Gastric Malignancies In Nigeria

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INTRODUCTION

Gastric malignancies constitute a major cause of morbidity and mortality worldwide. Whereas there has been a marked decline in the incidence of gastric malignancies in many industrialized nations such as the United States of America and England, it remains quite high in others such as Japan, Chile and Italy[1,2].

Gastric cancers rarely occur before the age of forty years but the incidence increases steadily afterwards. Most patients are over fifty years of age and the incidence peaks in the seventh decade. It is reputed to be the second most common cancer in the world following lung cancer.[3] Despite the advances made in the early diagnosis of gastric cancer, it remains among the leading high mortality associated cancers world wide.[4] A pertinent point about the most prevalent form of gastric malignancies namely gastric carcinoma is its strong association with environmental factors, besides certain clearly defined host and genetic factors[2,5] Perhaps environmental factors may largely explain the reasons why African Americans, Hispanic Americans and Native Americans are 1.5 2.5 times more likely to have gastric cancer than whites.[6] If this is the case, it stands to reason that economically disadvantaged regions of the world such as the world such as Africa, Nigeria inclusive run a great risk of developing gastric malignancies. It is also known that countries in which gastric malignancies are common such as China and South American countries are nations with endemic poverty. This confirms that low socio-economic status is generally associated with high risk, since the socioeconomic factors of an individual determines his dietary habits and lifestyle[3]. Various factors such as late clinical presentation, late diagnosis and inadequate medical care would most probably foreclose a bad prognosis most especially in Nigeria, the nation in which this study is being conducted. In addition, with increasing urbanization and industrialization; there is significant increase in the use of alcohol and cigarettes.

EPIDEMIOLOGY

WORLDWIDE EPIDEMIOLOGY OF GASTRIC MALIGNANCIES

In most countries, gastric cancer was the most important cause of cancer death during the 1950[20]s. Presently, it is the second most common cancer in the world following lung cancer[3]. Stomach cancer is particularly relevant in Italy because of its high mortality levels. It was the second most common cause of cancer death as at 1990 in Italy[20]. It is also the leading cause of cancer related deaths in Venezuela.[44]

Although gastric cancer has declined dramatically world wide in mortality and morbidity, gastric malignancies is the fourth most common cause of cancer death in the United Kingdom, coming behind the cancers of the bronchus, large intestine and breast respectively [3,5,54] . Data from Caucasian studies show that amongst the malignant tumours of the stomach, gastric carcinomas stand out overwhelmingly as the most important and the most common as they account for 90-95% of malignant tumours. Gastric lymphomas account for 4%, carcinoids 3%, and malignant stromal tumours 2%. Some other rare tumours have been described [1,5,55] Any discussion on the epidemiology of gastric cancer no doubt puts gastric carcinoma in the limelight since it accounts for 90-95% of gastric malignancies [5,56] Thus it stands to reason that any consideration of gastric caner is almost entirely synonymous with gastric carcinoma [22]. It is a worldwide disease with widely variable incidence from country to country. It is particularly high and infact inordinately so in Japan, Chile, China, Portugal and Russia, but 4-6 fold less common in the United States of America, United Kingdom Canada, Australia and France[1,3,5]. It is common in the low socio-economic groups and exhibits a male to female ratio 2:1 [3,5] It has been variably expressed as male to female of between 1.7:1 and 2.5:1 in Northern Ireland. [22] Approximately 800,000 new cases are discovered each year while 650,000 deaths are recorded worldwide. In Eastern Kenya, there was an incidence of 7.01/100,000 males and 3.7/100,000 females between 1991 and 1993 at a time the world incidence was 14.3 and 7.1/100,000 for males and females respectively [57] In Algiers , Algeria, Yaker reported and incidence of 3.6 and 1.4 for male and female respectively per 100,000 populations[58] Da Silva in Luanda reported that gastric cancer accounted for 9.8% and 4.7% of all cancers in males and females respectively in Angola[59] Nasr et al in Cairo, Egypt reported that gastric cancer accounted for 0.1% of all cancers in either sex[60] Walter et al in Libreville reported that gastric cancer accounted fo r 1.1% and 1.8% of all cancers in males and females respectively in Gabon [61] Kungu also working in Kenya found that gastric cancers accounted for 4.3% and 2.4% of all cancers in males and females respectively. [62] Sobo in Liberia reported that gastric cancer accounted for 3.5% and 1.3% of all cancers in males and females respectively in Liberia.[63] Coualanges in Madagscar reported that gastric cancer accounted for 1.3% and 0.5% of all cancers in males and females respectively in Liberia [64] Hutt in Malawi reported that gastric cancer accounted for 2.1% and 0.4% of all cancers in males and females respectively in Malawi.[65] Abioye et al in Ibadan reported that gastric cancer accounted for 6.0% and 2.2% of all cancers in males and females respectively and an incidence of 7.1 and 4.0 for males and females respectively per 100,000 populations in Ibadan, Nigeria [66] Cederquist el al in Zaria, Northern Nigeria also reported that gastric cancer accounted for 1.5% and 1.1% of all cancers in males and females respectively[67]. Ngendahjayo in Butare, Rwanda found that gastric cancer accounted for 9.9% and 6.5% of all cancers in males and females respectively in Rwanda. [68] Mukhtar in Sudan also reported that gastric cancer accounted for 2.7% and 1.5% of all cancers in males and females respectively in Sudan.[69] Peers et al in Swaziland reported that gastric cancer accounted for 2.3% and 0.3% of all cancers in males and females respectively and an incidence of 1.8 and 0.2 for male and females respectively per 100,000 populations in Swaziland[70] Mourali in Tunis found that gastric cancer accounted for 2.1% and 1.5% of all cancers in males and females respectively in Tunisia[71] Owor in Kampala found that gastric cancer accounted for 2.7% and 1.6% of all cancers in males and females respectively in Uganda. [72] Shaba et al in Dar es Salaam found that gastric cancer accounted for 1.7% and 1.5% o of all cancers in males and females respectively in Tanzania[73] Watts in Lusaka found that gastric cancer accounted for 5.0% and 4.9% of all cancers in males and females respectively in Zambia. [74] Skinner in Bulawayo, Zimbabwe; found that gastric cancer accounted for 4.5% and 2.6% of all cancers in males and females respectively in Zimbabwe [75] Gelves La Plata in Argentina also found that gastric cancer accounted for 6.4% and 2.6% of all cancers in males and females respectively in Argentina[76] De Bermudez el al in Costa Rica found that gastric cancer accounted for 23.5% and 11.5% of all cancers in males and females respectively in Costa Rica and an incidence of 57.5% and 25.7 of all cancers in males and females respectively per 100,000 populations . Fagart et al in Martinique found that gastric cancer accounted for 11.4% and 7.3% of all cancers in males and females respectively and an incidence of 22.7 and 10.0 in males and females respectively per 100,000 populations in Martinique. [80] Britton et al in Panama found that gastric cancer accounted for 10.6% and 4.8% of all cancers in males and females respectively and an incidence of 9.9 and 6.2 in males and females respectively per 100,000 populations in Panama.[81] Rolon in Paraguay found that gastric cancer accounted for 11.2% and 4.5% of all cancers respectively, and an incidence of 12.1 and 5.7 for males and females respectively per 100,000 populations in Paraguay.[82] Olivares in Peru found that gastric cancer accounted for 19.3% and 10.6% of all cancers respectively, and an incidence of 26.4 and 16.5 for males and females respectively per 100,000 populations in Peru.[83] De Stefani in Uruguay found that gastric cancer accounted for 7.7% and 6.1% of all cancers respectively for males and females in Uruguay.[84] Rahim in Bangladesh found that gastric cancer

accounted for 1.5% and 0.7% of all cancers respectively for males and females in Bangladesh.[85] Aung in Burma found that gastric cancer accounted for 11.4% and 8.3% of all cancers respectively for males and females and an incidence of 19.8 and 13.9 for males and females respectively per 100,000 populations in Burma.[86] Luthra in India found that gastric cancer accounted for 10.5% and 4.6% of all cancers for males and females respectively, and an incidence of 12.7 and 7.5 for males and females respectively per 100,000 populations in India.[87] Sugondo in Indonesia found that gastric cancer accounted for 0.6% and 0.3% of all cancers respectively in Indonesia [88]. Karamlou in Iran found that gastric cancer accounted for 9.5% and 3.8% of all cancers for males and females respectively in Iran.[89] Al-Fouadi in Iraq found that gastric cancer accounted for 4.4% and 3.2% of all cancers for males and females respectively in Iraq.[90]

Omar in Kuwait found that gastric cancer accounted for 4.4% and 2.0% of all cancers for male and females respectively and an incidence of 3.6 and 1.9 for males and females respectively per 100,000 populations in Kuwait.[91] Ahluwalia in Malaysia found that gastric cancer accounted for 5.7% and 20% of all cancers for males and females respectively in Malaysia. [92]Ahmed in Pakistan found that gastric cancer accounted for 1.7% and 0.9% of all cancers for males and females respectively and an incidence of 1.0 and 0.6 for male and females respectively per 100,000 populations in Pakistan.[93] Lee et al in South Korea found that gastric cancer accounted for 29.8% and 16.9% of all cancers for males and females respectively and an incidence of 29.1 and 12.5 for male and females respectively per 100,000 populations in South Korea.94 Sivayoham in Sri Lanka found that gastric cancer accounted for 1.2% and 0.6% of all cancers for males and females respectively and an incidence of 1.0 and 0.6 for male and females respectively in Sri Lanka. [95] Sontipong et al in Thailand found that gastric cancer accounted for 5.3% and 2.8% of all cancers for males and females respectively and an incidence of 2.6 and 1.2 for male and females respectively per 100,000 populations in Thailand. [96] Bilir in Turkey found that gastric cancer accounted for 6.4% and 4.7% of all cancers for males and females respectively and an incidence of 4.1 and 1.9 for male and females respectively per 100,000 populations in Turkey.[97] Truong in Vietnam found that gastric cancer accounted for 0.7% and 0.2% of all cancers for males and females respectively in Vietnam[98]. Singh et al in Fiji found that gastric cancer accounted for 8.6 and 2.4% of all cancers for males and females respectively and an incidence of 5.4 and 2.7 for male and females respectively per 100,000 populations in Fiji.[99] Thevenot in New Caledonia found that gastric cancer accounted for 6.4% and 2.2% of all cancers for males and females respectively and an incidence of 15.8 and 4.7 for male and females respectively per 100,000 populations in New Caledonia.[100] Misch et al in Pupa New Guinea found that gastric cancer accounted for 3.4% and 1.9% of all cancers for males and females respectively and an incidence of 1.1 and 0.5 for male and females respectively per 100,000 populations in Papa New Guinea. [101] In Japan the incidence is 78 cases per 100,000 men and 33 cases per 100,000 women. In China where 38% of all cancer cases occur, the incidence is 44 cases per 100,000 men compared with 19 cases per 100,00 women. The incidence in Eastern and Central European countries are 36 and 17 cases per 100,000 men and women respectively. In North America, the data revealed an incidence of 8.4 cases per 1000,000 men and 4 cases per 100,000 women. Between 1988 and 1991, there was an incidence of 77.5 deaths per 100,000 in Costa Rica. Data available from 1988 to 1991 revealed the following figures for deaths from gastric cancer per 100,000 populations for Russia, Japan, Chile, United Kingdom, Canada and the United States; 52.8, 50.5, 48.8, 17.6, 11.4, and 7.5 cases respectively. In most countries, there is a remarkable decline in both the incidence and mortality of gastric cancer over the past six decades. For instance gastric cancer was the commonest cause of cancer death in USA in 1930, but the annual mortality rate has dropped from 38 to 7/100,000 population and 28 to 4/100,000 for men and women respectively. In spite of these data, it remains a leading killer cancer, accounting for 2.5% of all cancer deaths in the USA and exceeding lung cancer as a cause of cancer death world wide.[5] Death rates from cancer exhibit a marked variation throughout the world, being highest amongst the Japanese, where death rates were three times higher than U.K values in 1985. Gastric carcinoma can be divided into two general histologic subtypes according to Lauren [102] (see table below),the intestinal subtype exhibiting a mean age of incidence of 55 years and a male to female ratio 2:1 and a diffuse type in slightly younger patients with mean age of 48 years and an approximately equal male to female ratio. The reduction in incidence of gastric cancer is related only to the intestinal type. Presently the incidences for intestinal and diffuse cancer approximate each other[5].

THE NIGERIAN EXPERIENCE

Age and Sex Incidence

Arigbabu [7] in Ile Ife, in his study of 57 patients between 25 and 76 years of age found a mean age of 53 years in his patients. He had the highest number of patients between 41 and 60 years of age. Arigbabu had no case of gastric malignancies between 0 and 20 years. He had 3(5.3% between 21 and 30 years old, 5(8.8% between 31 and 40 years, 10(17.5%0 patients between 41 and 50 years, 17 cases (29.8%) between 51d and 60 years, 14 cases (24.6%)

between 61 and 70 years and 8 cases (14%) between 71 and 80 years. The findings by Arigbabu showed a peak incidence in the sixth decade of life followed by patients in the seventh decade of life. Mabogunje [132] in Zaria studied 62 cases between ages 27 and 70 years. He found that the peak age incidence was between 40 and 49 years.

Almost 60% of his cases were between the ages of 40 and 59 years. This probably signifies that there is no significant variation between the pattern of occurrence for gastric carcinomas in South Western Nigeria and the North Central Nigeria.

Olurin et al[9] in studying 122 cases expressed an age range of 25-80 years. 10% of his cases were below 30 years of age while 57% were between 41-60 years. The oldest patient was 80 years old. The average age was 45.2 years as against that of our study, which was 53.5 years, but the peak incidence was between 40 and 50 years of age.[9] They saw just a case, a female between 71 and 80 year of age. Olurin et al found no cases above 80 years of age. The only significant variation in Olurin et al study series is the reduced mean age group. Elebute[8] in studying 86 cases had his youngest patient being 25 years and the oldest being 80 years. He did not characterize his cases further based on peak incidence. However, he found that most of his cases occurred between 40 and 59 years of age, followed by 60 and 70 years. He found no cases below 20 years of age. Very few cases were seen after the eighth decade of life in his study series. Again, our findings correlate well with Elebute's findings. Mabogunje[10] in Northern Nigeria had a mean age of 45.2 years. The peak age incidence was 40-49 year of age, while the mean age incidence was 47.5 years for intestinal types and 43.8 years for diffuse types of gastric carcinoma. This mean age is lower when compared to the mean age in his study suggests that his patients were relatively younger than our patients, perhaps by 5-10 years of age. Obekpa et al[11] working in the middle belt of Nigeria studied 50 cases. The age range was 24-70 years while the mean age was 51 years. [11] Edington's [103] work on gastric malignancies in Southern Nigeria founded a M:F ratio of 1.7:1In other studies such as was done by Elebute et al[8] in Ibadan, he found a M:F ratio of 2.6:1 Badoe[103] found a M:F ratio of 2:1 Mabogunje et al[10] (1978) working in Northern Nigeria found a M:F ratio of 1.6:1. A year later Mabogunje and Lawrie[132] found a slight reduction in the M:F ratio of 1.4:1 from their study in the same environment . The findings enumerated above show that there is a male predominance in the incidence of gastric malignancies, though significant male female ratio exists in different parts of the world.

Komolafe et al in studying 107 cases in Ile-Ife, South West, Nigeria which includes seventy-two (72) endoscopic biopsies and thirty-five (35) specimens gastrectomy specimens.

Topographical Distribution Of Gastric Malignancies

Elebute et al reported 74% of cases in the pylorus, 12% in the lesser curvature, 7% in the cardia, 6% of cases in the fundus and corpus while a case involved the whole of the stomach. Badoe[103] reported 64.3% in the pyloric antrum, 25% in the body, 5.4% in fundus, 3.6% in the lesser curvature and 1.7% in the cardia. Olurin et al 9 reported 65.5% of cases in the antrum, 23.8% in the lesser curvature, 2.4% at the greater curvature, 2.4% at the cardia, 3.3% at the fundus and 2.4% involving the whole of the stomach. Obekpa et al 11 reported 80% in the cardia, 12% in the antrum, the whole stomach was involved in 4% of cases while the unspecified involved was 4%. Mabogunje and Lawrie[132] reported 72% in antrum, 16% in the cardia, 10% in the corpus and 2% in the fundus. Arigbabu[7] reported 66% cases in the antrum, 19% in the fundus and 15% in the body. Our finding of a great majority of gastric malignancies occurring at the pyloric antrum is similar to findings seen in related studies done by the aforementioned authors, except Obekpa's finding of 80% in the cardia as against 12% in the antrum. This was clearly at variance with our findings and the findings of other researchers. Thus most malignancies of the stomach, of which carcinomas form a large bulk, occur more at gastric antrum. Komolafe et al[125] found the gastric antrum to be the site for 95.1% for their cases; 2.9% were found in the gastric cardia and 1.0% each was found in the corpus and in the fundus. The overall male to female ratio was 1.2:1 for all gastric malignancies and 1.1: 1 for carcinomas. This reflects a slight male predominance. Gastric malignancies were seen in virtually all age groups. The youngest patient was 7 years old while the oldest was 80 years old. The mean age was 53.5 years.

Distribution Of Histopathologic Subtypes

Elebute et al reported that all the cancers were adenocarcinomas. The degree of differentiation and histopathological subtypes were not specified. Most of our cases were adenocarcinomas. In this respect, our findings correlate with Elebute's. In Olurin's series, 32.8% were poorly differentiated adenocarcinomas, 21.3% were well differentiated, 19.7% were unspecified, 12.3% were mucin secreting carcinomas. Olurin's findings significantly differ from ours because most of his cases were poorly differentiated. It might be that many of his cases presented quite late and therefore with a worsening differentiation. Obekpa reported 88% adenocarcinomas, 6% as leiomyosarcomas, 4% as lymphomas and 2% as Kaposi's

sarcoma. Our findings have some similarity with Obekpa's except that there are more cases of sarcomas and lymphomas. Mabogunje and Lawson reported 75.64% of adenocarcinomas. 75% of the adenocarcinomas were well or moderately differentiated accounting for 56.73% of all the cases studied. A quarter of the adenocarcinomas were poorly differentiated that is 18.9%. Arigbabu found all cases to be adenocarcinomas. 73% were moderately and well differentiated adenocarcinomas. 27% were poorly differentiated carcinomas. Virtually every available local research has shown that adenocarcinomas are the commonest forms of gastric malignancies and that other histopathologic types such as sarcomas and lymphomas are infrequent compared with the adenocarcinomas. Komolafe et al
reported 95.3% of their cases as carcinomas. Three cases of sarcomas and two cases of lymphoma were seen. Of the carcinomas, well and moderately differentiated adenocarcinomas accounted for 52.0% of gastric carcinomas. Of these, tubular adenocarcinomas are more common as they accounted for 37.3% cases of carcinomas as against 14.7% cases of papillary adenocarcinomas found in this study. The mucinous and poorly differentiated carcinomas follow the well and moderately differentiated carcinomas, accounting for 19.6% cases each of gastric carcinomas. Signet ring carcinomas are the least common. They accounted for 8.8% cases of gastric carcinomas.
From the study by Komolafe et al [125], some premalignant conditions contributing to the oncogenesis were evaluated. This includes intestinal metaplasia, chronic gastritis, glandular atrophy and *Helicobacter pylori* infection. Only the carcinomas were associated with these premalignant conditions.
Intestinal metaplasia was seen in 16% of cases.[125]
Chronic gastritis was seen in 75% of cases. Glandular atrophy was seen in 36% of cases.[125]. Significant *Helicobacter pylori* infection was seen in 60% of cases. Fifty percent of the cases were seen between the 50-59 years of age.[125]

FACTORS IN GASTRIC ONCOGENESIS

The aetiology of gastric cancer is multi-factorial and it is believed that genetic familial, environmental as well as socio-economic factors may contribute Gastric carcinomas account for over 90% of gastric malignancies in different series. The major factors implicated in the oncogenesis of gastric cancers apply to the intestinal type of gastric carcinomas as the risk factors for the diffuse type are ill defined.[5] The factors are outlined below

Aetiology of Gastric Carcinoma[4,7-10]

1. Dietary factors
   (i) Malnutrition: - Gastric Cancer is commoner in areas with high incidence of malnutrition.
   (ii) Nitrates, nitrites and nitrosamines are present in certain food preservatives as well as smoked salted food.
   (iii) High NaCl salt intake causes suppression of parietal cells and induces atrophic gastritis
   (iv) Vitamin deficiencies: Vitamin C and E are antioxidants found in fresh fruits and vegetables and are known to inhibit intestinal metaplasia.Low intake leads to deficiency resulting in increased free radicals in the tissues.
   (v) Cigarette smoking and dust ingestion from various industrial processes can lead to irritation and metaplasia.
   (vi) Ethanol chronic consumption of alcohol acts by irritation and metaplasia.
   (vii) Aflatoxin ingestion
2. Helicobacter pylori infection. This has been associated with cancer of the corpus and distal stomach.[6-11]

? Colonization of the stomach mucosa, results in gastritis, atrophy and eventual metaplasia.
- ? Ammonia, other mutagenic chemicals also lead to neoplastic transformation of mucosa
- ? Infection results in infiltration by lymphocytes, neutrophils and macrophages leading to release of oxygen free radicals with induction of mutation in gastric epithelium.

The Role Of Helicobacter Pylori In The Pathogenesis Of Gastric Cancer.

Helicobacter pylori is a ubiquitous organism.[34,37,38,39] *H. pylori* infection is the most common gastrointestinal disease worldwide [34,40,41] Helicobacter pylori infection is present in 90% of gastric cancer including gastric lymphomas.[35] It is primarily found in the gastric antrum and also in the duodenum within areas of gastric metaplasia.[39] *Helicobacter pylori* is a sinusoidal gram negative spiral shaped bacteria measuring 2.5-3.5 micrometer long by 0.5-1.0 micrometer in diameter. It is motile, possesses 4-6 unipolar sheathed flagella with terminal bulbs.[37,40] H. pylori. is fastidious and slow growing. It requires an enriched selective media for culture. Growth is optimal at 37 C degrees centigrade under humidified microaerophilic conditions subserved by 10% carbon dioxide over a period of 4-6 days.[40] It produces large amounts of a powerful

urease which makes it well adapted to the lining mucous layer overlying the gastric epithelium, particularly at cell junctions [37,39,40] The urease protects it from the action of hydrochloric acid by using the acid resistant urease to convert physiological gastric urea to ammonia.[37,39] Thus a microclimate of less hostile pH is created.[39]

The strains of Helicobacter pylori are enormously diverse and they are known to mutate over decades in a single host and well as exchange genes with one another. [36] In developed countries, 10% of healthy individuals under 30 years have serologic evidence of infection is acquired at an earlier age in Africa than in developed countries. In all situations, the prevalence increases with age. In Africa and other third world countries, the infected from childhood.[5,35,37,40] In most developing countries, virtually 100% of individual are seropositive by early childhood. [40] Factors favouring the distribution of *H. pylori* in different populations include low socio-economic class , exposure to poor living conditions such as overcrowding and bed sharing, substandard hygiene levels and crude lifestyle habits in families.[37,40]

Genetic susceptibility to H. pylori in has been proposed. Male gender and polymorphism of the HLADQA gene have been shown to be associated with *H. pylori* infection.[35] *H. pylori* is associated with 80-90% of cases of chronic gastritis. The longer the chronicity, the more severe the gastritis such that there is eventual glandular atrophy, intestinal metaplasia and dysplasia. The risk of cancer is increased by 2-3 fold with chronic non atrophic antral predominant gastritis.[5,42] The risk of gastric cancer is up to 18 fold withy severe atrophy, pan atrophy and metaplasia.[42] Filipe reports on a study in Slovenia that while type I intestinal metaplasia (IM) does not carry a significantly increased risk, type II IM has twice the risk of type I and III IM has four and half times the risk of progressing to gastric cancer.[43] Intestinal metaplasia is associated more with intestinal type carcinoma.[44]

The pathogenesis of MALT lymphoma in the stomach is different. H. pylori infection induces chronic gastritis so that aggregates of lymphocytes or mucosal lymphoid follicles are formed. *H. Pylori* activates T cells which induces B cell proliferation. The risk of developing low grade MALT B cell lymphoma with H. pylori in the development of primary gastric mucosa associated lymphoid tissue (MALT) lymphoma is supported by studies by Cammarota et el which showed regression of primary gastric MALT lymphoma by eradication of Helicobacter pylori.[45] Wotherspon also reported that low grade MALT lymphoma regress while high grade lymphomas may be unresponsive.

3. Gastric Polyps, Pernicious anaemia and Menetrier's disease (hypertrophic gastropathy) are pre-malignant lesions.
4. Previous gastric surgery with drainage procedure as gastro-enterostomy or pyloroplasty: Chronic irritation by biliary reflux may result in metaplasia.
5. Chronic gastric ulcer, giant hypertrophy gastritis with chronic irritation.
6. Chronic atrophic gastritis and achlorhydia, pernicious anaemia .
7. Gastric intestinal metaplasia. Glandular mucosa is replaced by mucus containing glands akin to small intestine. This usually involves the distal part of the stomach with increased rate in neoplastic change.
8. Occupational factors: Mining as well as occupational exposure to rubber and asbestos has been implicated.
9. Host Risk Factors.

(i) Blood group A, family history gastric cancer as well as familial adenomatous polyposis.

(ii) Oncogenes. Many oncogenes have been implicated.

(iii) Advanced age - unstable cells

(iv) Male gender a high male preponderance has been reported in many studies.

MODE OF SPREAD

Gastric adenocarcinoma tends to spread more locally initially before any evidence of distant spread which is often uncommon. Nodal spread is not synonymous with distant metastases and spread varies between diffuse and intestinal types. The diffuse type spreads along the submucosal and serosal lymphatic plexuses and penetrate gastric wall at an early stage.

(i) Local spread: usually by direct extension to diaphragm, oesophagus, liver, spleen, pancreas and colon.

(ii) Lymphatic spread: This is to local and then distant nodes by permeation and embolization.

(iii) Haematogenous spread: This is to portal vein, liver, lung, bone and brain.

(iv) Peritoneal: This leads to ascites, Krukenberg's tumour and Sister Joseph's nodule.

(v) Transluminal spread to adjacent organs including the oesophagus and duodenum

CLASSIFICATION

Malignant tumours of the stomach may be outlined below on the basis of the specific tissue of cell of origin.[1, 50,105] This mode of classification essentially gives an overview of gastric malignancies.

1. Malignant Tumours Of Epithelial Origin
   a. Adenocarcinomas
      b. Adenosquamous carcinoma
      c. Squamous cell carcinoma
      d. Mucinous(mucoid) carcinoma
      e. Hepatoid adenocarcinoma
      f. Parietal gland carcinoma
      g. Tumours with endocrine differentiation: Carcinoid and atypical Carcinoid tumours.
      h. Poorly differentiated adenocarcinomas with lymphoid stroma (lymphoepithelioma like carcinoma)
      i. Paneth cell carcinoma
      j. Gastric collision tumour (Carcinoid and adenocarcinoma)
      k. Choriocarcinoma

2. Malignant Tumours Of Smooth Muscles
   l. Leiomyosarcoma
      m. Leiomyoblastom

3. Malignant Tumours Of Striated Muscle
4. Lymphoid Malignancies
   1. Non Hodgkin's lymphoma
   2. Hodgkin's lymphoma
   3. Plasmacytoma
5. Malignancies Of Vascular Origin
   1. Angiosarcoma
   2. Haemangiopericytoma
6. Other Malignant Mesenchymal Tumours
   1. Liposarcoma
   2. Malignant fibrous histiocytoma
   3. Alveolar soft part sarcoma
   4. Inflammatory Fibrosarcoma
   5. Kaposi's sarcoma
7. Malignant Tumours Of Neural Origin
   1. Plexosarcoma
   2. Neurogenic sarcoma
   3. Ganglioneuroblastoma.
8. Malignant Mixed Tumours
   1. Malignant teratoma
   2. Carcinosarcoma (Sarcomatoid carcinoma)
9. Secondary (Metastatic Tumours)

An epidemiological classification of gastric cancer has also been developed. This classification divides it to intestinal and diffuse types of gastric cancer with distinct epidemiological variations.

Table 1: Laurens' epidemiological classification of gastric cancer

INTESTINAL	DIFFUSE
(a) More common in endemic areas	(a) More common in low prevalence areas
(b) Associated with gastric atrophy	(b) Associated with Blood group A
(c) Glandular formation. Intestinal Metaplasia resembling colon cancer with nodular, polypoid or ulcerated lesions	(c) Poorly differented signed ring cells small groups or cord of cells with cytoplasmic mucin.
(d) Males > Females	(d) Females > Males
(e) Haematogenous spread	(e) Lymphatic spread
(f) Increasing incidence with age	(f) More in younger age group.

PATHOGENESIS OF GASTRIC CANCER.

A number of genetic changes are involved in the development of gastric cancer.

(i) Error in DNA replication: This result in microsatellite instability (MSI). This error may occur as a result of acquired mutation in the tumour itself or may be associated with the hereditary non-polyposis colorectal cancer syndrome (HNPCC) or the lynch syndrome.

(ii) Genetic mutation leading to inactivation of p53- a tumour suppressor gene

(iii) Mutation or loss of heterozygosity in the APC gene (responsible for familial polyposis) or -catenin gene

(iv) Mutation in the E-cadherin molecule

(v) Over expression of certain growth factors receptors (*c-met*, *k-sam, C-Erb*) or growth factors (transforming growth factor alpha, epidermal growth factor (EGF), vascular endothelial growth factor (VGEF) have been implicated.

(vi) Loss of heterozgosity of *bel2* gene, an inhibitor of apoptosis in intestinal type gastric cancer.

STAGING OF GASTRIC CANCER

1. Early gastric cancer: This is confined or limited to mucosa or submucosal layers with or without Lymph mode involvement.[11] Adequate surgery in early gastric cancer is associated with more than 90% 5-year survival in Japan Early gastric cancer accounts for 10% of all resected cases of gastric adenocarcinoma in Britain. In Nigeria, most patients present late perhaps due to late onset of the ominous signs such as haematemesis and epigastric mass and lack of a well established screening method.

In North America, Europe and Africa, many dyspeptic patients are kept back by primary or secondary physicians who place on anti-secretory agents or antibiotic. In Nigeria, many patients patronize quack drug peddlers for a considerable period before presenting to any hospital. Also many endoscopists in both developed and underdeveloped countries are unfamiliar with endoscopic appearance of early gastric cancer and may therefore miss the diagnosis at the early stage.

Early gastric cancer has been classified by the Japanese into three types, namely:Type I: (Protruded), Type at or superficial), Type III: (Excavated)[11].

II: (flat or superficial), Type III: (Excavated)[11].
2. Advanced gastric cancer. These are tumours deeper than submucosa, and usually precludes surgical cure. These may be classified according to Borrmann's morphological description of the gastric lesion namely:
Borrmann I: Polypoid, fungating type.
II: Cancer ulcer without infiltration of surrounding mucosa (excavating crater cancer)
III: Carcinomatous ulcer with infiltration of surrounding mucosa.
(IV) Diffuse infiltrating cancer with thickening of wall, local or generalized (Linnitis plastica)

AJCC & UICC staging of gastric cancer[12]
AJCC = American Joint Committee on Cancer. In AJCC, staging is ultimately based on the histology of the resected specimen.
UICC = International Union against cancer
T = Tumour depth; N= nodal status, M = distant metastasis
T_1= Tumour extends to Lamina Propria or submucosa
T_2= Tumour extends to muscularis propria
T_3= Tumour extends to serosa layer
T_4= Tumour involves adjacent structure
No = No lymph node involvement
N1= Less than 7 lymph node involvement.
N2 = 7-15 lymph node involvement
N3 = >15 lymph node involvement
MO = No metastasis
M1 = Metastasis present
In AJCC system, absolute number of positive lymph node is counted irrespective of the location in the resected specimen. However, the Japanese Research Society for gastric cancer (JRSGA) uses lymph node stations rather than absolute numbers i.e.
N_1 Invasion of perigastric node within 3cm of the primary tumor
N_2 Invasion of nodes > 3cm from the primary tumor (extragastric)
N_3 Retropancreatic, hepatoduodenal, portal and mesenteric nodes.
N_4 Paraoartic and mesocolic nodes.
In AJCC, N_3 + N_4 = distant metastasis.

CLINICAL FEATURES OF GASTRIC MALIGNANCY
In early stage, the symptoms may be subtle with indigestion, flatulence or dyspepsia, and may be difficult to distinguish from benign peptic ulcer or gastritis.

Advanced cases tend to be obvious and associated with epigastric pain (relieved by vomiting), nausea, progressive early satiety or easy fullness (by space occupying lesion especially prominent in diffused infiltration or Linitus plastica).

There may be abdominal bloating, distention, indigestion, bleeding (haematemesis/melaena), retrosternal pain and dysphagia especially if proximal stomach and lower oesophagus is involved. Other features include back pain (local penetration), weight loss, and iron deficiency anaemia with fatigue, epigastric mass (in locally advanced), gastric outlet obstruction, malnutrition and metabolic alkalosis if the antrum is involved. There may be features of distant metastases such as jaundice (from liver spread or compression of bite duct by enlarged lymph nodes), hepatomegaly, ascites and spurious diarrhoea (peritoneal or pelvic spread) and intestinal obstruction from deposits on the bowel.

Also, Virchow's (Supraclavicular) nodes and Sister Mary Joseph's umbilical nodule from lymphatic spread may be seen. Rectal examination may reveal Blummer's shelf or Krukenberg's tumour from pelvic deposits.[13] Non Metastatic effects of the maligriancy may include migratory thrombophlebitis (Troussaeus signs), acanthosis nigricans, and multiple seborrhoic keratosis.

INVESTIGATION OF SUSPECTED GASTRIC CANCER

Aims of investigation include confirmation of diagnosis, staging of the disease and general assessment for complications and treatment.
? Upper gastrointestinal endoscopy (UGIE) is the gold standard of diagnosis. It allows for visual diagnosis of the tumour, its location and gross morphology. Biopsies for histological diagnosis can also be taken at the same time. In many centers, endoscopic ultrasonography is done to assess the depth of the tumour.
? Barium Meal and follow through may show a filling defect in the stomach or an irregular ulcer crater.
? Abdomino-pelvic ultrasound will show any hepatomegaly, ascites, or intrabdominal masses.
? CT-Scan, MRI for abdominal masses and retroperitoneal lymph nodes. Helical CT-Scan may help predict lymph node metastases
? Laparoscopy and laparoscopic ultrasonography for small metastases within the liver or minimal ascites.
? Haematological investigations:
o Full blood count: PCV, White Cell Count and Differentials, Platelet Count.
o Blood Group
? Biochemical investigations
o Serum electrolytes, urea and creatinine.
o Liver function test
o Tumour markers like carcinoembryonic antigen (CEA) and carbohydrate antigen (CA 19-9). The levels correlate with degree of tumour invasion lymphatic spread

SURGICAL TREATMENT FOR GASTRIC CANCER

These includes

a. Minimal access procedures: appropriate for early gastric.[15-17]

-endoluminal intragastric resection of gastric cancer

-laparoscopic intragastric surgical resection

Endoscopic placement of self expanding endoluminal stents may be a useful palliative measure in advanced cases.[18,19]

b. Open curative procedures: in early and late cases.[20,21]

-Total gastrectomy: commonly done for proximal gastric tumours

-Proximal subtotal (partial) gastrectomy; for proximal tumors,

-Distal subtotal (partial) gastrectomy, for distal gastric tumours.

In each of these open procedures, given the propensity for submucosal spread of the tumour, margins of 5-6cm from the macroscopic edge, confirmed also by frozen section analysis, should be taken.[22,23] Proximal and distal anastomoses are also established along with regional lymph node dissection. En block distal pancreatectomy and splenectomy may be done if necessary.[24]

c. Palliative procedures. These are indicated in advanced cases to relieve symptoms such as outlet obstruction or undue pain. Bypass procedures such as gastrojejunostomy and limited resection may be done.

CHEMOTHERAPY FOR GASTRIC CANCER[25]

Surgery remains the only proven option for localized gastric cancer. However, long-term survival rates after surgery alone remains suboptimum for all but the earliest state (T_1 N_0 M_0) Neoadjuvant therapy is given before an anticipated definitive surgical procedure, while adjuvant is given after a potentially curative resection to reduce or eliminate the chance of recurrence of cancer at local or distant sites. Adjuvant immunotherapy and radiotherapy are also used.

Examples of chemotherapeutic agents used include 5-Fluorouracil, Folinic acid, Epirubicin, Cisplatin, Mitomycin, FAM, MECCNU etc.

Neoadjuvant Therapy

The biology of gastric tumours predisposes patients to micrometastatic disease at the time of presentation. Thus, neoadjuvant therapies expose these cells to anticancer drugs when the cell growth fraction is high and the tumour volume is relatively low. Early initiation of systemic therapy will therefore eliminate these micrometastases. This may enable the physician to assess the tumour response to chemotherapy even before surgery. This may be of prognostic value as it has been shown that patients who responded to neoadjuvant therapy had a higher 5 year survival rate than non-responders.[26]

Preoperative radiotherapy has also been found to improve survival in some patients.[27]

Intraperitoneal chemotherapy: ongoing researches suggest that post gastric resection, intraperitoneal injection of anticancer drugs could improve patient survival and prevent relapse from peritoneal cavity especially in tumours with gross serosal invasion.[28-30] Continuous hyperthermic peritoneal perfusion has also been found to increase the 5yrs survival rate in Japan[31,32]

Chemo-radiotherapy: This involves resection followed by post operative chemotherapy (5-FU +Folinic acid) then followed by external beam irradiation. This has been shown to improve patient survival. It is especially important when complete resection is not feasible.[33,34]

CONCLUSION

Incidence of gastric cancer varies among the different regions of the world with carcinomas accounting for the highest number of gastric malignancies in the world. They are associated with increasing age. The most common location of malignant conditions of the stomach is the gastric antrum. The most important factor implicated in the development of gastric carcinomas is *Helicobacter pylori* infection. Early presentation and complete surgical resection may offer cure while chemotherapy and radiotherapy along with surgery offers little hope in advanced disease.

(Please Contact the Editor-in-Chief of IFEMED for the references to this article)