

High Incidence of Gastric Cancer in Kargil Ladakh

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Abstract: *The Gastric Cancer rates shows marked geographical variation in the world. Although India has a low incidence of gastric cancer, population and hospital based cancer registries of certain regions of India 2012-2014 shows stomach cancer as among the five leading cancers in India. This descriptive study was undertaken for the first time in Kargil Ladakh region, over a period of 10 years (April 2009 to April 2019), to analyze the incidence of gastric cancer in the region. Gastric Cancer accounted for 42.12% of all the cancers in the region. The age -standardised incidence rate of gastric cancer in Kargil Ladakh was 19.03/100 000 per year. As majority of the population does not consume alcohol and H. pylori strains from Ladakh are genetically distinct and possibly less virulent, other prevalent habits and risk factors of 187 gastric cancer patients were studied in detail.*

Keywords: Gastric Cancer, Dietary habits, Risk Factors, Kargil Ladakh

1. Introduction

Gastric Cancer is the 5th most common cancer and the 3rd most common cause of cancer deaths worldwide. There were over 1 million new cases of gastric cancer in 2018, with an estimated 783,000 deaths in 2018 [1]. The Gastric cancer rates shows marked geographical variations, with high-risk areas in South Korea, Mongolia, Japan, China, Eastern Europe and certain countries in Latin America. Low-risk areas are North America, India, Philippines, most countries in Africa, some Western European countries and Australia [2]. Globally, the highest incidence of gastric cancer was seen in South Korea in 2018, followed by Mongolia, with almost 60/100,000 new cases annually for males, 25/100,000 for females and the age-standardised rate of 39.6/100,000 population in South Korea.

The variations in gastric cancer incidence seen in India have been quite marked. The data obtained from the National Cancer Registry Programme 2012-2014 indicates that gastric cancer is a leading problem in North-eastern and southern states of India. The SKIMS-Srinagar Hospital based Cancer Registry 2012-2014 of neighboring Kashmir region of Jammu and Kashmir also shows the gastric cancer as the most common cancer of the region [3]. Multiple studies from Kashmir region have shown high rate of gastric cancer in Kashmir population compared to other parts of the country. Even within the state of Jammu and Kashmir various districts showed varying rates [4]. Different dietary and peculiar life style habits of the natives have been implicated for such variations. Such remarkable differences called for special studies.

The stomach is lined with a mucous membrane composed of columnar epithelial cells and glands. These cells are prone to inflammation, known as gastritis, which can lead to peptic ulcers, and ultimately, gastric cancers. Gastric adenocarcinomas (95% of gastric cancer) are primarily classified as cardiac and non-cardiac based on their anatomical site. Cancers of gastric Cardia arise in the region adjoining the esophago-gastric junction and thus share epidemiological characteristics with esophageal adenocarcinoma. Cardia cancers are usually associated with gastroesophageal reflux disease (GERD). There is an increase in the incidence of cardiac gastric cancer in the past

decades, especially in the developed world. Non cardiac cancer, also known as distal stomach cancer, is more common, and is brought about by chronic gastritis, caused by a variety of environmental factors. Histologically the two main types of gastric cancer are the Diffuse (undifferentiated) type especially seen in young people and females and the more common Intestinal (well differentiated) type especially seen among older males and carrying better prognosis [5].

Kargil Ladakh is a land-locked area of highest plateau in the state of Jammu and Kashmir at a very high altitude ranging from 8780 ft. to 23,000 ft., in the Trans-Himalayan region. Total area of Kargil Ladakh is 14,086 km² with a population of 1, 40,802 and having Zanskar as its sub-division. The population consists of 77% Muslims and 15% Buddhists and having unique cultural practices, dietary habits and life-styles.

In the historical prospective, the first documented cases of cancer was reported in 1868 by Caley H. He presented the incidence of diseases in the Ladakh region at that time from July-August 1867 and documented 61 cases of dyspepsia, 6 cases of carcinoma, 1 case of hepatitis, besides 24 other ailments diagnosed by him at that time [6]. Though he has not mentioned the organ affected, probably stomach could be the site as he reported Dyspepsia as the most common disease. He highlighted the importance of socio-economic and cultural practices in occurrence of disease in the middle of the nineteenth century. More and more cases of cancer of various organs are being diagnosed during the last 3 decades by doctors in Ladakh due to improved health care delivery system in the region.

It has been suggested from clinical experience that gastric cancer is very prevalent in Kargil Ladakh. Due to non-existence of Population or Hospital based cancer registry or any other cancer related study, no previous data of magnitude of this dreaded disease was available in Ladakh. The present study was conducted for the first time to determine the incidence of gastric cancer and an attempt was made to study profile of gastric cancer patients of this geographic region.

2. Methods

The present descriptive epidemiological study was carried out at District Hospital Kargil which is the only Multi-specialty hospital of the region. There is no any other alternative private hospital. As Kargil Ladakh remains cut-off from the rest of the state and country for 6 months in the harsh winter, district hospital Kargil serves as the first Sentinel multi-specialty hospital for the entire population, for initial diagnosis, treatment, referral to tertiary centres outside the region, follow-up of the patients after their management at tertiary centres, Chemotherapy of few selected cancer patient and palliative treatment and care of advanced cancer patients. Hence data collection from District Hospital Kargil represents the magnitude and pattern of Gastric cancer of the closed community of whole District. However it cannot be ruled out that still a few patients might have been missed out being a single centre study.

The data was collected from gastric cancer patients attending district hospital Kargil after the initial diagnosis by clinical examination, Upper G.I endoscopy, C.T scan findings and Histopathological Reports. The data collections were started from April 2009 up to April 2019(Figure 1) from patients diagnosed with Gastric cancer in the hospital. Patients who were suspected of cancer and where tissue diagnosis was not made initially, were followed-up after they were referred to attend super-specialty care outside the region and their tissue diagnosis were recorded latter on. In few cases, however, additional endoscopic and Histopathological proof of cancer were not required as the diagnosis was obvious from clinical or radiological studies and patients were in advanced stage

needing only palliative care or where attendants were reluctant to take patient to tertiary hospital in view of advanced stage of cancer and financial constrains. Details of the patient profile, demographic informations, life-style and dietary habits were recorded in detail using a pre-tested semi-structured questionnaire, especially amount of consumption of traditional salted tea per day, frequency of intake of fresh fruits per week and amount of intake of meat per week on a predefined proforma. Their habit of smoking was also recorded in detail. Their sign and symptoms, details of diagnosis and treatment modalities and staging were recorded in detail. Follow-up of the patients were done for recording the progress of disease, treatment, follow-up investigations and palliative care, in the hospital wards. All the informations were then pooled and processed regularly, using Microsoft Excel and analyzed and presented in the form of tables and figures. Every attempt was made to avoid duplication of data.

The age standardised/ adjusted incidence rate (ASIR) is the rate that would have occurred if the observed age specific rate (ASR) had operated in a standard world population age structure. The number of individuals in each age group (five-year age group) in a standard world population was multiplied by the corresponding incidence rate observed to obtain the number of cases that would have been expected to occur in one year in a standard world population (U.S 2000 Standard Population). The expected numbers were added and the sum obtained was divided by the total number of individuals in the standard population to give the age standardised/ adjusted incidence rate.

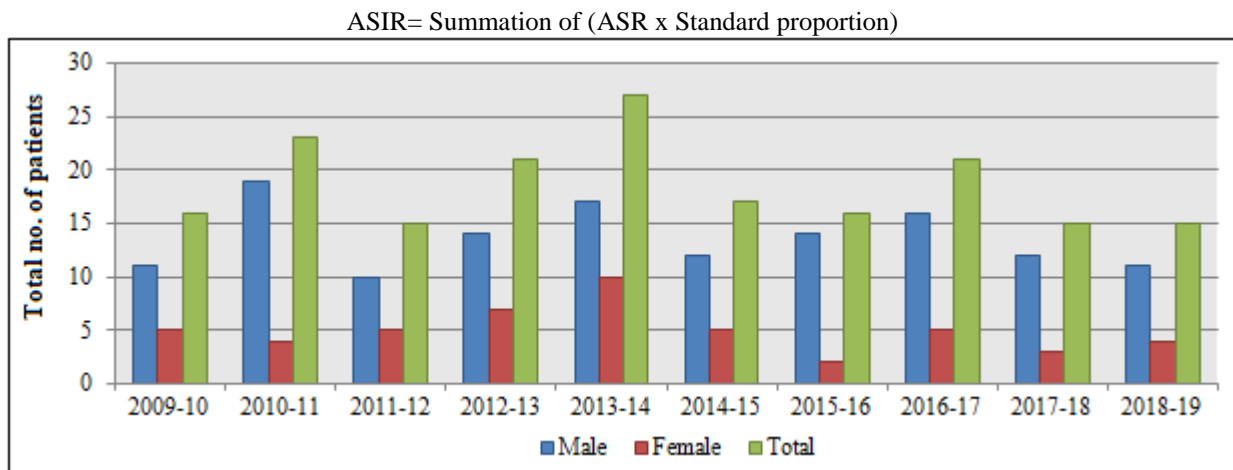


Figure 1: Showing yearly distribution of gastric cancer patients over 10 years.

3. Results

During the ten year period, 187 cases of gastric cancer patients were registered. Out of 187 gastric cancer patients, 134 (71.65%) were males and 53 (28.35%) were females with M: F ratio of 2.6:1. The median age of gastric cancer patients was 56 years with age range of 25-102 years. The age distribution of gastric cancer patients are shown in table 1.

The age standardised incidence rate of gastric cancer (both sexes) in Kargil Ladakh was 19.03 cases/100 000/year.

The most common clinical presentation was dyspepsia, seen in 166 (88.78%) patients, followed by vomiting, weight loss and abdominal distension, seen in 57 (30.48%) patients each (Table 2).

Regarding distribution of cancer within the stomach, most of the patients had distal stomach cancer involving Antrum and pylorus (41.72%). The distribution of cancer within stomach is shown in table 3. Seven patients had simultaneous esophageal and gastric cancer. 98% of gastric cancer was adenocarcinoma and the rest were gastrointestinal stromal tumor (GIST) and lymphoma.

Regarding the dietary pattern and smoking habits associated with gastric cancer patients in this study (table 4), 42.24% patients were smokers and 17.65% patients were ex-smokers, who had quit smoking for more than 2 years. More than 78% patients in the study had the habits of taking >4 cups of traditional salty noon tea. All the patients in the study group were non-vegetarian and 35% of them used to take red meat with fats for >4/week. Another worrisome risk factor found to have in the study group was the fewer intakes of fresh fruits and vegetables. More than 50% patients had the habit of taking fresh fruits and vegetables <1/week, especially during the winter 6 months, from November - April.

Table 1: Showing the age distribution of gastric cancer patients.

Age Group (years)	Total	Males	Females
25-29	1	1	-
30-34	1	1	-
35-39	1	-	1
40-44	7	6	1
45-49	11	8	3
50-54	17	9	8
55-59	20	15	5
60-64	30	22	8
65-69	38	25	13
70-74	35	24	11
75-79	13	12	1
80+	13	11	2
Total	187	134	53

Table 2: Showing clinical presentation of gastric cancer patients in our series.

Symptoms	No. of patients (n=187)	Percentage
Dyspepsia	166	88.78%
Vomiting	57	30.48%
Loss of appetite	47	25.14%
Anemia	52	27.80%
G.I Bleed	47	25.13%
Weight loss	57	30.48%
Abdominal distension/ascitis	57	30.48%

Table 3: Showing site of lesion within the stomach of gastric cancer patients.

Site of lesion	No. of patients (n=187)	Percentage
Proximal Stomach(Cardiac, Fundus)	20	10.69%
Mid stomach(Body)	62	33.15%
Distal Stomach(Antrum, pylorus)	78	41.72%
Diffuse	27	14.44%

Table 4: Showing the dietary pattern and smoking habits associated with gastric cancer patients

Risk Factors	Amount of consumption	No. of Patients with Cancer	Percentage
Salted tea	<4 Cups /day	42	22.46%
	4-10 Cups/day	91	48.67%
	>10 Cups /day	54	28.87%
Fruits	<1 /Wk	108	57.76%
	<4/Wk	38	20.32%
	>4/wks	41	21.92%
Red meat	1-3/m	36	19.26%
	1-2 /wk	41	21.92%
	2-4/wk	43	22.99%
	>4/wk	67	35.83%

Tobacco Smoker	79	42.24%
Ex-Smoker	33	17.65%
Non-Smoker	75	40.11%

4. Discussion

Globally, variations observed in gastric cancer incidence in populations have provided leads to study the risk factors associated with stomach cancer.

Ladakh, one of the three provinces of Jammu and Kashmir State, is the northern most part of the country with rough terrains, extreme cold, and high altitude with hypoxic conditions, having unique food habits and peculiar culture and life-style of the people of this region. Earlier study by the same author regarding cancer burden in Kargil Ladakh, found gastric cancer as the most common cancer in the region (42.12%). Esophageal cancer was seen in 4.96% patients, colorectal cancer in 4.28% of cancer patients and the gastrointestinal malignancies together accounted for half (51.535%) of all the cancers in the region [7].

According to GLOBOCAN-2018, South Korea had the highest age adjusted incidence rate of stomach cancer in 2018 as 39.6/100 000/year for both sexes, followed by Mongolia- 33.1, Japan- 27.5, and China-20.7, with India having low incidence rate of 5.5 [1]. In India, the incidence of gastric cancer has been relatively high in Southern India, namely in Chennai; however, recent data indicates that the incidence rates are the highest in the north-eastern region. In Iizawab, in the state of Mizoram, the incidence rate is 57.3 in men and 33.6 in women [2].

Out of 187 gastric cancer patients in our study, 134(71.65%) were males and 53(28.35%) patients were females. Stomach cancer was also the leading cancer in both males and females in the region. The age standardised incidence rate of gastric cancer was 19.03 cases/100 000, for both the sexes. Two year cancer registry record of neighboring Leh District also showed cancer of the stomach as the leading cancer with 19 cases in 2017-18 and 22 cases in 2019-19[8], almost similar in comparison to our study in Kargil district with 21 cases in 2017-18 and 19 cases in 2018-19. Prevalence of gastritis and gastro-esophageal reflux disease (GERD) are also very high in Ladakh region [9, 21]. A hospital based study in Kashmir also showed Stomach cancer as the most common reported cancer [4, 10], but another study in 2012 [11] showed Esophageal cancer as the most common cancer of Kashmir. The Hospital based cancer registry of SKIMS-Srinagar from 2012-2014 shows Stomach cancer as the most common cancer in males, where as it is the third most common cancer in females after Esophageal and Breast cancer, in Kashmir.

In another study from the four major hospitals of Jammu and Kashmir state viz. Govt. Medical College (GMC) hospital Jammu, Acharaya Shri Chander College of Medical Science and Hospital (ASCOMS) Jammu, Sher-i-Kashmir Institute of Medical Science (SKIMS) Srinagar and Govt. Medical College (GMC) Hospital Srinagar, the oncology department of hospitals from January 2017-January 2018 showed Stomach cancer as the most common cancer in their registries [23].

Our findings are in direct contrast to national cancer registries (2012-2014) where cancer of the Oral Cavity is the most common cancer in males especially in Delhi and Mumbai and Breast cancer is the most common cancer in females as per the National Cancer Registries of Mumbai, Delhi, Chennai and Chandigarh [3]. In hospital based cancer registries (2012-2014) of India, stomach cancer is the 3rd most common cancer in males in Chennai, 4th most common cancer in Thiruvananthapuram and Bangalore, 6th most common cancer in Guwahati and 7th most common cancer in Mumbai.

The high incidences of gastric cancer in Ladakh region is alarming and may be due to the fact that majority of the risk factors are prevalent in this region.

In regions of the world with high incidence of gastric cancer, extensive studies have failed to identify specific etiological factors. These studies have, however, strengthened the view that food habits and life-style are closely associated with a high incidence of gastric cancer. In Kargil Ladakh, the most important specific food habits are consumption of large quantities of hot salted tea, excess of red fatty meat and a very less consumption of fresh fruits and vegetables.

Dietary habits, Smoking, H.Pylori infection, Genetic susceptibility etc. are widely studied [13]. In Ladakh, the most important specific food habit is the consumption of large quantities of hot, salted, butter tea; locally known as "noon" tea or "Gurgur" tea; which is made of local butter added to boiling water mixed with common salt (NaCl), Sodium bicarbonate (soda), milk and green tea leaf extracts. In our study, all the cancer patients had the habit of taking this traditional tea, with 22.46% patients taking <4 cups/day, 48.67% patients taking 4-10 cups/day and 28.84% having the habit of taking >10 cups/day of "Noon" tea, especially during the winter 6 months (table 4). The sodium bicarbonate (soda) and common salt (NaCl) are well-known irritants of gastric epithelium and have been considered as risk factor for gastric cancer. Salt-tea showed the formation of high amount of N-nitrosopipercolic acid with several unidentified non-volatile N-nitroso compounds on nitrosation of green tea extracts, which all are irritants to the gastric mucosa [14]. Ingestion of salt has been shown to increase gastritis and the carcinogenic effects of known gastric carcinogens such as N-methyl-N-nitro-N-nitrosoguanidine (MNNG). Salt is known to erode the mucosal barrier of the stomach, thereby leading to inflammation. Cultures whose diets are rich in salt and pickled foods, such as the Koreans and Japanese, exhibit higher rates of gastric cancer. Japanese immigrants to the United States who assimilated and adopted Western foods exhibited a substantially lower rate of gastric cancer relative to those who did not assimilate their diet [29]

High consumption of red-meat and fatty meal are another worrisome risk factors of the area, with all the cancer patients in this study taking the red-meat frequently and >35.83% patients taking >4/week, especially in the winter 6 months, to keep the body warm. Habit of taking barbecued meat was found to be prevalent in the Zaskar sub-region. Another important risk factor seen in our study was the less intake of fresh fruits and vegetables, with 57.76% patients taking <1/week, 20.32% taking <4/week, and only 21.92%

taking fresh fruits and vegetables >4/week. This was due to loss of air and road connectivity with other parts of the state and country, for 6 months (November-April) in harsh winter, forcing the population to eat excess of dry, raw food stuffs, stored meats, stored tinned food items, besides traditional spicy foods and pickles. All these traditional food habits are the risk factors for gastro-esophageal and many other varieties of cancer [4, 9, 10, 15]. Preserved meats are rich in N-nitroso compounds, which can illicit similar effects in the body as already mentioned above. Grain-fed red meat is specially rich in saturated fats and low in protective fats such as omega-3 which contributes to its inflammatory processes and thus increases gastric cancer risk. Fruits and vegetables are rich in carotenoids, folate, phytochemicals and vitamin C, which help modulate xenobiotic metabolizing enzymes during digestion. They contain numerous antioxidants that prevent against metabolic damage. Case-control studies found that a higher intake of fruits and vegetables was associated with a 37% lower risk of gastric cancer [5]. Hence, fresh vegetables and fruits are considered to be probable protective factors and other food habits like high rice intake, pickled food, spicy food, smoked, dried, salted meat, use of soda etc. are the significant dietary risk factors of cancer [2].

Other risk factors involved in the rise of gastric cancer in this region may be due to vanishing habit of high fiber ancestral diets like "Khulak" and "Pappa", and increased westernization such as Obesity, Physical inactivity including less of agrico-farming activities in modern generation, heavy metal contamination of soil, food and water, use of pesticides, dyes and artificial coloring agents (like Tartazine), food adulteration, reuse of frying oils, increased intake of Killer foods (junk food, snacks, cold-drinks etc.) that are added with dangerous activities and adulterants. Even the milk and milk products in the market contain chemicals such as detergents (caustic soda). Artificial coloring agent or dyes like Tartazine has been found in many edibles, spices and condiments in the area. Tartazine metabolizes to Benzidine and 4-amino bi phenyl, listed under 'known- carcinogenic' category in 13th report on carcinogens by U.S Department of Health and Human Services. Many international studies have linked presence of Heavy Metals (potential carcinogen) in soils, vegetables, fruits and drinking water, to gastrointestinal cancers. All such trends are leading to a health catastrophe especially cancer in Ladakh as there is very little research and monitoring locally. There definitely is a need to investigate role of these potential carcinogens and contaminants vis-à-vis cancer in the region.

Another risk-factor in Ladakh is the high colonization of H.Pylori in this population [16-18]. H.Pylori is carcinogenic to humans based on epidemiological evidence [2]. There is 2-3 fold increase in gastric cancer among individuals exposed compared to non-exposed ones. The Cag A gene of H.Pylori is the main virulence factor which is responsible for the development of gastric cancer through derangement of cellular architecture and signaling pathway. The prevalence of H.Pylori is high in India due to low socio-economic condition and poor hygiene. The frequency of Cag A IgG was found to be more common in the healthy controls (89%) compared to gastric cancer patients (76%) [19]. The studies

conducted in India over the last 10 years, however, failed to confirm the association between H.Pylori infection and gastric cancer. This is mainly because of high prevalence of H.Pylori infection in Indian population and small sample size of most of the studies [2]. There might be complex interaction between dietary and life-style related factors, H.Pylori infection with certain strain types, in presence of genetic polymorphism, along with heightened inflammatory response that may produce a cascade of changes at molecular level and ultimately cancer cells of the stomach, and needs an in-depth research in future [20, 22]. H.Pylori strains from Ladakh are genetically distinct and possibly less virulent than the isolates from East-Asian countries, such as china and Japan where the prevalence of gastric cancer are very high [18].

Another worrisome risk factor is the cigarette smoking. Use of Tobacco in the form of cigarette smoking, hukka and chewing were seen in 42.24% patients. 17.65% patients were ex-smokers and had quit smoking for ≥ 2 years. Surprisingly, not a single female patient was smoker. Only 5(1.37%) patients were alcoholic and were mostly from Zanskar subdivision where local drink called "Chang" is very popular and keeps the body warm at this high altitude area. Tobacco is an independent risk factor for Lung cancer, Stomach cancer and many other cancers while Alcohol may be carcinogenic to Esophagus, Cardia and Liver [2]. All the patients in our study were exposed to smoke with domestic wood cooking practices with traditional "chullahs" at home with the practice of closing all the windows and sealing them with plastic in winter, thus leading to heavy smoke exposure. International Agency for Research on Cancer (IARC) has reported that there is association between Tobacco use and smoke with cancer of Lung, oral-cavity, Stomach, Pharynx, Esophagus, Larynx, Urinary Bladder, Ovary, Colon and Rectum [24, 25]. It is estimated 11% of global stomach cancers, and 17% of case in Europe, are attributable to smoking [5]. Tobacco related cancers contribute to two-thirds of all cancers, with three-fourths of cancers among men and more than half of cancers among women.

Alcohol use has been shown to increase the risk of gastric cancer, moderate alcohol consumption was shown to increase the gastric cancer risk by 39%, while heavy consumption further worsen the odds. Alcohol is known to irritate and erode the stomach lining, resulting in gastritis, a precursor for stomach cancer [5].

Another worrisome factor in Ladakh region is the high prevalence of gastritis and gastroesophageal reflux disease [9, 16, 21], again because of above mentioned peculiar food habits of the region and life style. The risk of gastric cancer is almost twice the expected rate among patients with gastric ulcers [5]. Helicobacter pylori eradication in gastric ulcer patients may reduce the risk of developing gastric cancer [26]. Cardia gastric cancer is seen to be positively associated with both severe gastric atrophy and with frequent GERD symptoms. Multiple distinct pathways of tumorigenesis exist at esophagogastric junction, including one in which tumors arise from dysplastic intestinal metaplasia, and one potentially involving dysplasia of the cardiac-type mucosa. Incidence rate trends in reflux-related cardia cancer and

esophageal adenocarcinoma are very similar, suggesting that these two cancers share a similar etiology and pathophysiological process [27, 28].

Obesity is considered to be a risk factor in the occurrence of gastric cancer. A statistical meta-analysis from around the world found that those with an excess body mass index (over 25kg/m²) have a 1.13 odds ratio of developing cancer. The strength of the association increased with increasing BMI. Obesity was an especially strong predisposing factor for cancer. Obesity may induce inflammation of the stomach lining via tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1). Those with a diet of heavily inflammatory foods, such as a diet high in meat and low in fruits and vegetables, also have a higher risk of being obese [30].

Other risk factors associated with gastric cancer are genetic mutation to CDH1 gene, chemical exposure in industries, radiation exposure, obesity, pernicious anemia, Previous gastric surgery, Epstein-Barr virus infection, and blood group A. Those with a family history of stomach cancer, or who have personally had invasive lobular breast cancer before age 50, are recommended to undergo genetic testing for abnormal changes in the CDH1 gene, which greatly increase the risk of gastric cancer [31].

Due to the alarming rise of gastric cancer in Ladakh region, the Jammu and Kashmir Govt. has already established a chemotherapy centre in the twin frontier districts of Kargil and Leh as it was increasingly becoming difficult for the cancer patients from these districts to visit Srinagar for Chemotherapy doses. Oncologists attribute the increase in cancer deaths to inadequate cancer-related infrastructure and lack of awareness among the people about the disease. Majority of the gastric cancer patients in our study presented late with advanced stage of disease. There is need for urgent mass awareness programme and need for urgent screening protocol to identify patients at earlier stages of the cancer. The optimal interval for gastric cancer screening has not been established in randomized trials. In South Korea, endoscopy or UGI series is recommended every two years for individuals aged 40 years and older. In Japan, screening is done annually for all residents aged 40 years and older [32].

Diet and lifestyle modification have been revealed to be the most effective means of preventing gastric cancer. It was necessary to measure the burden of gastric cancers in the area to ensure well informed policies on management and prioritization of resource allocation as gastric cancer was the most common cancer in the region.

5. Conclusion

Gastric cancer accounted for 42.12% of all the cancers in the Kargil Ladakh, with age standardised incidence rate of 19.03/100 000. Majority of the risk factors of gastric cancer are prevalent in this Cancer endemic zone. Majority of the patients presented late, in advanced stage. As Gastric Cancer is the most common cancer in this region, cancer awareness programme, and establishment of a screening protocol is the need of the hour. Further, Population based studies are

needed in future to find a correlation between various possible etiological factors and the occurrence of gastric cancer in the region.

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