Updates in Surgery (2018) 70:233–239
https://doi.org/10.1007/s13304-018-0527-3

ORIGINAL ARTICLE

Gastric cancer in India: epidemiology and standard of treatment

Chandramohan Servarayan Murugesan[1,2] · Kanagavel Manickavasagam[1,2] · Apsara Chandramohan[3] · Abishai Jebaraj[1,2] · Abdul Rehman Abdul Jameel[4] · Mayank Shikar Jain[5] · Jayanthi Venkataraman[5]

Received: 12 November 2017 / Accepted: 14 March 2018 / Published online: 2 April 2018

Abstract
India has a low incidence of gastric cancer. It ranks among the top five most common cancers. Regional diversity of incidence is of importance. It is the second most common cause of cancer related deaths among Indian men and women in the age between 15 and 44. *Helicobacter pylori* carcinogenesis is low in India. Advanced stage at presentation is a cause of concern. Basic and clinical research in India reveals a globally comparable standard of care and outcome. The large population, sociodemographic profile and challenges in health expenditure, however, remain a major challenge for health care policy managers. The newer formation of National Cancer Grid, integration of national databases and the creation of social identification database Aadhaar by The Unique Identification Authority of India are set to enhance the health care provision and optimal outcome.

Keywords Gastric Cancer · India · National Cancer Grid · Therapy · Stage Based · Aadhaar

Introduction

In the Global scenario of Gastric Cancer, India falls under the low incidence category. In India, it is the fifth most common cancer amongst men and sixth most common in women [1]. It is the second most common cause of cancer related deaths among Indian men and women in the age between 15 and 44; it ranks among the top five most common cancers [2–4]. Majority of the patients, present at an advanced stage at the time of first presentation itself. This directly translates into a decrease in 5-year survival rate compared to countries where early diagnosis is made, especially in countries where screening facilities are available. The treatment protocols and standard of treatment is standardized in most of the institutions which is comparable to any other country, though it is not uniformly observed all over the country.

Epidemiology

Worldwide, there is at least a tenfold variation in the incidence of Gastric Cancer. Countries from South East Asia such as Japan, China, and South Korea, record a high incidence [3]. India falls under lower risk of gastric cancer countries, other than Whites of USA, Philippines, Africa, and Australia.

Within India, there is a wide regional variation in the occurrence of gastric cancer. The data available in India is from the National Cancer Registries (NCR)—population-based tumor registries and Hospital based cancer registries. But only 7% of the Indian population is covered by these registries.

From the reports available on date the North Eastern part of India, the district of Aizawl in the state of Mizoram has recorded the highest incidence in the country as per NCRP 2013 (64.2/100,000 population). This is followed by a Southern Indian state, namely Tamil Nadu, where the incidence is 12.2/100,000 population in men. For women, Bangalore

The article is part of topical collection on Gastric Cancer Surgery.

✉ Chandramohan Servarayan Murugesan
drmkvel@yahoo.com

1 Center for Gastroesophageal Disorders, ESOINDIA, Chennai, India

2 Department of General, GI and Minimal Access Surgery, St. Isabel's Hospital, Chennai 600010, India

3 Government Kilpauk Medical College and Hospital, Chennai 600010, India

4 Department of Gastrointestinal Surgery, Saveetha Medical College, Saveetha University, Thandalam, Chennai 602105, India

5 Institute of Gastroenterology, Gleneagles Global Hospital, Chennai 600100, India

had the highest incidence of AAR—age-adjusted incidence rate 5.5 (Indian Council of Medical Research). The lowest incidence in the entire country is in the state of Gujarat 1.1/100,000 population in men and up to 0.5/100,000 population in women from certain communities [5–7].

Age incidence

Worldwide, there is a sharp increase in the incidence after 50 years and the common age group is in their late 60's and 80's.

Our analysis of 687 patients with gastric cancer (which was presented in the International Gastric Cancer Congress 2015) [8] revealed the following factors. 102 (14.4%) were under 40 years of age 585 (85.15%) were above 70 years of age. The male, female ratio was 1.5:1 in younger patients, which increased to 3:1 above 40 years and it was 5.6:1 in patients above 70 years indicating the fact that as age advances male sex predominates. Sub group analysis showed that, distal gastric cancer to be common in both groups, though the incidence was 70.58% in under 40 age group and it was 66.03% at patients above 70 years.

Age-adjusted incidence rate (AAR)

Age-adjusted (world) incidence and mortality rates of gastric cancer and its relative proportion in population-based cancer registries have shown large regional variation. Urban registries from India report an AAR of Gastric Cancer Incidence to vary from 3.0 to 13.2, while world over it is reported to be 4.1–95.5 [5, 6]. In Mizoram, with highest incidence in India, the AAR in men is 57.3 and 33.6 in women per 100,000 populations [5, 6].

Epidemiological trend

Worldwide, most of the countries show a steady decline. On the contrary the projected incidence for India comparing 2015 and 2020 is on the increasing trend. The number of new gastric cancer is approximately 34,000 which is expected to go up to 50,000 annually in the year 2020.

Proximal vs distal gastric cancers

Majority of the countries show a proximal shift of gastric cancer over the past two decades. A 16-year survey done by Jejocherian et al. in 2007 revealed that antrum and mid body continues to be the dominant site with no proximal shift [8, 9].

We have analyzed our experience over a period of four decades. The first presentation was made at the first International Gastric Cancer Congress at Kyoto in 1995 with analysis from 1980 and the subsequent presentation at the 11th International Gastric Cancer Congress in Brazil with analysis up to 2014 [8–10]. The first group was between 1979 and 1983, second group between 1989 and 1993 and the third group between 2012 and 2014. Antrum/distal gastric cancer were the commonest in all groups (68.05, 65.8 and 65.6%). The incidence in body was 16.44, 19.5 and 16.44% in group I, II and III, respectively, and proximal growth was 11.6, 8.9 and 6.7% in group I, II and III. Our study concluded that there was no proximal shift in Indian populations over four decades.

Risk factors

Many factors have been identified as risk factors for stomach cancers. It varies between countries. Risk factors differ between proximal and distal cancers also. Gastric adenomas, atrophic gastritis, *H. pylori* infection [11] and previous gastric surgeries are considered to be common risk factors across the world.

India, especially the Southern India pose a different problem. Peptic ulcer disease warranting surgical intervention in the form of Truncal Vagotomy and gastrojejunostomy used to be very common few decades back. Cancer developing in these patients is called "Stump Carcinoma" and the average duration between the first surgery and the development of cancer is between 23 and 43 years.

H. pylori infection is considered to be one of the major risk factors for gastric cancer. In India the general prevalence of *H. pylori* positivity is between 80 and 90% and gastric cancer is reported to develop in 0.1–3% of patients [12, 13]. Our observations on *H. pylori* in gastric cancer patients on endoscopic biopsy revealed the following. Of 141 patients with gastric cancer 39.7% showed presence of *H. pylori* in carcinomatous areas and in adjacent gastric glands, whereas in 60 patients with GE junction tumors, it was positive in 20 (33.3%).

In a study from Kashmir on 1314 patients, no association was found between gastric cancer and *H. pylori* [14] and the study by Phukan et al. from the North India reported the prevalence of 68% in gastric cancer patients. Study from Mizoram by Parkin et al. [15] failed to show any significant association. But a noticeable observation was the possible interaction between *H. pylori* infection and smoked, salted meat and Sa-um—a locally made dish. Overall, studies from India do not confirm the direct association between *H. pylori* infection and gastric cancer.

The association of *H. pylori* to gastric carcinogenesis is influenced by multiple factors which include the geographic

location, dietary practices and other potential risk factor exposure. More so the dietary habits of the people keep dynamically changing based on their urbanization, social empowerment and improving economic status. The type of method used for *H. pylori* estimation and quantification variation could be a potential reason which one should exercise caution when interpreting these data.

Dietary habits, lifestyle and gastric cancer in India

India is a country where dietary habits and lifestyle vary according to the state where they live. Every state has different dietary habit and they play a significant role in the development of gastric cancer. But the main factors seem to be high intake of salt in various dietary preparations, smoked and salted food and preserved food [16, 17]. In study from Kerala, high temperature food and increased consumption of rice and chilli were found to be independent risk factors [18].

Our study on life style and Dietary pattern in gastric cancer (International Gastric Cancer Congress, 2011) revealed 83% were tobacco users, 84% were used to ethanol, 37% were used to Areca catechu/Chewable tobacco, 98% of them were non-vegetarians, 97% of the consumed re-used oil. Sumathi et al. reported a protective effect of the consumption of pulses showing a 55% reduction in risk [10].

Role of tobacco as independent risk factors has been studied worldwide and in India there are various forms in which tobacco is used as snuff, or smoking in the form of hukka, cigarettes, beedi and taibur and maizol [19]. The highest incidence of gastric cancer in Mizoram has been attributed to smoking local cigarettes like maizol and Taibur-tobacco smoke infused water [20, 21].

Alcohol

There are not many studies from India that has shown a link between alcohol and gastric cancer as an independent risk factor.

Ethnicity

The state of Sikkim has a combination of urban and rural areas and dissimilar incidence rates. Age-adjusted incidence rates (AARs) analysis by ethnic group reveals definite variance when compared to the standard Population Based Cancer Registry (PBCR) data when compared to both the urban and rural data. Stomach cancer AARs of 60.4 and 29.4 per 100,000 in males and females, respectively, of the Bhutia [22] population is also higher than that of the highest AAR (55.4 in males and 24.4 in females) in Aizawl district reported among the PBCRs in India during this time period (National Cancer Registry Program, Indian Council of Medical Research, 2010).

Genetic polymorphisms

Several studies from India have addressed polymorphisms in patients with gastric cancer.

Pavithra et al. [23] in a study on polymorphisms in 200 gastric cancer subjects have highlighted the importance of association with socio-economic lifestyle and dietary influences. They have noted, the TT genotype for TGFβ C-509T had an increased risk and CC genotype for TGFβ T869C had a decreased risk of gastric cancer in south Indian population after adjusting for socio-economic factors and lifestyle factors.

Study done by Ghosh et al. [24], has looked into the association of DNA repair and xenobiotic pathway gene polymorphisms with genetic susceptibility to gastric cancer. Their findings indicate that c.1196G > A: Arg399Gln of XRCC1 gene and c.313A > G: Ile105Val of GSTP1 gene could identify the gastric cancer susceptible population. GSTP1 Val allele was significantly increased the risk of gastric cancer associated with tobacco smoking and alcohol consumption.

The study done by Prasad et al. [25] suggests that Pro-12Ala PPARγ polymorphism is associated with gastric adenocarcinoma and PUD and is a potential marker for genetic susceptibility to these two diseases in the presence of *H. pylori* infection.

Betel-quid chewing is an important cause for upper gastrointestinal cancer in India. A study on Association of interleukin-1b e511 C/T polymorphism with tobacco-associated cancer in northeast India on gastric cancer has reported a significant gene environment interaction of the C/T allele genotype of IL-1b [26].

Standard of treatment

India has diversified population where people live in urban, semi urban and rural areas, with varying literacy rate. Added to it are the socio-cultural barriers, ignorance about symptoms, myths, misbeliefs and social stigma. All these contribute to the delayed presentation at an advanced stage at the time of first presentation itself.

This decreases the possibility of curative therapeutic strategies even with Multi-Disciplinary Team approaches. This directly translates into decreased 5-year survival of only 10.1%. We have analyzed 782 patients [27] with gastric cancer who presented at an advanced stage to our

institution: 585 were males and 197 were females. Bloating sensation (30.2%) followed by dyspepsia (18.9%) and reflux like symptoms (16.1%) were the first symptoms experienced by them. 37.46% of them ($n=293$) did not consider the symptoms significant enough to be reported followed by socio-cultural reasons 24.55% ($n=192$) and economic factor 13.42% ($n=105$) as to the reasons for delayed presentation. 96.8% ($n=757$) of the patients admitted that they would have reported to physician earlier, had they known that their symptoms are the one due to gastric cancer. The mean delay from the time of first presentation of symptom to first consultation with a doctor was 116.8 days.

The resource level in the country for management varies from basic, limited, enhanced and maximal. Majority of the patients with gastric cancer live in rural areas where basic and limited facilities are available and most of the specialist and tertiary care centers with enhanced and maximal level benefits are available in urban centers only. The added factor which contributes to the outcome is the belief by many that the diagnosis of cancer is a stigma and they do not reveal it till it reaches an advanced stage.

Centers with basic level facilities have endoscopy and ultrasound and the surgery usually performed is D0 or D1 gastrectomy. Centers with limited level facilities have CT scan also and they do D2 gastrectomy. Enhanced level facility centers have enhanced endoscopy for diagnosis of even early gastric cancer, HER-2 testing and they undergo D2 gastrectomy with chemotherapy. Maximal level centers have facilities for PET-CT, laparoscopy and also availability of trastuzumab.

Majority of the surgeons treating gastric cancer in India believe in doing a standard gastric resection with D2 lymphadenectomy though few of them believe D1 lymphadenectomy is enough. Sentinel lymph node mapping is used essentially in early gastric cancer with the aim to do a conservative, but curative surgery. But, it is not usually followed for advanced gastric cancers.

Studies done by us on sentinel node mapping in advanced gastric cancer has helped us improve on nodal harvesting:

Our initial study on using sub mucosal injection of India ink the day before surgery and intra operative sub serosal injection of methylene helped us detect involvement of tier 2 lymph nodes in 18.8% of patients (International Gastric Cancer Congress 2011). Subsequent analysis done by us to find out whether node mapping has improved nodal harvesting revealed that average number of nodes harvested by lymph node mapping increased significantly to 17.76 with maximum of 29 nodes against 8.68 in control arm. There was no increase in morbidity or mortality.

An audit of 175 consecutive gastrectomy specimens on adequacy of surgical resection and nodal harvesting revealed the following:

97 were subtotal and 78 were total gastrectomies. 85.4% of subtotal and 85.8% of total gastrectomy specimens were T3. The adequacy of lymph node yield for staging ($n>15$) was higher in total gastrectomy (91%) than subtotal (81.4%). The mean lymph node yield was higher in total with a mean of 18.17 nodes, than subtotal gastrectomy with a mean of 15.6 [29].

Her 2 neu gene amplification over expression will help patients benefit from target therapies. Facilities for this are available in centers with maximal level resources. A study done by us on 50 patients, showed ten patients (20%) it was 3+: three patients (6%) had 2+and ten patients (20%) had 1+and 27 patients (54%) had a score of zero—0 by IHC [28]. There was no correlation between HER 2 neu positivity and T stage, presence of ascites, metastasis and grade of tumor.

Special situations

There are certain special situations which may require tailored treatment strategies and innovative approaches.

Bleeding gastric cancer

Bleeding gastric cancer, especially those not amenable to endotherapy can pose a serious problem especially when they present to a center without enhanced facilities. The decision making on the type and extent of resection will also be difficult as bleed may be the first manifestation [30]. Of the 55 patients with bleeding gastric cancer tumors, managed surgically in our center, pre-operative histology was available in 42. Surgery was considered when conservative and interventional therapy failed. Surgery on these patients had a high mortality—11 of 55.

Perforated gastric cancer

The issues in management of perforated gastric cancer are complex. In most of the situations patients may present to the emergency department and the initial investigation may be only a plain X-ray of the abdomen and chest. When it reveals pneumoperitoneum, the commonest diagnosis made is perforation due to ulcer disease. Very few of them present with a previously established diagnosis of gastric cancer and some of them undergoing chemotherapy.

Treatment strategy depends upon the level of resource and expertise available. When they present to a center with basic or limited resource, they will be referred to center with enhanced facilities, where re-operation may be undertaken.

Our analysis of 35 patients with spontaneous perforation [31] only six had pre-operatively established diagnosis of gastric cancer. Primary resection was possible only in 11 of 35 patients. The in-hospital mortality was 9 of 35 as most of them present late or referred after intervention in another center (International Gastric Cancer Congress 2015).

Nationwide survey

We have done a Nationwide Survey to analyze the epidemiology pattern of presentation, evaluation strategies and therapeutic modalities adopted by surgeons managing gastric cancer in India and we had representation from all zones.

The survey was based on a 43-point questionnaire. General surgeons, gastro intestinal surgeons and oncology surgeons were included in the study [32]. From a total of 1500 surgeon pool, survey was completed by 495 (33%). More than 50 cases per year were seen by 66.65%. The common age group was 41–50 years as reported by 456 (46%), 75.96% responded that the male, female ratio was 70:30.

The commonest presentation was vomiting (47.17%) followed by dyspepsia (40.28%) indicating that majority of them presented at an advanced stage with outlet obstruction due to distal gastric cancer. 96.73% of the respondents have used CECT as the primary modality of staging. EUS and PET-CT has been selectively used by 46.07 and 58.38%, surgeons, respectively. 57.67% of the respondents were always doing a staging laparoscopy. Neo-adjuvant chemotherapy was used selectively by 80.96%. The standard practice of D2 lymphadenectomy was followed by 83.13%. Total laparoscopic surgery was done by 22.40% of the surgeons. Successful 5-year follow-up has been done by 87.19% of respondents (International Gastric Cancer Congress 2015).

Pertinent challenges and government's initiatives

A recent assessment of 5,56,400 deaths due to cancer in India in 2010 based on a nationality representative survey found that stomach cancer with a mortality rate of 12.6% is the second most fatal cancer [1]. Even the incidence of gastric cancer is stabilizing or on the regression trend in the west, the low and low middle income will be facing an increased demand of infrastructure and funding as the dynamics of presentation is evolving due to multiple factors [33]. The sheer magnitude of the Indian population, influence the policy makers and providers towards the provision of care as the priority.

Indian traditional health systems: AYUSH (ayurveda, unani, siddha and homeopathy)

India has multiple systems of medicine [34]. The AYUSH—ayurveda, unani, siddha and homeopathy apart from the widely prevalent allopathic system. The traditional way of learning alternative systems were of a gurukul mode. The dedicated ministries and national institutes are rapidly accumulating the wealth of familial and regional knowledge on how to standardize text books and newer evidences are being accumulated. However, oncology predominantly remains the domain of allopathy. Significant claims of the AYUSH systems are to be supported by more statistical evidence. The traditional beliefs are rapidly giving way to newer evidence systems as awareness is on the raise.

Health care policies in India

The creation of the National Cancer Grid of India [35] in 2012 (a partnership of all the major regional cancer centers across India) and the drive to improve the quality of services across the public sector has provided a major opportunity to improve cancer outcomes.

National databases

Treatment data of gastric cancer patients are at this point a limited domain in India. A central treatment database is the current need of the hour. Integrated database is feasibility now. The Aadhaar-National Population identification database integration will be a robust future interface [36]. The medically certified deaths at this point of time in India stands at 22% of all registered deaths with death registry [37]. The optimization and integration of medical data into death registry will enhance the evidence.

Endotherapy for gastric cancer in India

The science of endotherapy for gastric cancer has been developing rapidly in the east especially in Korea and Japan, where screening program are in place. The low pick up of early gastric cancer in India precludes the development of this science. Limited experience has been reported across few centers.

The Master and Slave Transluminal Endoscopic Robot (MASTER) combined robotic technology and endoscopy. A multicenter study was conducted in Singapore, India, and Hong Kong using the MASTER endoscopic robot to perform

gastric ESD in human beings. The initial experience was excellent, with the shortest submucosal dissection time of only 16 min [38].

Conclusion

The demanding priority at the moment is improvement in basic, clinical and translational research and skill transfer to set the optimum outcome in management of gastric cancer. Diagnosis of early gastric cancer in India continues to be a problem and routine screening is neither feasible nor cost effective considering the population and over all incidences. But the overall outcome is expected to improve as awareness is being created by governmental and non-governmental organizations and the facilities to manage gastric cancer are improving all over the country.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals This article does not contain any experimental studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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