa involvement	
T4 invades adjacent structure or organs	
Stage I	Involvement of one site of the digestive tract with no lymph node involvement
Stage II	Involvement of one site of the digestive tract and regional lymph nodes with no extra-abdominal involvement  Musshoff modification: stage IIIE= involvement of only contiguous lymph nodes; stage II2E= involvement of regional noncontiguous lymph nodes
Stage III	Localized involvement of digestive tract associated with lymph node involvement of both sides of the diaphragm*
Stage IV	Involvement of one or several extranodal and/or extra-abdominal organs with or without associated lymph node involvement

\* This stage is not generally seen in GI lymphomas

**Table 5. Paris Staging System for GI Lymphomas**<sup>14</sup>

NX lymph node involvement not assessed
NO no lymph node involvement
N1 regional lymph node invasion
N2 distant abdominal lymph node
N3 spread to extra-abdominal lymph node
MX dissemination of lymphoma
MO no evidence of extranodal dissemination
M1 involvement of other site in gastrointestinal tract

noted to be very high, with an incidence as high as 13.2 cases per 100,000 per year, which is significantly higher than that of other European countries,<sup>42</sup> presumably related to the difference in the prevalence of the oncogenic strain of *H. Pylori*.

Several studies have shown the association between *H. Pylori* infection and Mucosa Associated MALT lymphoma.<sup>43,44</sup> The development of MALT lymphoma may be related to the strain of *H. Pylori* expressing the CagA protein. Serum Ig G antibody to the CagA protein was much more common in patients with *H. Pylori* who developed MALT lymphoma as compared to patients who did not have MALT lymphoma.<sup>45</sup> The very low prevalence of MALT lymphoma despite very high global prevalence of *H. Pylori* could be possibly because of the rarity of the strain producing the Cag A protein. A recent study has shown that *H. pylori* may translocate CagA protein into B-cells.<sup>46</sup> In the B-cells, CagA protein induces extracellular signal-regulated kinase activation and Bcl-2 expression up-regulation. This in turn inhibits apoptosis and leads to cancer or lymphoma.<sup>46</sup>

The predominant site for the development of MALT lymphoma is the stomach, however, other sites in the GI tract such as caecum can also be involved rarely.<sup>47</sup> Other infection that has been linked but not causally proved to cause GI lymphoma is *Campylobacter jejuni*, which has been associated with small bowel lymphoma.

## Burkitt's Lymphoma

Denis Burkitt, working as a surgeon in Kampala, Africa, noted a special type of lymphoma mostly in children, who had dysmorphic facies, at times with proptosis. Some children were also noted to have distended abdomen. This malignancy was initially thought to be a sarcoma. In the initial epidemiological studies carried out by Burkitt, it was found that the lymphoma was seen in the region 15 degrees north and south of the equator, a region found to be hot and wet with high rainfall year round. Subsequent epidemiological studies have been done which will be discussed later, however the original epidemiological investigation had a significant impact on the understanding of this disease entity.<sup>48,49</sup>

According to the WHO, there are 3 types of Burkitt's lymphoma - endemic, sporadic and HIV associated.

## Endemic Burkitt's Lymphoma

Endemic Burkitt's lymphoma (BL) is seen in many countries of Africa. The endemic zone is both north and south of the equator extending from Nigeria, Mali, Uganda up to Tanzania covering all central African countries near the equator. The endemic area is bisected by the equator.<sup>50</sup> The incidence, however, is noted to be 100-fold more common in tropical Africa and Papua New Guinea.<sup>51</sup>

Endemic BL, seen predominantly in children between 4-7 years, is the most common childhood malignancy in Africa.<sup>52</sup> Male dominance is noted and the male: female ratio is 2:1. Burkitt's lymphoma commonly involves the jaw bones. However, kidneys, gastrointestinal tract, ovaries, breast and other extranodal sites can also be involved.<sup>53</sup> This endemic form is almost always associated with Epstein Barr virus infection. The prevalence of this form is about 60 times higher than the prevalence of Burkitt's lymphoma in the United States.<sup>54</sup>

In a recent study carried out in north eastern Nigeria, majority (63.3%) of the affected children were in the 6-10-year age bracket with male predominance. The majority of children affected were the Fulani ethnic group (30.6%), from Borno state (36.7%) and were living in rural areas (40.8%).<sup>55</sup>

In a recent major study from Uganda, the extent of abdominal involvement in Burkitt's lymphoma was quantified. The mean age for abdominal tumor was higher (7 compared to 6 for overall BL, p values < 0.001). Interestingly although overall BL was more

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common in males, abdominal involvement was seen more in females. The age adjusted incidence noted to be 2.4 per 100,000, was lower in districts that were far from Lacor and higher in districts that were close to Lacor. While districts close to Lacor were also more urbanized, the incidence was higher in the close by semi-rural areas also.<sup>56</sup> This is in contrast to Nigerian study where incidence was noted to be high in rural areas.

### Sporadic Burkitt's Lymphoma

Sporadic Burkitt's lymphoma is seen all across the world. There is no specific geographic or climatic association. In the United States and Western Europe, it constitutes about 1-2% of all lymphomas in adults and about 40% of all lymphoma in children.<sup>54</sup>

Interestingly, abdomen and specifically ileocecal area is the most common site of involvement in sporadic BL. This is in contrast to endemic BL which mainly involves the facial bones. In addition to abdomen, other sites that are affected include ovaries, kidneys, omentum and Waldayer's ring.

HIV associated Burkitt's lymphoma is discussed separately.

### Immunoproliferative Disease of the Small Intestine (IPSID)

IPSID lymphoma has interesting epidemiological features. IPSID, a type of MALT lymphoma, occurs exclusively in the small intestine. It was previously called alpha-heavy chain disease because it expressed monotypic truncated Immunoglobulin Alpha chain. Also called Mediterranean lymphoma because of its geographical epidemiology, it is seen in regions bordering the Mediterranean sea and Cape region of South Africa.

The stomach, as in the Western population, is the most common site for GI lymphoma even in the Mediterranean region. The median age for IPSID is 25-30 years, with no gender preponderance.<sup>22</sup> In comparison, the Western type MALT lymphoma occurs mainly in the elderly. In a recent study published from Tunisia,<sup>57</sup> epidemiological data from the past 28 years was presented in a cohort of about 210 patients. Surprisingly, there was a significant decrease in the annual incidence of primary small intestinal lymphoma. Interestingly, it was also noted that there was a significant transition of IPSID or "Mediterranean" lymphoma, progressively being replaced by "Western" lymphomas.

**Table 6. Sites of Origin in Primary GI NHL: Data From the Literature**

First Author	Period	No. of Patients		Stomach		Intestinum		Multiple GI Sites	
		Total	No./Year	No.	% of Total	No.	% of Total	No.	% of Total
This report, 2001†	10/'92-11/'96	371	92.8	277	74.7	70	18.9	24	6.5
Gurney, 1999 <sup>36</sup> ‡	1986-1993	882#	110.3	463	52.5	419	47.5	NS	
d'Amore, 1994 <sup>34</sup> ‡	1/'83-12/'91	306#	34.0	175	57.2	109	35.6	22	7.2
Liang, 1995 <sup>20</sup> §	1/'75-6/'93	422	22.4	238	56.4	184	43.6	NS	
Radaszkiewicz, 1992 <sup>12</sup>	1/'74-12/'88	307**	21.9	264	86.0	59	19.2	5**	1.6
Otter, 1989 <sup>33</sup> ‡	6/'81-9/'86	86#	17.2	54	62.8	29	33.7	3	3.5
Ruskoné-Fourmestreaux, '93 <sup>15</sup> †	1/'84-1/'90	91	15.2	55	60.4	15	16.5	16	17.6
Morton, 1993 <sup>16</sup> ¶	1974-1988	175	12.5	78	44.6	95	54.3	4	2.3
Lewin, 1978 <sup>5</sup> §	1968-1975	74#	9.3	28	37.8	46	62.2	NS	
Hansen, 1998 <sup>35</sup> ‡	1985-1990	55	9.2	NS	51.0	NS	45.0	2	4.0
Azab, 1989 <sup>32</sup> §	1975-1986	106	8.8	55	51.9	43	40.1	8	7.5

Abbreviation: NS, not stated.  
 \*Cited because of the large numbers presented.  
 †Prospective study.  
 ‡Registry.  
 §Single institution.  
 ||Single institution for pathology.  
 ¶Registered within British National Lymphoma Investigation studies.  
 #Including children.  
 \*\*Only stages IE and IIE.

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## Mantle Cell Lymphoma (MCL)

Mantle cell lymphoma is a rare GI lymphoma, constituting about 4-9% of all GI lymphoma and 5-8% of all NHL. In previous studies MCL has been noted to affect the GI tract in 15–30% of cases.<sup>58</sup> However, in a recent study this view has been challenged. Microscopic evidence of MCL was noted in 84% of the cases with normal macroscopic appearance by colonoscopy and 45% by Upper GI endoscopy. Due to this high level of involvement noted, it was suggested that MCL may originate in the MALT region of the GI tract.<sup>59</sup>

The median age at diagnosis is 60 years. The male: female ratio is close to 3:1.<sup>60</sup> MCL arising primarily from GI tract has better prognosis as compared to MCL arising from lymph nodes.<sup>61</sup>

## GI Lymphoma and Celiac Disease

Celiac disease (CD), an autoimmune disorder, has a prevalence of about 1% in Western world with many more undiagnosed cases.<sup>62</sup> As the incidence of CD is higher in Caucasians, the prevalence of EATL is higher too in this ethnic group.<sup>63</sup> CD appears to increase the incidence of many GI and extra intestinal cancers, in particular lymphoma of the small intestine, probably related to villous atrophy. EATL is of two types: Type 1, which is associated with CD and Type 2, which is possibly a separate disease entity, occurring sporadically with different morphological features.<sup>64</sup>

The majority of EATL (65%) cases are of the T cell immunophenotype and are called Enteropathy-type T cell lymphoma (ETTL). ETTL not associated with CD is a rare entity. However, most lymphomas that occur as a complication of CD are not of the ETTL-type.<sup>65</sup> It was found that there was a significant link between female gender, CD, autoimmune or inflammatory disorders and B-cell NHL. The degree to which concurrent autoimmune or inflammatory disorder contributed to the risk is unknown.<sup>66</sup> ETTL develops in approximately 5% of the patients with celiac disease who were followed for a 30 year period.

In most of the patients, the diagnosis of CD is established just preceding or at the time of lymphoma diagnosis. It occurs only in small portion of patients with established history of childhood CD, and in these cases the disease has often been not well controlled. Conversely, 80-90% of the patients with EATL have CD.<sup>64</sup> The median age of onset is in the seventh decade of life, with male predominance (64%) despite the fact

**Table 7. Risk Factors for IPSID\* Lymphoma<sup>21</sup>**

Male gender
Age - median age of presentation is 25 years
Low socioeconomic status and poor sanitation
High rates of infection enteritis and parasitic infestation as children
Campylobacter infection
Genetic risk factors - linkage with HLA-B12, A9 and Aw19 haplotypes

\*Abbreviation:

IPSID - immunoproliferative disease of the small intestine

that CD is more common in females as compared to males.

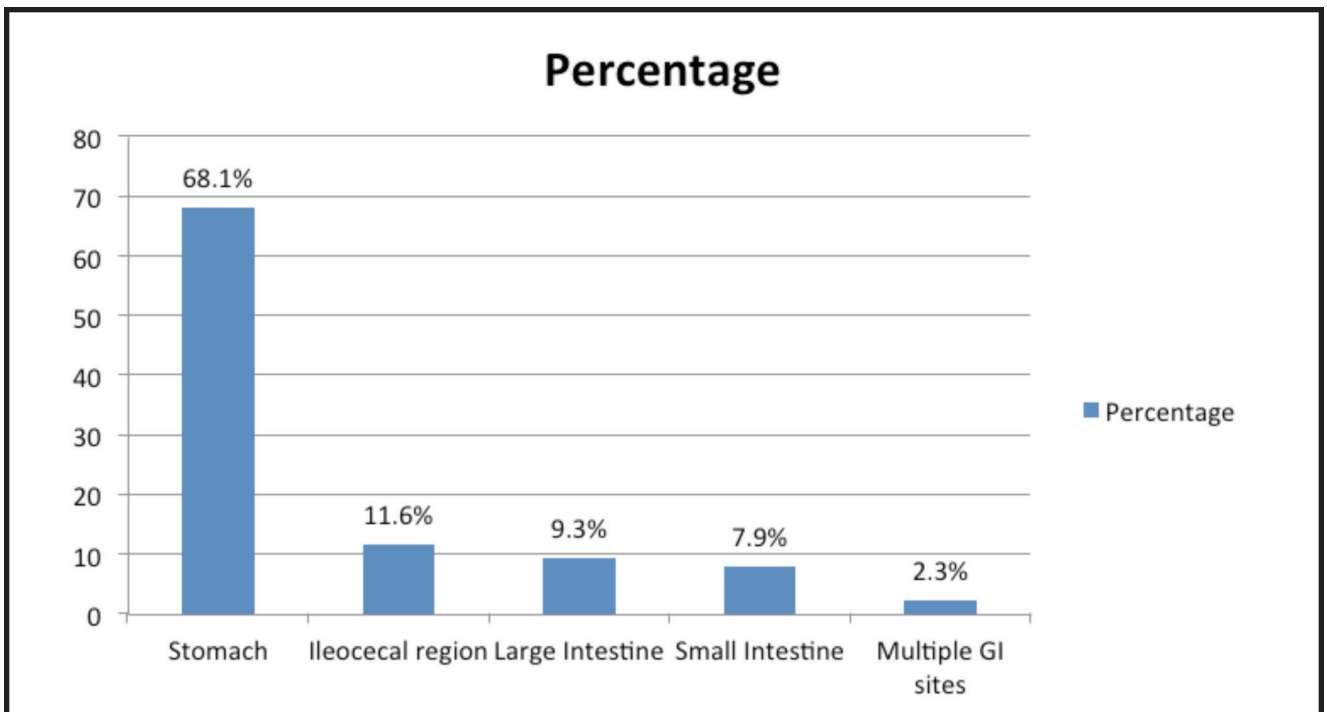
Celiac disease was also found to be associated with small intestinal adenocarcinoma, pharyngeal and esophageal squamous cell carcinoma.<sup>36,67</sup>

The risk for GI lymphoma decreases over time subsequent to the diagnosis of CD. This could be due to the introduction of a gluten-free diet. The risk, although decreased, remains persistently elevated in comparison with the general population.<sup>68</sup>

## GI Lymphoma and Inflammatory Bowel Disease (IBD)

A considerable amount of advancement in the knowledge of lymphomas in the setting of IBD has been made since it was first described at Mayo Clinic by Bargen<sup>69</sup> There are three important aspects to the association of lymphomas with IBD:

- Is there a risk for lymphoma independent of the treatment for IBD?
- Is there a link between the use of immunosuppressants used for treatment such as Azathioprine or 6-mercaptopurine (6-MP) and the development of lymphomas?
- Is anti-tumor necrosis factor (TNF) therapy a risk for development of lymphomas?



**Figure 4. Anatomical Distribution of GI Lymphoma in a Chinese Cohort**<sup>28</sup>

Multiple population based studies have been done to determine if there is an increased risk of lymphoma in patients with IBD as compared to the general population.<sup>6,70,71,72</sup> Review of all the data generated from these studies collectively do not suggest an increased risk of lymphoma in patients with IBD.<sup>73</sup>

It is not clear if the use of conventional immunosuppressants like azathioprine or 6-MP is associated with an increased risk of developing lymphoma.<sup>74</sup> Most of the studies to date have found no risk, however they lacked sufficient power to detect the risk. A large meta-analysis of a total of six cohort studies found a fourfold increase in the risk of lymphoma in patients with IBD who were treated with azathioprine or 6-mercaptopurine.<sup>75</sup> It is not clear from this meta-analysis whether the increase in risk is from the medications per se or from the increased severity of the underlying IBD.

Similarly, the data about the risk of lymphoma with the use of anti-TNF treatment are contradictory. The United States Food and Drug Administration (FDA) along with the manufacturer of Infliximab issued a boxed warning about the risk of lymphoma with its use in October 2004. Up until the end of 2010 a total of 20 cases of hepatosplenic T cell lymphoma (HSTCL) associated with infliximab have been identified by the FDA. However, several other studies have failed to

confirm an increased risk of lymphoma in patients receiving anti-TNF treatment.<sup>76,77</sup>

### GI Lymphoma and HIV Infection

There has been a significant decline in the infectious and non infectious complications of HIV, including GI lymphoma, with the increasing availability of antiretroviral therapy (ART). Amongst HIV associated NHL, the GI tract is the most frequent extranodal site, being involved in 30-50% of the cases. GI lymphomas are mainly seen late in the course of HIV and with advanced immunosuppression and believed to be causally linked to immunosuppression. They are usually of high grade B-cell histology with multifocal involvement affecting several regions of the GI tract simultaneously.<sup>78</sup>

HIV associated BL mainly affects adults, unlike endemic BL which occurs mainly in children.<sup>51</sup> HIV associated BL is also associated with EBV virus infection.

Compared with other HIV+ patients with NHL of the diffuse large B-cell type, those with BL are younger in age with higher mean CD4 counts (usually >200 cells/ $\mu$ l). In studies conducted before ART became widely available, HIV associated BL was 1000 times more common in HIV patients as compared to the general population.<sup>79</sup>

*(continued on page 26)*

(continued from page 24)

### GI Lymphoma and Autoimmune Diseases

A number of autoimmune diseases have been linked to an increased risk of lymphoma. These include:

- Sjogren's Syndrome
- Systemic Lupus Erythematosus
- Granulomatosis with polyangiitis
- Rheumatoid arthritis
- Hashimoto's thyroiditis

It is believed that the immunosuppressive therapy used for the treatment of these conditions, rather than the disease per se, is responsible for the increased risk.<sup>80</sup>

### GI Lymphoma and Immunosuppression

Both congenital and acquired immunodeficiency are associated with increased risk of developing B-cell lymphoma.

Congenital immunodeficiency syndromes linked with GI lymphoma include:

- Wiskott-Aldrich syndrome
- Severe combined immunodeficiency syndrome
- Ataxia telangiectasia
- X-linked agammaglobulinemia

Acquired immunodeficiency syndromes linked with GI lymphoma include:<sup>81,82</sup>

- Human immunodeficiency virus (HIV) infection
- Immunosuppressive therapy for autoimmune disease or post organ transplant

Most of such patients have secondary GI lymphoma, however primary GI involvement of stomach and small bowel has been reported.<sup>83</sup>

### GI Lymphoma and Nodular Lymphoid Hyperplasia

Nodular Lymphoid hyperplasia (NLH) is a polyclonal follicular reactive hyperplasia characterized by the alteration of the small intestinal lamina propria or colonic lamina propria.<sup>84</sup> The behavior of NLH is different in children and adults. In children, NLH often has a benign course and typically regresses spontaneously. In adults however, there is an association

of NLH with immunodeficiency including common variable immunodeficiency, selective IgA deficiency and giardiasis.<sup>85</sup> The benign nature of NLH in adults is less certain with several studies and case reports showing association between NLH and malignant lymphomas including high grade NLH.<sup>86, 87,88</sup> Evidence of association between NLH and GI lymphoma is stronger in the absence of immunodeficiency.

Recently an entity called "indolent T-cell lymphoproliferative disease of the gastrointestinal tract," or indolent T-LPD has been described.<sup>89</sup> It is an indolent clonal proliferation of T cell. It is important to recognize this entity because it can be easily misdiagnosed as intestinal T cell lymphoma and lead to aggressive therapy.

### Epidemiology of Natural Killer (NK) Cell and T Cell Lymphomas Involving GI Tract

The majority of GI lymphomas are B-cell lymphomas with NK cell/T cell lymphomas of the GI tract being very rare comprising about 3.1% of all GI lymphomas.<sup>90</sup> In a retrospective population based study from Asia, NKT cell GI lymphoma had a median age at diagnosis of 45 years with a male predominance (Male: Female 7:3). NKT cell GI lymphomas tend to be more aggressive, occur at a younger age and have poorer prognosis compared to B-cell GI lymphomas.<sup>91</sup> Small intestine is the most common anatomical site for primary NKT cell GI lymphomas, rather than stomach.

### SUMMARY

Primary GI lymphomas are far less common than secondary GI lymphomas. The GI tract is the most common extra nodal site involved in NHL. Primary GI lymphomas can affect any site, or multiple sites with the stomach being the most common site. The epidemiology and risk factors for GI lymphoma differs in different populations. Disease entities associate with GI lymphomas include H. Pylori infection, inflammatory bowel disease, immunosuppression and auto immune diseases. ■

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