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REVIEW ARTICLE

Gastric cancer in India

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ABSTRACT

The incidence of gastric cancer in India is low compared to developed countries, though there are certain geographical areas (Southern part and northeastern states of country) where the incidence is comparable to high-incidence areas of world. Despite the large number of patients being treated for gastric cancer, there are not sufficient publications discussing associated risk factors and outcomes in these patients. This article discusses relevant Indian epidemiological and clinical studies about gastric cancers. This article also highlights the gap in publication from India and developed countries regarding gastric cancer and stresses on collaborative efforts of the Indian scientific community to conduct epidemiological, pathological, and clinical studies to have a new standard of care for Indian patients.

Key words: *Clinical, epidemiological studies, gastric cancer, India*

INTRODUCTION

Gastric cancer is the fifth most common cancer among males and seventh most common cancer among females in India.[1] The aggressiveness of the disease and need for improvement in therapeutic options is discerned by the fact the gastric cancer is the second most common cause of cancer death globally.[2] The high incidence of local and distant recurrence even in patients with completely resectable gastric cancer indicates the systemic spread of cancer very early in the disease, thus emphasizing the need for multimodality treatment including surgery, radiotherapy, and chemotherapy for treating the disease.

EPIDEMIOLOGY

There is a worldwide variation in the incidence of gastric cancer. A high incidence of gastric cancer has been reported from Southeast Asia, most commonly from Japan, China, and South Korea, and this has been attributed to the consumption of preserved food containing carcinogenic nitrates.[2] The incidence of gastric cancer in India is overall less compared to the worldwide incidence. The age-adjusted rate (AAR) of gastric cancer among urban registries in India is (3.0–13.2) compared to the worldwide AAR (4.1–95.5).[3-6] Worldwide and more so in the developed world, there has been a decline in the incidence of gastric cancer and this has been attributed to improved food hygiene, sanitation, and food preservation techniques. However, this declining trend has not been seen in certain parts of India.[3] The regional variation in incidence and presentation can be ascertained by the fact that gastric cancer in South Indian males has been reported to be more common and occurring a decade before their North Indian counterparts.[7] Differences in some dietary pattern and use of tobacco and alcohol have been considered as potential risk factors. In a case–control study from Trivandrum, a high consumption of rice and chili, and consumption of high-temperature food were found to be independent risk factors for gastric cancer in multivariate analysis.[8] In a study from Hyderabad comparing 94 gastric cancer patients and 100 normal age- and sex-matched controls, smoking ($P<0.01$) and alcohol ($P<0.05$) were significantly associated with gastric cancer.[9]

The incidence of gastric cancer in Mizoram has been reported to be the highest in India. The AAR in males and females has been reported at 50.6 and 23.3, respectively.[10] Hospital-based data from Mizoram have shown gastric cancer to be the most common cancer accounting for 30% of all cancer cases. The male-to-female ratio was 2.3:1; the median age for males was 58 years and that for female was 57 years.[11] The high prevalence of gastric cancer in Mizoram has been attributed to dietary and possibly some unknown genetic differences. In a case–control study from Mizoram among the cases, the risk of stomach cancer was significantly high in current

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smokers (odds ratio (OR), 2.3; 95% confidence interval (CI), 1.4–8.4).[12] Higher risks were seen for meiziol (a local cigarette) smokers (OR, 2.2; 95% CI, 1.3–9.3). Tuibur (tobacco smoke-infused water), used mainly in Mizoram, was associated with the risk of stomach cancer among current users in both univariate and multivariate models (OR, 2.1; 95% CI, 1.3–3.1. In another report from Chennai, alcohol consumption and use of pickled food were found independent risk factors for gastric cancer.[13] On the other hand, use of pulses was found to be offering a protective effect. Hospital-based data are prone to selection and referral bias and hence the above results need to be viewed with caution. In another hospital-based study from Kashmir, there was no association found between gastric cancer and *Helicobacter pylori* infection in 1314 patients.[14] Similar to Mizoram, the incidence was higher in males and the cancer occurred most commonly in the fifth decade of life. The most common site of tumor was the body of stomach (40.7%) followed by the pylorus (35.5%). In conclusion, the epidemiology of gastric cancer suggests that it is not a single disease or caused by a single factor, but a combination of genetic, sociocultural, and environmental factors in a given region dictates its presentation. Gastric cancer can broadly be classified as intestinal or diffuse as proposed by Lauren *et al*. based on histological findings.[2] It can also be classified according to the anatomic site as proximal (cardia, fundus, and gastroesophageal junction) and distal (pylorus). Interestingly, the incidence of proximal cancers is increasing in the developed world in concordance with the increase in esophageal cancers suggesting that these might have similar risk factors and pathologies.[2] *H. pylori*, a Gram-negative bacteria, is associated with gastric mucosal infection. In underdeveloped countries with poor hygienic conditions, 50–90% of the population is infected asymptomatically in childhood. *H. pylori* has been attributed to cause distal gastric cancers and it is believed that the overall decline in gastric cancers and more so distal cancers worldwide is due to reduction and eradication of *H. pylori* infection with improved sanitation.[15] However, it should be assumed that countries with a very high prevalence should have the highest incidence but this is not true as Asia and Africa although with a high incidence of *H. pylori* infection have a low incidence of gastric cancer. This Asian or African paradox suggests that *H. pylori* by itself cannot cause gastric cancer and various other factors are needed for causation.[16] It is also believed that the poor study design and inaccuracies in techniques quantifying *H. pylori* may account for such paradoxical results. Various etiological factors including smoking, alcohol, nitrates, and *H. pylori* have been proposed as causative factors for gastric cancer.

TREATMENT

Surgery

Surgery is the mainstay for the treatment of gastric cancer. Subtotal gastrectomy is the preferred modality in distal cancers and total or proximal gastrectomy is preferred in proximal cancers.[17] A tumor-free resection margin of at least 4 cm is needed for the adequacy of the surgery. Patients are considered surgically unresectable if there is evidence of metastasis or locoregional spread involving the peritoneum or encasement of major vessels. There is no role of palliative surgery or debulking surgery in gastric cancer.[17] There is a considerable controversy regarding the role and extent of lymphadenectomy in gastric cancer. Extensive lymphadenectomy also called as D2 dissection is widely practiced in far eastern countries like Japan and Korea. The survival advantage and decreased mortality seen with D2 lymphadenectomy by Japanese surgeons has not been translated in Western countries.[18,19] Data from Europe and USA have shown that more conservative D1 lymphadenectomy is equal to D2 lymphadenectomy in terms of overall survival with lesser morbidities.[20,21] A middle path approach of less aggressive D2 lymphadenectomy also called as modified D2 lymphadenectomy excludes splenectomy and pancreatectomy and has been found to be equivalent to D2 lymphadenectomy.[22] Surgical skills and the volume of surgery done in a center also influence the outcomes of lymphadenectomy; results with D2 lymphadenectomy are better in Japan because of more experienced surgeons and large volume of surgeries for gastric cancer.[17] A minimum of 15 lymph nodes should be sampled by the surgeon and reported by the pathologist for an adequate pathological staging.[23] A study from Tata Memorial Hospital, Mumbai, has shown D2 lymphadenectomy to be safe with outcomes comparable to Japanese studies. The study included 159 patients with resectable gastric cancer who underwent radical gastrectomy with D2 lymphadenectomy.[24] The median number for lymph nodes dissected was 15 and the rate of major morbidity was 4.4% with the mortality due to surgery being 1.25%. This study shows that Indian surgeons in high-volume centers can achieve results comparable to best centers in the West.

Chemotherapy

The importance of chemotherapy in the treatment of gastric cancer is gaining ground. A significant proportion of patients with completely resected gastric cancer still relapse locally as well as at distant sites, suggesting that gastric cancers tend to metastasize early in the course of the disease. Chemotherapy can be used prior to surgery to shrink the tumor and make it operable; this is called neoadjuvant chemotherapy (NACT). Chemotherapy

can also be given in the adjuvant setting after complete surgical resection. The only randomized control trial on perioperative chemotherapy was the MAGIC trial conducted by the Medical Research Council, UK.[25] The trial randomized 503 patients between surgery alone and surgery and perioperative chemotherapy with epirubicin, cisplatinum, and 5-flurouracil (ECF). Patients who received perioperative chemotherapy had better overall survival and progression-free survival in comparison to patients who underwent surgery alone. Twenty-five percent of patients in the study had cancer of the gastroesophageal junction or lower esophagus. There are very little data from randomized control trial (RCT) in adjuvant chemotherapy in gastric cancer. A Japanese study has showed improved survival with S1, a prodrug combining fluropyrimidine (tegafur) with oxonic acid, in patients with stage 2 and 3, completely resected gastric cancer.[26] The drug is not easily available outside Japan. Significant proportion of Indian patients present with inoperable, locally advanced, or metastatic gastric cancer. These patients have an incurable disease and the role of chemotherapy in them is purely palliative. Various chemotherapeutic agents have shown an activity in gastric cancer; typically, these agents have a response rate of 10–20% when used individually. The commonly used chemotherapy drugs are cisplatinum, 5-flurouracil, capecitabine, paclitaxel, epirubicin, docetaxel, paclitaxel, oxaliplatin, and irinotecan.[27] Chemotherapy combinations are preferred to single agents for a faster response, although toxicity increases with the use of combination chemotherapy. Chemotherapy in metastatic gastric cancer improves the overall survival when compared to best supportive care.[27] However, the median survival with various chemotherapy combinations or single agents has ranged from 9 to 11 months. Significant proportions of Indian patients present with advanced gastric cancer and have a poor performance status, which makes their tolerability to chemotherapy poor. A phase 2 study from AIIMS, New Delhi, evaluated low-dose cisplatinum (15 mg/m^2), etoposide (40 mg/m^2), and paclitaxel (50 mg/m^2), CEP, chemotherapy given on day 1 and 4 every 3 weeks in 33 patients with locally advanced or metastatic gastric cancer.[28] A total of 26 of 33 patients showed response to CEP chemotherapy (2 complete responses, 21 partial responses, and 3 stable diseases). Four patients were operable after CEP chemotherapy. The median age of the patients was 52 years; a median of two cycles of chemotherapy was given and the median overall survival and progression-free survival was 10 months and 8 months, respectively. The incidence of grade 3 and 4 toxicity was 35% (most common being neutropenia); overall the chemotherapy was well tolerated. This study suggests that patients with advanced disease can also benefit from combination low-dose chemotherapy. The role of NACT has also been explored in Indian patients with unresectable gastric cancer. In a study from AIIMS, New Delhi, 10 patients with locally advanced unresectable gastric cancer received NACT with two cycles of cisplatin (30 mg/m2) and 5-fluorouracil (1000 mg/m2). Eight of them showed objective response, six could undergo curative surgery, and the median survival was 10 months (range 1–60 months).[29]

Combined modality therapy

A combination of chemotherapy and radiotherapy has been very effective in certain malignancies like head and neck cancers and anorectal cancers. The chemotherapy potentiates the effect of radiation therapy and helps in controlling distant metastasis. Preoperative chemoradiotherapy looks attractive as it has the potential to downsize tumors and make unresectable gastric cancer resectable. In a phase 3 study by Stahl *et al.*, patients with unresectable gastric cancer were randomized to preoperative chemotherapy followed by surgery or induction chemotherapy followed by preoperative chemo-radiotherapy and surgery.[30] Patients in the chemo-radiotherapy group had a statistically significant higher pathological complete response rate (15.6% vs. 2%), with the overall survival at 3 years showing a trend toward better survival with chemo-radiotherapy (47.4% vs. 27.7%). Even in patients with resectable gastric cancer, preoperative chemo-radiotherapy improves pathological complete response rates and increases the success of D2 lymphadenectomy.[31] Postoperative chemo-radiotherapy was evaluated in the SWOG9008/INT-0116 trial, now famously referred as the Macdonald trial.[32] The trial included 556 patients with adenocarcinoma of stomach and lower gastroesophageal junction, stage 1–4 (nonmetastatic) operated tumors. Patients were randomized to surgery alone or surgery followed by chemo-radiotherapy. The chemo-radiotherapy protocol included 5-flurouracil and folinic acid (bolus regime) given in a schedule of one cycle before radiotherapy, two cycles concurrent with radiation, and two cycles after the completion of radiotherapy. Patients in the chemo-radiotherapy arm had a better overall survival (50% vs. 41%, P=0.05), 3 years' relapse-free survival (48% vs. 31%), and lesser local recurrence (19% vs. 29%). This study showed that the chemo-radiotherapy can be effective as adjuvant treatment in gastric cancer. However, the Macdonald trial has faced several criticisms some of which include inadequate surgery as only 10% of patients underwent D2 lymphadenectomy, and 54% underwent a less extensive D1 dissection. Critics argue that a more extensive surgery would have probably negated the advantage obtained from chemo-radiotherapy.

There are no published data on radiotherapy or chemo-radiotherapy in gastric cancers from India and all our practice has been based on findings of the Western literature. There is an urgent need for well-designed randomized control trials on chemotherapy and chemo-radiotherapy from the

Indian subcontinent, as we believe that the biology of gastric cancer from the subcontinent differs from the rest of the world. Extrapolating data from the rest of the world might not serve the best interests of our patients.

Targeted therapy

Targeted therapy including monoclonal antibodies and tyrosine kinase inhibitors have shown efficacy in various solid tumors in breast, lung, and colon cancer. The presence of HER2 in gastric cancer has been associated with poor prognosis. HER2 belongs to the human epidermal growth factor receptor family and its function is blocked by the monoclonal antibody trastuzumab. The efficacy of trastuzumab is well established in HER2-positive breast cancer. The TOGA study was a phase 3 RCT, which evaluated trastuzumab along with cisplatin and 5-flurouracil therapy in 594 patients with HER2-positive advanced gastric cancer.[33] Trastuzumab addition to chemotherapy improved the overall survival significantly (13.5 months vs. 11.5 months). There were no increased adverse effects with trastuzumab therapy.

CONCLUSION

The incidence of gastric cancer is decreasing in developed countries and more proximal cancers are reported. However, among the major population-based cancer registries in India, only Mumbai and Chennai have reported a decline in incidence. A shift from distal to proximal as the site of disease has not been reported from India. Though the AAR of gastric cancer is low in majority of PBCR, the absolute number is still high because of the size of India's population. However, when we search for the contribution of the Indian scientific fraternity to the world medical literature for gastric cancer, it is clear that a lot more is to be done; the possible reason may be a busy clinical schedule or lack of initiatives. Clinicians need to take out time from their busy clinical schedule and devote more time to research for the larger benefit to the society. There is an urgent need for research in various aspects of gastric cancer from India including epidemiological and therapeutic areas. We suggest that the scientists/clinicians from high-incidence areas take lead in this regard and we are sure that they will get all the support from well-recognized academic centers and other government agencies in this aspect. Chemotherapy and radiotherapy protocols designed to meet the requirement of our population should be designed and validated in prospective trials so as to confirm the benefit of adjuvant chemo-radiotherapy or and evaluate the tolerance and effectiveness of newer aggressive chemotherapy regimes containing docetaxel or epirubicin combined with standard cisplatinum and 5-flurouracil.

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