*Original Article*

# Histopathology of gastric cancer in Yemen: A seven years retrospective analysis

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**ABSTRACT**

**Background:** Gastric cancer (GC) is a major contributor to the global burden of cancer morbidity and mortality. It is the fourth most commonly occurring worldwide.

**Objective:** To describe the general pattern of primary GC in Yemen and compare the findings of patients' age, sex, histological type and degree of differentiation to findings from other Middle Eastern countries and the rest of the world.

**Methods:** This is a descriptive record-based study of 517 cases of GC in the Department of pathology, Sana'a University, Yemen, for seven years period. The diagnosis was made on hematoxylin and eosin stained sections and categorized the cases of gastric malignancies according to histological type.

**Results:** Out of 517 cases of GC, 183 (35.4%) were females and 286 (64.6%) were males with 1:1.8 female to male ratio. The commonest type of GC was adenocarcinoma comprising, 462 (89.3%) of which female and male cases were 166 (36%) and 296 (64%) respectively. Non-Hodgkin's lymphomas accounted, for 38 (7.4%). The rest of the cases were nine undifferentiated malignancies, four leiomyosarcoma, two gastrointestinal malignant stromal tumors, one adenosquamous and the last one was carcinoid. Male preponderance was seen in all malignancies. The mean age for adenocarcinoma in females was 55.9 years and 59.5 years in males. Well-differentiated adenocarcinomas accounted for 45.7% followed by moderately-differentiated 22.1%. The poorly differentiated and signet ring cell carcinomas accounted for 16.2% and 9.5% respectively.

**Conclusion:** The frequency of GC in Yemen revealing similar features in age, sex and hitological types with that reported from high incidence areas.

**Key words:** Gastric cancer - adenocarcinoma- lymphoma - Yemen.

Gastric cancer (GC) is a major contributor to the global burden of cancer morbidity and mortality. It is the fourth most commonly occurring worldwide, with an estimated 933,000 new cases diagnosed annually[1].Moreover, because of its poor prognosis, it is the second most common cause of cancer death after the lung cancer. There are substantial variations in the incidence of GC by region and nation, with highest rates being observed in East Asia, Eastern Europe, and parts of Central and South America.

The incidence in the Middle East countries is relatively low, with rates 5-15 times lower than in Japan[1,2].

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Annual age-standardized incidence for males varies from four to 42 per 100,000, and the rates in females are generally about half those in males[2]. The trend in GC incidence over time has been declining[1]. It is thought that much of the decline is due to changes of lifestyle and environmental risk factors, such as salt consumption, which has decline as refrigeration replaced salt preservation[3]. Gastric cancer, like other cancers, is the end result of the interplay of many risk factors as well as protective factors. Environmental and genetic factors are also likely to play a role in the etiology of the cancer among the environmental factors, diet and infection with Helicobacter pylori are the most common suspects in gastric carcinogenesis. Various epidemiological and pathological studies have suggested that gastric carcinogenesis develops with the following sequential steps. Chronic gastritis, gastric atrophy, intestinal metaplasia

and dysplasia[2,4]. The epidemiology of GC has been widely studied in the Western world as well as in Japan[5,6,7]. However, only a few scattered reports from the developing world have been published[8,9,10]. There is a lack of good descriptive data on GC from Middle Eastern countries, where both registration and the prevalence of risk factors are relatively unknown.  Several reports from the Republic of Yemen have recently described general patterns of cancer, and those of gastrointestinal tract malignancies[11, 12].  No report has been devoted to the study of the pattern of gastric cancer. And due to the lack of Cancer Registration Center in Yemen, the incidence and prevalence of risk factors are unknown.  So the present study was undertaken to provide an overview and describes the general pattern of primary gastric cancer in Yemen for the first time. Our findings of patients' age, sex, histological type and degree of differentiation are compared to findings from other Middle Eastern countries and the rest of the world.

## Methods

 A descriptive record-based study of 517 cases of GC was carried out in the department of pathology, Faculty of Medicine and Health Sciences, Sana'a University during the period of seven years from 1st January 2005 to the 30th November 2011.  The diagnoses were made primarily in private laboratories of two consultant pathologists in Sana'a who received the histopathologic biopsies from Sana'a and   other Yemeni provinces. Most cancer patients are referred to Sana'a for further investigations and therapy, where most of the histopathologists and all oncologists are practicing. The endoscopic biopsies and sections taken from the resected tumors were fixed in 10% formalin solution before being processed by manual and automatic tissue processor (Shandon Southern product –England – Cheschire).   After embedding in paraffin blocks several thin sections of 2 to 3 micrometer thickness from each block were cut.   The sections were stained with hematoxylin and eosin stain for routine histological diagnosis.  During the histological analysis the sample was

evaluated regarding the type of epithelial lining, morphology and arrangement of cancer cells, and   grading of cancer. Finally we categorized the cancers into the main  subtypes; adenocarcinoma, Non-Hodgkin's lymphoma, stromal and smooth muscle malignancies, and other rare types. The clinical aspects were collected from the request forms.  The present study focuses on those cases that revealed invasive picture of GC on light microscope, and excludes the doubtful cases of suggestive cancer, or non-invasive neoplasms. Ethical clearance was obtained from the Ethics Committee of the Faculty of Medicine and Health Sciences of Sana'a University.   Statistical analysis was carried out using the Statistical Package for Social Sciences version 15 (SPSS Inc., Chicago, IL, USA) to calculate Chi square and $p$-value. The $x^2$ was used to evaluate the statistical significance of differences, and P values less than 0.05 were considered statistically significant.

## Results

A total number of 517 cases of GC   were studied. Four hundred and seventeen   cases were endoscopic biopsies and 100 cases were total resections of cancers. Out of 517 cases, 183 (35.4%) were females and 286 (64.6%) were males with 1:1.8 female to male ratio. The commonest types of GC encountered was adenocarcinoma comprising   462 (89.3%) of which female and male cases were 166 (36%) and 296 (64%) respectively with 1.78:1 male to female ratio. Non-Hodgkin's lymphomas account for 38 (7.4%) of cases.  The rest of the cases were nine undifferentiated malignancies, 4 leiomyosarcoma, 2 gastrointestinal malignant stromal tumors, one adenosquamous carcinoma and last one carcinoid tumor (Table 1). There is marked male preponderance in all subtypes. The mean age for gastric carcinoma in females was 55.9 years with median of 60 years whereas the mean age in males was 59.5 years with median of 65 years (age range in females was 20-90 years and 16-100 years in males). The mean age for NHL was 46 years in females and 43.2 years in males with median of  52.5 years in females and 40 years

in males (age range was 20-70 years in females and 8-80 years in males) (Table 2). The peak incidence for adenocarcinoma was found in the age group of fifth decade for females 47 (31.1%) and in sixth decade for males 80 (28.9%). Patients aged below 41 years and over 71 years showed low incidence of carcinoma accounting for 11.2% and 15.2% respectively (Table 3). Well-differentiated adenocarcinomas accounted for 45.7% followed by moderately-differentiated 22.1%. The poorly differentiated and signet ring cell carcinomas accounted, for 15.9% and 9.4% respectively. Mucinous and undifferentiated subtypes were the least common (Table 4). Table 5 depicts the international formula classification for Non-Hodgkin's lymphomas with gender differences; high grade type was the most common and represents, 30 (79%) of cases.

Table 1: The histological subtypes and gender distribution for gastric malignancies in the study population

|  | Female | | Male | | Total | |
| --- | --- | --- | --- | --- | --- | --- |
| Types | No | % | No | % | No | % |
| Adenocarcinoma | 166 | 90.7 | 296 | 88.6 | 462 | 89.3 |
| Non-Hodgkin's Lymphoma | 09 | 4.9 | 29 | 8.7 | 38 | 7.4 |
| Undifferentiated carcinoma | 04 | 2.2 | 05 | 1.5 | 09 | 1.7 |
| Leiomyosarcoma | 03 | 1.6 | 01 | 0.3 | 04 | 0.8 |
| Gastrointestinal malignant stromal tumor | - | - | 02 | 0.6 | 02 | 0.4 |
| Adenosquamous carcinoma | 01 | 0.6 | - | - | 01 | 0.2 |
| Carcinoid | - | - | 01 | 0.3 | 01 | 0.2 |
| Total | 183 | 100 | 334 | 100 | 517 | 100 |

Female to male ratio: 1:1.8    $Chi^2 = 2.31$ $p=0.123$

Table 2: Differences in age distributions for adenocarcinoma and Non-Hodgkin's lymphoma

|  | Adenocarcinoma | | Non-Hodgkin's lymphoma | |
| --- | --- | --- | --- | --- |
| Age (years) | Female | Male | Female | Male |
| Mean | 55.9 | 59.5 | 46 | 43.2 |
| Median | 60 | 65 | 52.5 | 40 |
| Maximum | 90 | 100 | 70 | 80 |
| Minimum | 20 | 16 | 20 | 08 |

Table 3: Age and sex distribution of patients with gastric adenocarcinomas ( N= 428)

|  | Female | | Male | | Total | |
| --- | --- | --- | --- | --- | --- | --- |
| Age group | No | % | No | % | No | % |
| ≤ 40 | 20 | 13.2 | 28 | 10.1 | 48 | 11.2 |
| 41-50 | 30 | 20 | 44 | 15.9 | 74 | 17.3 |
| 51-60 | 47 | 31.1 | 73 | 26.3 | 120 | 28.0 |
| 61-70 | 41 | 27.1 | 80 | 28.9 | 121 | 28.3 |
| ≥ 70 | 13 | 8.6 | 52 | 18.8 | 65 | 15.2 |
| Total | 155 | 100 | 282 | 100 | 428 | 100 |

*In thirty four of cases the ages were not mentioned.

Table 4: Differences in histological differentiation for the adenocarcinomas (N= 471)

| Degree of differentiation | Female | | Male | | Total | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| Well-differentiated | 69 | 41.6 | 142 | 48.0 | 211 | 45.7 |
| Moderately differentiated | 28 | 16.9 | 74 | 25.0 | 102 | 22.1 |
| Poorly differentiated | 36 | 21.7 | 39 | 13.2 | 75 | 16.2 |
| Mucinous | 08 | 4.8 | 11 | 3.8 | 19 | 4.1 |
| Signet ring cell | 20 | 12.0 | 24 | 8 | 44 | 9.5 |
| Not- specified | 05 | 3.0 | 06 | 2 | 11 | 2.4 |
| Total | 166 | 100 | 296 | 100 | 471 | 100 |

Table 5:  NHL subtypes according to international formula classification

| NHL Grade | Female | | Male | | Total | |
|---|---|---|---|---|---|---|
| | No | % | No | % | No | % |
| Low grade  Maltoma | 3 | 33.4 | 03 | 10.4 | 06 | 15.8 |
| Intermediate grade | -- | -- | 01 | 3.4 | 01 | 2.6 |
| High grade | 5 | 55.5 | 25 | 86.2 | 30 | 79 |
| Non-specified | 1 | 11.1 | -- | -- | 01 | 2.6 |
| Total | 9 | 100 | 29 | 100 | 38 | 100 |

**Discussion:**

Gastric cancer remains to be a prevalent disease worldwide with a dismal prognosis[13]. Gastrointestinal cancer is the most frequent malignancy in Yemen[11,12]. There is a lack of good descriptive data on GC from Middle Eastern countries, where both registration and the prevalence of risk factors are relatively unknown.  If GC is diagnosed at an early stage, patients can have a highly favorable prognosis and avoid extended surgery and its complications. Several studies have shown that the prognosis of GC has not changed in the past 20 years[6,14]. The only method that is likely to improve the prognosis is early detection of cancer. Our patients tended to be diagnosed late, because many people in our country who have gastric problems visit the non-specialist physicians who either prescribe medications for long term or use drugs in order to relieve the pain. However, subsequently, some of these patients who suffer from cancer are diagnosed late. In addition, elderly patients usually fail to consult the available medical services and hence are not subjected to diagnostic procedures and remain undiagnosed.

However, greater efforts in education of patients and the improvement of diagnostic technical skills may improve chances of early diagnosis. The total number of GC during the period of study was 517 cases that confirmed by microscopic study, this may indicate that many cases were not microscopically confirmed and they were not notified. In this study adenocarcinoma arising from gastric epithelium was the commonest type of GC in all age groups and in both sexes, it accounts for 462 (89.4%). This result was compatible with many researches carried out in the Middle East countries and global countries[8,9,15,16]. Slight high percentage was found in the high incidence countries[17,18]. The variation that exists between different places and countries may be simply due to variations in diagnostic techniques, number of patients studied, and due to different prevalence or susceptibility to risk factors. Gastric cancer, like other cancers, is the end result of the interplay of many risk factors as well as protective factors. Environmental and genetic factors are also likely to play a role in the etiology of the cancer. Among the environmental factors, diet and infection with

Helicobacter pylori are the most common suspects in gastric carcinogenesis. Asakaet al[19] has been shown a clear association between gastric adenocarcinoma and Helicobacter Pylori. The prevalence of infection with the bacteria in dyspeptic patients in Yemen appears high[20]. Therefore, it is suggested that infection by this bacteria may play a role in the development of gastric carcinoma in our patients. Fresh vegetables and fruits, starch natural unprocessed wheat products are the major constituents of traditional Yemeni food. However, during the last decades Yemen, like other Arabian countries, has experienced a rapid change in the diet habit with dominant of animal proteins, canned food, hot spices and fermented food. These types of food have been implicated as risk factors for GC in many studies. Another risk factor is the organophosphorous compounds which used in agriculture especially Qat (Catha Edulis) as fertilizer, pesticides and insecticides and may have increased the magnitude of cancer. Improvements in diet habits and storage, public health education, reducing tobacco and Khat usage and control of H pylori infection are likely to offer great potential for the prevention of GC in this area. In Western countries NHL represented only 2% to 5% of GC[21] while it represented 7.4% of our series, which was similar to the 8% figure from Jordan, but different from the 14% and 22% figures reported from neighboring Saudi Arabia[8,22]. During the past three decades the site of primary gastric lymphomas in the Middle East has changed. Small intestinal involvement become less common and gastric involvement more frequent, this varying pattern seemed to be environmental in origin[23].      There was a slight male predominance in all types of gastric malignancies (Table 1) and comprising 334 (65%) with (p value=0.12). However, the male preponderance seen in our result is consistent with the fact that gastric cancer is more common in males as reported repeatedly in the literatures[15,24,25]. In the neighboring gulf countries, the incidence of stomach cancer in males was approximately twice that of females; a similar two-fold difference in risk has been documented in many other countries[10]. Also we found that the male to female ratio was 1.8:1 which is very much comparable to the finding of many literatures[8,9,15]. The peak frequency of gastric carcinoma was at the age group of 51-70 years (56%) with median age of 65 years for males and 60 years for females.It appears to occur a decade earlier than in developed countries. A similar to this finding was documented in some Middle Eastern countries[9,15,25]. Forty eight  (11.2 %) patients were under the age of 41 years and this is lower than the 18.2% reported by Al-Radi AO et al[25] from Saudi Arabia and 20.9% by Alsir K et al[15] from Sudan and fairly comparable with that reported  from  Jordan[9] and Iran[24]. In developed countries lower than this percentage (3.7%) was reported by Su-Shun LO et al[27].  So, our finding reveals mild inconsistency with those countries having similar anthropologic and demographic profiles. The causes for this variation are not understood and the late diagnoses of disease can explain part of the reasons. In general GC occurring below 45 years of age is called early onset gastric cancer. It has a higher genetic component than GC occurring in the 45 and above group, which is initiated more by the environmental risk factors[28].

Gastric cancer has also been classified according to the degree of differentiation exhibited by the tumor. For many years there was a wide-spread belief among clinicians and pathologists that histological grading of GC adds nothing further to the assessment of prognosis over and above what may be derived from the TNM stage of the tumor[29]. Martin and his colleagues[30] reported that the histological grading system shows substantial and statistically significant differences in survival among patients with GC, after tumor stage has been taken into account. Our study shows the degree of differentiation of adenocarcinoma as demonstrated in table 3 with prominence of well-differentiated grade 45.7% in both sexes followed by moderately differentiated 22.1% and poorly-differentiated

16.2%. Similar figures have been documented in Nigeria[31]. Inconsistent figures were reported form Jordan which showed the reverse of our findings; 46.9% poorly differentiated, 24.1% moderately differentiated and 22.8% well-differentiated[32]. Since cancer is primarily diagnosed by histopathologists, a consensus about diagnostic criteria is important when making inter-country comparisons. However, it appears that such consensus has been lacking in the diagnosis of stomach cancer and the agreement between any two pathologists on histological type ranged from 68-83%.[33]. So, misclassification is still present especially in our society. In addition, 417 cases in this study were endoscopic biopsies hence some cases pose a diagnostic difficulty for the degree of differentiation. Our study has some limitations such as lack of the information about the anatomical site (cardia, fundus and pyloric) and histological type according to Lauren's classification (diffuse and intestinal). Also, the data for this study have principally been obtained from private laboratories. Therefore, it is not possible to derive specific explanations for staging, treatment and follow up. In spite of these limitations, it has serve as a baseline description of GC in the Republic of Yemen and reveals some striking information which indicates the need for establishing a national cancer registry in the Yemen.

**Conclusion:**

The frequency of GC in Yemen revealed similar features in age, sex, and histological type with that reported from high incidence areas. Adenocarcinoma accounts, for the highest number of GC in 5th and 6th decades with male preponderance as well as high frequency of well-differentiated grade. This study is however, useful in highlighting the distribution of the histological types of GC in Yemen. The cause of the high incidence of gastric cancer in our country is unknown. We strongly feel that supported research is needed as well as further environmental and immunohistochemical studies to find out the influence of genetic predisposition and local risk factors especially insecticides used in Khat agriculture.

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