



Clinico-Endoscopic and Histopathological Profile of Gastric Cancer Patients in Southern Kashmir, India

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Abstract

Aim: To determine the clinical, endoscopic and histopathological profile of gastric cancer patients of a high-risk region of southern Kashmir, India.

Methods: This retrospective multi-centric study of 18 years (2001-2019) was carried out at three different government district hospitals of southern Kashmir located at Anantnag, Shopian, and Kulgam and comprised 1,433 Gastric Cancer (GC) patients with 1,025 males and 408 females who were in the age group of 38 to 80 years. These cancers were diagnosed by performing Esophagogastroduodenoscopy (EGD). Six to eight tissue bits were taken from gastric cancer growths and subjected to histopathological examination for confirmation of endoscopic diagnosis.

Results: Out of 1,433 gastric cancer patients there were 1,025 (72%) males and 408 (28%) females. The major clinical presentation in these patients was anorexia (69.08%), anemia (62.10%), and postprandial fullness (48.7%). Forty-five patients presented with metastasis. Lesser curvature was the most common site for gastric cancers (68.1%) followed by pylorus (23.72%). *Helicobacter pylori* (*H. pylori*) was found in 35.38% of gastric cancers. Endoscopically majority of the gastric cancers were polypoid type (63.56%) followed by ulcerative type (33.44%). Histopathologically majority of the gastric cancers were intestinal type of adenocarcinomas.

Conclusion: Kashmir Valley especially its Southern part is emerging as a highly prevalent gastric cancer region. These cancers have peculiar endoscopic and histopathological patterns. Although the exact etiopathology of these cancers and their high prevalence is largely unknown yet the unique personal and dietary habits, socioeconomic conditions, genetic characteristics, and other unknown factors have an important role in the pathogenesis of these cancers.

Keywords: Adenocarcinoma; Gastric cancer; *H pylori*; Histopathology

Introduction

Upper Gastrointestinal Tract (GIT) cancers are the most common GIT cancers throughout the world.

Stomach cancer is the 5th most common cancer and the 3rd most deadly cancer after lung and colorectal cancers. About 1 million gastric cancers are diagnosed per year globally. Gastric cancer is one of the most behaviorally influenced cancers and thus preventable cancer. Some regions like China, Japan, Iran, Russia, South Korea and Chile have a higher incidence of gastric cancers. Gastric cancer is more common in males than in females. The cumulative risk of developing gastric cancer from birth to the age of 74 years is 1.87% in males and 0.79% in females worldwide. The various risk factors for gastric cancer are gender (more common in males than females), age (older age), ethnicity, geography, *H. Pylori* infection, obesity, diet (increased salt consumption, smoked foods, salted fish, pickled vegetables) and alcoholism besides previous gastric surgery, pernicious anemia, radiation, chronic atrophic gastritis, and some hereditary factors [1-7].

In India, gastric cancer is the third most common cancer but there is a marked difference in the incidence of GIT cancers between North and South India because of diverse food habits differences between the various regions in the country. There is higher incidence of gastric cancer in Karnataka, Tamil Nadu, Kerala, and Assam [8,9].

Kashmir Valley is a high-risk area for GCs (3 to 6 times higher incidence than rest of the India).

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Although the reasons for the high prevalence of GCs in Kashmir are largely unknown, yet the unique personal, dietary, economic and social habits of the common population have a definite role in the pathogenesis of this disease. Various genetic factors, environmental factors, and some still unknown etiological factors also have a role in the pathogenesis of this disease. The high prevalence of *H. pylori*-associated chronic gastritis in a normal healthy population and peptic ulcer disease ulcer patients may also be a predisposing cause [10-13].

This is the first large retrospective multicentric study from the southern part of the Kashmir Valley undertaken to determine the clinical, endoscopic, and histopathological profile of gastric cancer patients. Furthermore, this study highlights some possible etiopathological causes of Gastric cancers in the region [14].

Methods

Kashmir Valley lies in the northernmost region of India between latitudes 33°20'-34°40' N and longitude 73°40'-75°40' E characterized by a temperate climate [15]. The altitude of the valley ranges from 1073 m to 5236 m above sea level (the other two regions of the state are Jammu and Ladakh). The total population of the valley is 6.9 million and the Southern districts of Kashmir (Anantnag, Kulgam, Shopian, and Pulwama) comprise 47.94% of the area and 33.71% of the total population of Kashmir with the majority of the population being Muslims (<https://censusindia.gov.in/>) (Figure 1). This study was conducted at three government district hospitals of southern Kashmir - Anantnag, Kulgam, and Shopian.

All the gastric cancers diagnosed on endoscopy and confirmed by histopathology at these district hospitals were included in this study. Gastroesophageal cancers with involvement of proximal 2/3rd of lesser curvature or involvement of cardia or fundus were taken as gastric cancers. The patient details like presenting symptoms, age, sex, residence, socioeconomic status, dietary habits, ultrasonography findings, endoscopic findings, and histopathological reports were analyzed from the records maintained at the endoscopic sections of these hospitals. Contrast-Enhanced Computed Tomography (CECT) abdomen/chest wherever available was also recorded.

Kashmiris are predominantly rice eaters, and non-vegetarians (consuming large amounts of mutton, beef, chicken, and fish) besides various vegetables, pulses, and cereals. They are mostly non-alcoholic but a large number of the population is smoking (cigarettes and hookah). Snuff is also used by a significant number of Kashmiris (especially in rural areas). Fruits are also consumed in large quantities by the inhabitants. Traditionally, people used to consume dried and pickled vegetables, sun-dried and smoked fish, and mixed spice cake (Wari) especially during winter (when it used to snow heavily and all the roads used to get closed for weeks). However, the consumption of these food items has markedly decreased in recent times.

The main source of income for the people of Kashmir is agriculture and horticulture. The application of various toxic chemicals including fertilizers, insecticides, fungicides, and rodenticides in these fields has markedly increased in recent times for better crop production and protection [16].

Due to adverse climatic conditions with 3 to 4 months of the winter season, only one agricultural crop production is possible in a calendar year. In Kandi areas (i.e., mountainous areas with rocky and non-fertile soil having hydrological problems) only maize is grown once a year which leads to scarcity of food complicated by lesser avenues of livelihood in these areas.

Results

This multi-centric retrospective study comprised 1,433 gastric cancer patients with 1,025 males (71.52%) and 408 females (28.48%). The other characteristic of these patients is shown in Table 1 and Figure 2, 3. One-third of these patients were smokers (both hookah and/or cigarettes) whereas two-third of these patients belonged to low socio-economic groups (Kuppu Swami socioeconomic class IV and V) [17].

The major clinical presentation of these gastric cancer patients was loss of appetite (anorexia) observed in 990 patients (69.08%) followed by anemia in 890 patients (62.10%) and post prandial distension in 697 patients (48.70%). Epigastric pain was also seen in 697 patients. The other presenting symptoms of these gastric cancer patients are shown in Table 2. Forty-five patients had metastatic lesions in the liver, lungs, bones, or lymph nodes (Virchow's nodes) who on subsequent endoscopy had Gastric cancers. Many patients had more than one presenting clinical feature.

Endoscopically majority of the growths were polypoid growths (63.56%) followed by ulcerative type growths (33.44%). 88.86% (886 patients) of lesser curvature growths were ulcerative friable growths as per Bormann's classification [18] (Figure 4).

Anatomically majority of the gastric cancers were seen along the

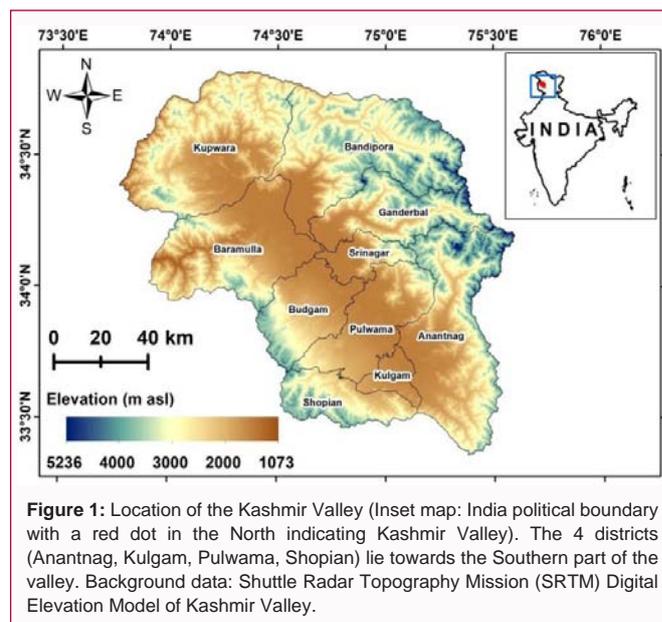


Figure 1: Location of the Kashmir Valley (Inset map: India political boundary with a red dot in the North indicating Kashmir Valley). The 4 districts (Anantnag, Kulgam, Pulwama, Shopian) lie towards the Southern part of the valley. Background data: Shuttle Radar Topography Mission (SRTM) Digital Elevation Model of Kashmir Valley.

Table 1: Characteristics of the study patients (N=1433).

Mean age	30-80 years
Males	1025 (71.53%)
Females	408 (28.47%)
Male: female	2.5:1
Anantnag District	701 (48.91%)
Kulgam District	424 (29.58%)
Shopian District	236 (16.46%)
Pulwama District	39 (2.27%)
Others neighboring districts	33 (2.30%)
Smokers	943 (65.80%)
Low socioeconomic condition	968 (67.55%)

Table 2: Clinical features of patients* (presenting symptoms) (N=1433).

Symptoms	GC (N=1433)
Loss of appetite	990 (69.08%)
Dysphagia	85 (5.93%)
Postprandial Distention	697 (48.70)
Epigastric Pain	697 (48.70 %)
Recurrent Vomiting	323 (22.54%)
GI Bleeding (Malena/hematemesis)	193 (13.46%)
Anemia	890 (62.10%)
Metastasis (Lungs/liver/bone/Virchow's nodes)	50 (3.49%)

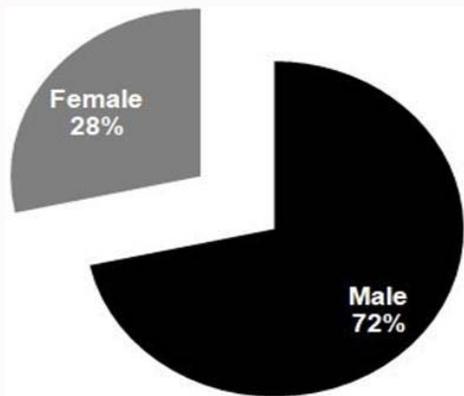


Figure 2: Gender composition of GC patients.

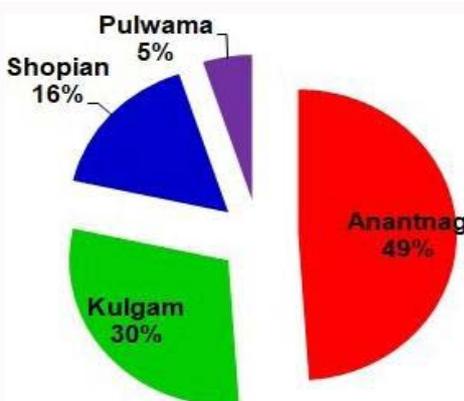


Figure 3: District-wise distribution of gastric cancer patients.

lesser curvature followed by pyloric growths (Figure 5).

Histopathologically majority of the gastric cancers were intestinal type followed by well-differentiated adenocarcinoma as shown in Figure 6.

Discussion

Gastric and esophageal cancers are the most common gastrointestinal cancers worldwide. There is a wide geographical variation in its prevalence from continent to continent and from region to region within a country. Japan, Iran, Russia, and China have a higher prevalence of these cancers [1-3,19]. Gastric cancer is the third most common cancer amongst Indian men and women. Although the etiopathogenesis of gastric cancer is multi-factorial in nature yet dietary habits have an important role in all GIT cancers. Since India is a country of people having diverse dietary habits from

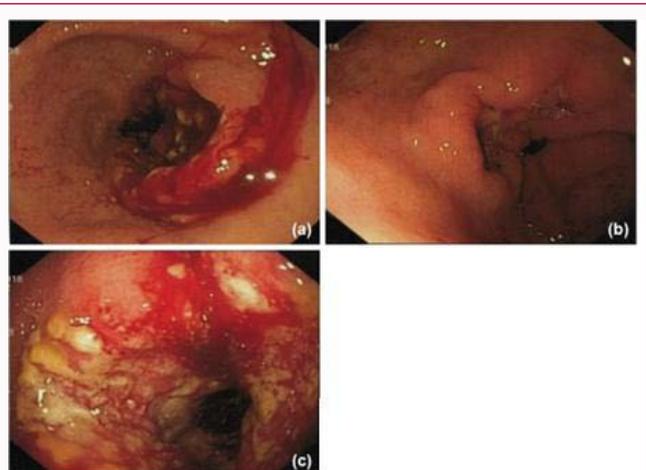


Figure 4: (a) Pyloric growth, (b) Malignant gastric ulcer, (c) Ulcerative growth.

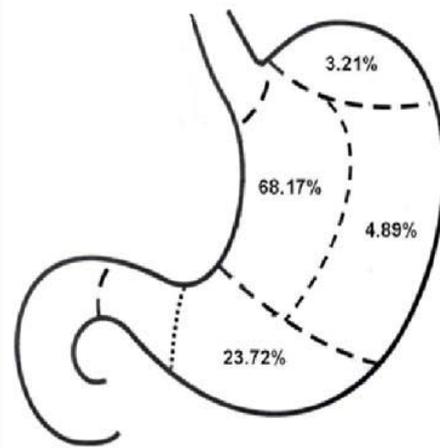


Figure 5: Anatomical distribution of Gastric cancers in study group.

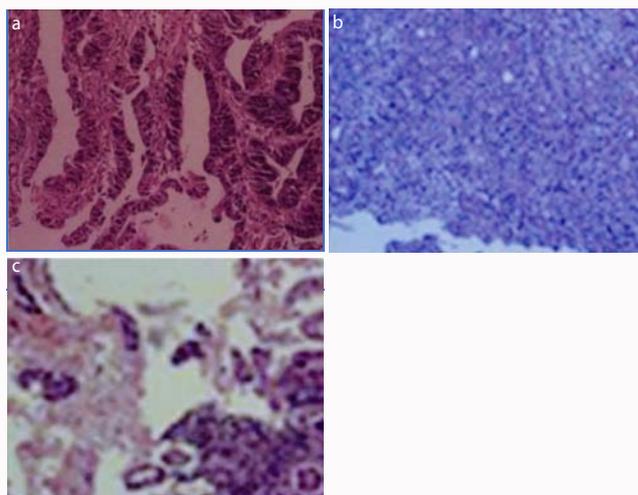


Figure 6: Histopathological examination of the biopsy tissue showing (a) Low-grade adenocarcinoma, (b) Intestinal-type adenocarcinoma, and (c) Well-differentiated adenocarcinoma.

North to South and East to West, the incidence and prevalence of GCs vary from region to region e.g., Maharashtra, Karnataka, Tamil Nadu, Kerala, and Assam have a higher prevalence of these cancers

than other states of India [8,20,21].

Kashmir valley has a 3 to 6 times higher incidence of Gastric cancers than Karnataka, Tamil Nadu, or Maharashtra [20,22,23]. The pattern of prevalence, incidence, and histopathology of GCs in Kashmir is similar to Iran [24]. Kashmir is also called Iran-e-Saghir (miniature Iran) because there are a lot of social, cultural, religious, dietary habits, and environmental similarities between the two regions. These include consumption of salt-tea, spicy food intake, high rice consumption, hot food intake, hot beverages and foods, sun-dried fish, smoked fish, and high-calorie intake of non-vegetarian food (Wazwan). Many studies have shown the importance of these dietary habits in the etiopathogenesis of gut cancers because of the higher concentrations of nitrosamines and other well-known carcinogens [13,24-26].

In contrast to the previous studies, our study found the prevalence of gastric cancers more common in lesser curvature than in the pyloric region. Similar findings from Iran by Abdi-Rad et al. [24] suggest an increase in the prevalence of upper and middle third of stomach cancers in their region. Though the actual reason for this is unknown one of the hypotheses may be that hot beverages and other hot food items consumed by the inhabitants cause mucosal injuries at the GE junction and cardia. Additionally, the high salt content present in beverages and foods increases the degree of inflammation. This chronic inflammatory mucosa when exposed to carcinogens initiates the process of mutagenesis which leads to dysplasia, metaplasia, and ultimately to anaplasia [13,25-28]. The other reason could be a higher incidence of chronic esophagitis (74.7%) and dysplasia (7.5%) amongst the Kashmiri population [13]. Furthermore, being close to the Asian cancer belt (which extends from the southern shore of the Caspian Sea in Iran through Soviet Union, Central Asia, and Mongolia to northern China), the epidemiological risk factors may be the same for Kashmir as well.

The consumption of the above-mentioned foods has markedly decreased during the last four decades and that of fresh vegetables, salads, and fruits has markedly increased throughout the world including the Kashmir region but the prevalence of gastric cancers has not shown any decline. The reason could be the scarcity of natural food products and food adulteration [29,30]. The fruits and vegetables are ripened and grown by using various growth-promoting chemicals which in turn may have an additional carcinogenic effect by promoting apoptosis due to nucleic acid damage. The use of chemicals for promoting the growth and development of various poultry products may also have a carcinogenic effect in human beings [31].

H. pylori infection-associated antral gastritis has been found in 90% of peptic ulcer patients and 87.5% of the healthy population. It is strongly associated with intestinal metaplasia of the stomach and could be another factor responsible for the high prevalence of gastric cancer in Kashmir [32-36].

Two-third of our gastric cancer patients were smokers. Smoking has been reported as an important behavioral risk factor for gastric cancer by many studies. Smoking increases the risk of GCs by about 1.5-fold and is higher in men. Smoking is strongly associated with GCs of cardia than non-cardia. Smoking delivers multiple carcinogens to the body directly and also acts synergistically with cagA- positive *H. pylori* infection [37].

The quality and quantity of food consumed is a very important

factors as most of the patients in our study were from the Kandi belt where both the quality and quantity of food are always compromised because of low socioeconomic status. Low socioeconomic status has been found as an additional important etiological factor for the high prevalence of GC throughout the world [8,36]. Inadequate food leads to the deficiency of various micronutrients, macronutrients, and trace elements which along with some genetic and environmental factors may lead to the development of GIT cancers [8-10,22,25,26].

Gastric Cancers are thought to be the disease of the elderly population with a majority of patients being more than 60 years [23], but in this study, an appreciable percentage of patients (42.23%) were middle aged (40 to 50 years). The actual reason for this is unknown but could be the earlier and prolonged involvement of the population to various carcinogens in agriculture and horticulture sectors.

Furthermore, our study found the proportion of involvement of the female gender higher than reported by various global studies. The reason for this higher prevalence among females is unknown and could be attributed to the more active involvement of female folk and the younger generation in day-to-day activities in agriculture, horticulture, and sericulture-based occupation. This makes them more vulnerable to the development of cancers and that too at early age.

The major histological type of GC was adenocarcinoma-intestinal type and Borrmann classification type III (Polypoid and ulcerative growths). Similar findings have been reported by other studies [38-40]. Because of the ignorance, carelessness, and phobia of invasive endoscopic procedures, the majority of the patients were diagnosed with an advanced stage of disease (stage III). Similar observations have been reported from other global studies [20]. Also, the reason for the advanced stage of gastric cancer presentation could be the irrational use of PPI/H2 blockers that suppress the symptoms and signs of the disease.

Conclusion

Upper GIT cancers are the most common GIT cancers throughout the world. Kashmir is a highly endemic region of GCs owing to the unique food habits, low socioeconomic status along with various environmental/genetic factors, and some still unknown reasons. This first large multi-centric retrospective study from Southern Kashmir having a high prevalence of gastric cancers have found a younger age involvement and the lesser difference between male and females. The major site of gastric cancer has been lesser curvature and fundus rather than the pylorus. Since the improvement of socioeconomic conditions has not changed the prevalence of the disease, there is a need for primordial prevention along with the need for early genetic evaluation. The most feasible method to reduce gastric cancers is to change dietary habits and the need to adopt a healthy lifestyle among the population. This study also suggests the need for precisely quantifying the role of various etiological factors implicated in the pathogenesis of gastric cancers.

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