Gastric Cancer - An Update

Neeraj Nagaich¹* and Radha Sharma²

¹Department of Gastroenterology, Fortis Escorts Hospital, India

²Department of Pathology, RUHS CMS Medical College, India

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*****Corresponding author:** Neeraj Nagaich, Department of Gastroenterology, Fortis Escorts Hospital, Jaipur, India, Email: drneerajn@gmail.com

Introduction

The incidence of gastric cancer is highest in eastern Asia, Eastern Europe, and South America, and it affects twice as many men as women. Risk factors for gastric cancer include *Helicobacter pylori* infection, cigarette smoking, high alcohol intake, excess dietary salt, lack of refrigeration, inadequate fruit and vegetable consumption, and pernicious anaemia. Patients present with weight loss and abdominal pain, although those with proximal or gastro-esophageal junction tumours may present with dysphagia. Upper gastrointestinal endoscopy with biopsy is used to confirm the diagnosis; precise tumour stage is defined by more sophisticated radiological investigations. Multidisciplinary approach to treatment: early gastric cancer is treated with surgery alone, whereas advanced disease is usually managed with chemotherapy before and after surgery, or postoperative chemo radiation.

With improvements in detection, staging, and treatment, the over- all mortality rate from gastric cancer has similarly decreased. In spite of these gains, the overall prognosis for patients with gastric cancer remains poor, with approximately 30% surviving 5 years past their initial diagnosis. The optimal therapeutic strategy for patients with gastric cancer, particularly those classified as locally advanced, remains undefined. Although surgical resection is the mainstay of treatment for non-metastatic gastric cancers, significant controversy persists over the role of extended lymph adenectomy. Selecting an ideal treatment strategy in the neo-adjuvant or adjuvant setting is perhaps even more challenging. Metastatic disease is managed with chemotherapy or chemo radiation as well as supportive care measures.

Epidemiology and Aetiology

Globally, Gastric Cancer (GC) incidence has been shown to be more common in men and the increase with age, with most case occurring after the age of 60 years. However, GC incidence rates vary dramatically across countries. The geographic distribution of GC has been mainly attributed to difference in dietary patterns, socioeconomic status, and the prevalence of *Helicobacter pylori* infections. The highest GC incidence and mortality rates occur in Eastern Asia, Central and Eastern Europe, and South America. Mortality rates associated with GC, even in developed countries, are still very high only 28.3% of newly diagnosed cases are expected to survive 5 years of longer after diagnosis.

Stomach cancer is the second-most common cancer among men and third-most among females in Asia and worldwide. The symptoms and sign of stomach cancer are often reported late when the disease is already in advanced stages and 5-year survival is less than 30% in developed countries and around 20% in developing countries. Despite of large number of such patients being treated in, there is lack of sufficient publications on the epidemiology of gastric cancer from India. Most of the reported studies on gastric cancer from India are case reports or case series and few are case-control studies and they often deal with few specific risk factors associated with gastric cancer without looking into the entire spectrum of the disease. Hence there is an urgent need for more research is to understand the etiology, develop suitable screening test, to demarcate high-risk population.

Gastric cancer is the fourth most common cancer in the world and the second leading cause of cancer deaths worldwide with more than 700000 deaths annually [1]. After the discovery of *Helicobacter pylori (H. Pylori)* in 1983, the casual relationship between this bacterium and gastritis or gastric cancer has been steadily elucidated. In 1994, *H. Pylori* was classified as a carcinogen by the International Agency for Research on Cancer of the World Health Organization (WHO). A 2009 meta-analysis showed that *H. Pylori* eradication appeared to reduce the risk of gastric cancer [2]. In Japan, approximately 99% of gastric cancers are caused by H. Pylori; thus, *H. Pylori*-negative gastric cancer constitutes less than 1% of all cases [3]. There has been a progressing decrease in the incidence of gastric cancer around the world largely due to eradication of *Helicobacter pylori* and other risk factors that are not completely understood [4].

Across the globe and particularly in Asia, Gastric cancer remains the most common cancer among men and the most common cause of cancer related deaths in countries such as Japan. In Japan and other parts of the Asia, non cardiac tumors continue to be more common compared with the west.

Gastric Cancer Causes and Risk Factor

Infectious Agents Associated with Gastric Cancer:

Helicobacter pylori

In 1994, the international Agency for Research on Cancer classified *H pylori*, the first formally recognized bacterial carcinogen, as a class I human carcinogen for GC. *H Pylori* are involved in 90% of all gastric malignancies. *H. pylori* incidence varies according to age, ethnicity, and geographic location. In location such as Mexico, Argentian and Asia countries the prevalence of H. pylori ranges from 30% to 70% by the age of 20 years and 70% to 90% by the age of 60 years. In the US and France, the prevalence is approximately 20% and 40% for younger and older ages, respectively.

H. Pylori contributes to the development of gastric neoplasia by promoting inflammation in the gastric mucosa (gastritis), which leads to sequential histopathology changes that may result in the development of GC. However, not every individual infected with *H pylori* will develop GC. The exact path physiological mechanisms, as well as the contribution of environmental risk factors and host genetic susceptibility in the progression of gastric carcinogenesis, have yet to be fully elucidated. *H pylori* virulence factors have been associated with a higher risk of GC. Infection with *H pylori* strains with vacAC1-, vacAm-1, and cagA - Positive genotypes are associated with an approximate 6-fold increases in GC risk. Increasing evidence supports that the extent of the inflammatory response to *H pylori* is in large part determined by polymorphisms in host genes encoding cytokines and cytokine receptors individuals with pro inflammatory interleukin genotypes infected with *H pylori* strains with VacAs-1-, vacAm1-, and cagA-positive genotypes were reported to have up to an 87-fold higher risk of GC compared with H pylori-infected individuals without pro inflammatory IL -1 polymorphisms. Recently, GC stem cells were also proposed as a gastric carcinogenesis mechanism. Chronic infection with H pylori induces recruitment of bone marrow-derived cells that, once recruited, differentiate with local gastric epithelia cells, ultimately inducing stem cell properties and leading to cell metaplasia, dysplasia, and adenocarcinoma. Unfortunately, there are currently no robust biomarkers clinically available to reliably predict who will develop GC cancer after *H pylori* infection.

Epstein-barr virus

Multiple studies in different parts of the world have found the prevalence of Epstein-Barr virus (EBV) in 5% to 16% of gastric carcinomas, which supports its possible role as an etiologic agent of GC. In Asia, Europe and the America's prevalence of EBV is close to 9% of all GC cases reported. Male patients have been found to be twice as likely to have EBV-positive tumors compared with females. Tumors in the gastric cardia or corpus were found to be twice as likely to be EBV-positive compared with those in the antrum. Although the role of EBV in gastric carcinogenesis is not yet clearly defined, EBV-positivity has been reported to be associated with favorable prognosis.

Genetic predisposition

Familial gastric cancer: An estimated 20% of GC patients have a family history of GC. According to the racial or ethnic group, family history was shown to confer 2-fold to 10-fold increased risk of GC. Although most GCs are sporadic, 10% of the cases have familial clustering and 1% to 3% are hereditary. Hereditary GC includes syndromes such as hereditary diffuse GC (HDGC), gastric adenocarcinoma and proximal proximal polyposis of the stomach, and familial intestinal GC. HDGC is a rare, autosomal dominant disorder that is responsible for 1% to 3% of all familial GC cases. About 40% of individuals with HDGC have germline mutations in the CDH1 gene, which encodes E-cadherin. In the presence of CDH1 mutations, the lifetime risk of developing GC is 70% to 80%. GC can also develop as part of familial cancer syndromes, including Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, and Li-Fraumeni syndrome. GC is part of the Lynch syndrome tumor spectrum; GC risk is 2.9 times higher subjects with germline MLH1 mutations.

Demographic, environmental and risk factors

In addition to infectious agents and family history, additional GC risk factors include age, gender, certain occupations, tobacco use, diet, and being overweight, among others. The risk of developing GC is twice as high in men as in women and it is usually diagnosed between the ages of 60 to 80 years. Individuals with certain occupations, such as those who work in the coal, metal, and rubber industries, have been reported to have an increased risk of GC. Tobacco smoking has been reported to cause a 60% and 20% increase in GC risk in men and women, respectively. It is estimated that 18% of GC cases are attributable to tobacco smoking. No association has been found between smokeless tobacco and GC. In contrast, alcohol consumption has not been consistently shown to be associated with GC; however, it has been identified as a risk factor for disease progression. A 5-fold increased risk of GC has been observed as a result of the combined effect of alcohol and smoking. A high intake of salted, pickled or smoked foods, and preserved foods rich in salt and nitrites have been reported to be associated with an increased risk of GC, whereas foods rich in fiber, vegetables, and fruit were found to be protective. Individuals with moderate and high salt intake had a 1.41 and 1.68 relative risk (RR) for GC, respectively, compared with those who consumed low levels of salt. Additionally, in the presence of H pylori infection, high salt intake further increases the risk of GC. Significant associations were found between the consumption of processed meat (RR 1.45 95%, CI 1.26-1.65) and GC risk. This association between processed meats and GC been described to be stronger in subjects infected with H pylori.

Although obesity has not been found to be associated to all GCs, several meta-analyses have reported a positive association between increased body mass index (BMI) and risk of GC in the cardia.

Eradication of *Helicobacter Pylori* for Gastric Cancer Prevention

H. Pylori eradication has been one of the major therapeutic strategies to reduce gastric cancer incidence in healthy individuals and gastric cancer patients who have undergone endoscopic mucosal resection. The number of gastric cancers diagnosed and treated at an early stage increased after the development of endoscopic treatments. Ten years ago, more than 50% of early-stage gastric cancers were endoscopically treated, and the 5-year survival rate of early-stage gastric cancer patients after endoscopic treatment was 90% [4]. Large lesions can be resected en block, including both the mucosa and sub mucosa by endoscopic sub mucosal resection (ESD), which has improved histopathological diagnosis and decreased tumor recurrence. The endoscopic removal of early-stage gastric tumors does not affect the overall cancer risk. Research on gastric cancers after *H. Pylori* eradication has been conducted for more than a decade. In 2008, an open-label, randomized controlled trial indicated that the occurrence of meta chronous gastric cancer is reduced by approximately 1/3 after eradication [5]. This study led to the recommendation of *H. Pylori* eradication in patients with endoscopically treated gastric cancer. In Japan in 2013, health insurance covered *H. Pylori* eradication as a treatment for gastritis, and this treatment was expected to reduce the incidence of gastric cancer [5]. However, a subsequent Japanese study indicated that even after *H. Pylori* infection is cured and gastric inflammation is eliminated, the risk for developing gastric cancer remains; furthermore, this risk was dependent on the level of gastric mucosal atrophy present before eradication therapy [6]. Thus, the gastric mucosa endures continuous *H. Pylori*-induced inflammation that increases the risk of metachronous gastric cancer even after treatment. Previous studies revealed that *H. Pylori* eradication does not reduce the incidence of metachronous gastric cancer in patients who underwent endoscopic resection and recommended that eradication should be performed before the progression of gastric mucosal atrophy. Extensive atrophy in the stomach and intestinal metaplasia of multiple areas causes gastric cancer and may increase the risk for metachronous gastric cancer when compared with cases of chronic gastritis mucosal [7-10].

Currently, the success of a gastric cancer prevention strategy depends on timing because the treatment must be introduced before the progression of gastric carcinogenesis. However, recent studies on gastric cancer suppression suggested that critical features of gastric carcinogenesis can be reversed via molecular mechanisms.

Thus, monitoring patients for signs of gastric cancer after eradication is important. Here, we review the observed macroscopic and histological gastric mucosal changes, risks for metachronous gastric cancer, and possible approaches for reducing gastric cancer. We also discuss some of the potential molecular mechanisms for gastric cancer development after eradication.

Meta-analysis shows that *H pylori* eradication is associated with a reduction of gastric cancer risk even among high-risk individuals, supporting that *H pylori* eradication is beneficial in individuals with atrophic gastritis and/or intestinal metaplasia. Other lines of evidence also support our finding. First, almost all gastric cancer patients have atrophic gastritis and/or intestinal metaplasia, [11] and our meta-analysis showed that eradicating *H pylori* after endoscopic resection of early gastric cancer reduced the risk of metachronous cancer by 54%. Second, our population-based mass eradication program on Matsu Island of Taiwan found that *H pylori* eradication could reduce the severity or reverse the presence of atrophic gastritis among subjects with premalignant gastric lesions at baseline and reduced gastric cancer incidence by 25% from 40.3 to 30.4 per 100,000 person years.

A meta-analysis published this month in the journal Gastroenterology [1] found that treatment of the bacterium *Helicobacter pylori (H pylori)* with antibiotics in a population at high risk for stomach cancer is associated with a reduced incidence rate of stomach cancer [4].

The reduction was statistically significant when researchers looked at the effect in high-risk populations (P=.037), or older patients (P=.023). After adjustment for baseline risk, eradication of *H pylori* was associated with a risk reduction of stomach cancer amounting to approximately 50%, according to lead author Yi-Chia Lee [4] attending physician and clinical associate professor at National Taiwan University Hospital in Taipei.

Researchers concluded that past meta-analyses, which found no statistically significant benefit [2], were flawed because they did not take into account the extended follow-up time required to determine the results in a population with less risk for stomach cancer. The topic has been controversial, as the possibility of eradicating *H pylori* has been intensely studied as a possible strategy for reducing stomach cancer since 2005, when Barry Marshall and Robin Warren received the Nobel Prize for discovering the role of the pathogen in gastritis and peptic ulcer disease.

The bacterium is thought to cause stomach cancer by first giving rise to chronic inflammation of the gut, which develops into multifocal atrophic gastritis (MAG), and eventually intestinal metaplasia in which the tissue of the stomach resembles colon tissue, leading to frank adenocarcinomas. For this reason, H Pylori, which infects half the world's population, is thought to be a major global public health threat.

In the study, Lee et al. [3] performed a review of scientific literature through May 2015 of studies that examined the effect

of eradication, using sources such as PubMed, the Cochrane Library, ClinicalTrials.gov, and Digestive Disease Week abstracts. Researchers compiled data on 48,064 individuals with 715 cases of gastric cancer from the studies and abstracts, the article said. Of the studies, 14 were conducted in asymptomatic individuals with H pylori, while 10 studies were done in patients who had undergone endoscopic resection of early gastric cancers. Looking at the data set as a whole, there was no statistically significant difference in prevalence between those who underwent eradication therapy compared with those who did not (P=.67). But the baseline rate of gastric incidence varied widely between studies, ranging from 34.3 to 10,256.4 per 100,000 person-years, the article said. But when the researchers looked only at those populations with intermediate or highest tertiles of risk, the reduction in gastric cancer following H pylori eradication was statistically significant.

Helicobacter pylori eradication

Because only a very small proportion of *H Pylori*-infected subjects develop GC, the benefit of mass *H pylori* eradication campaigns to prevent GC remains unsubstantiated. However, treatment and eradication of *H Pylori* infection is recommended in patients with gastritis. *H pylori* eradication has been reported to restore gastric histology to normal in individuals with chronic gastritis and atrophic gastritis without IM. Atrophic gastritis has been reported to undergo regression within 1 or 2 years after successful eradication of *H pylori*. The presence of IM in *H pylori*-associated chronic gastritis suggests a less reversible stage compared with atrophic gastritis alone. Evidence suggests that eradication at the IM stage is less effective and that lesions are more likely to progress. In a randomized 6-years follow-up clinical trial examining the role of anti-*H pylori* treatment and dietary antioxidant micronutrient supplementation in reducing the progression of precancerous lesions, use of anit-*H pylori* treatment or antioxidants was associated with significant inhibition of precancerous lesions including IM. This reversion of gastric atrophy and IM was confirmed after 12 years. The eradication of *H pylori* in GC patients with prior endoscopic resection reduces the incidence of new tumors and the extent of 1m. There are controversial data regarding the effect of *H pylori* eradication on the development of gastric epithelial dysplasia. At present, prophylactic *H pylori* eradication is strongly recommended after endoscopic tumor resection in EGC to prevent recurrence of malignancy.

Signs and Symptoms

Early gastric cancer has no associated symptoms; however, some patients with incidental complaints are diagnosed with early gastric cancer. Most symptoms of gastric cancer reflect advanced disease. All physical signs in gastric cancer are late events. By the time they develop, the disease is almost invariably too far advanced for curative procedures.

Signs and symptoms of gastric cancer include the following:

i. Indigestion

ii. Nausea or vomiting

iii. Dysphagia

iv. Postprandial fullness

v. Loss of appetite

vi. Melena or pallor from anemia

vii. Hematemesis

viii. Weight loss

ix. Palpable enlarged stomach with succession splash

x. Enlarged lymph nodes such as Virchow nodes (i.e. left supraclavicular) and Irish node (anterior axillary)

Late complications of gastric cancer may include the following features:

1. Pathologic peritoneal and pleural effusions

2. Obstruction of the gastric outlet, gastro esophageal junction, or small bowel

3. Bleeding in the stomach from esophageal varices or at the anastomosis after surgery

4. Intrahepatic jaundice caused by hepatomegaly

5. Extra hepatic jaundice

6. Inanition from starvation or cachexia of tumor origin

Diagnosis

Testing

The goal of obtaining laboratory studies is to assist in determining optimal therapy. Potentially useful tests in patients with suspected gastric cancer include the following:

a) CBC: May be helpful to identify anemia, which may be caused by bleeding, liver dysfunction, or poor nutrition; approximately 30% of patients have anemia

b) Electrolyte panels

c) Liver function tests

d) Tumor markers such as CEA and CA 19-9: Elevated CEA in 45-50% of cases; elevated CA 19-9 in about 20% of cases

e) Imaging studies

f) Imaging studies that aid in the diagnosis of gastric cancer in patients in whom the disease is suggested clinically include the following:

i. Esophagogastroduodenoscopy (EGD): To evaluate gastric wall and lymph node involvement

ii. Double-contrast upper GI series and barium swallows: May be helpful in delineating the extent of disease when

obstructive symptoms are present or when bulky proximal tumors prevent passage of the endoscope to examine the stomach distal to an obstruction

   iii.   Chest radiography: To evaluate for metastatic lesions

   iv.   CT scanning or MRI of the chest, abdomen, and pelvis: To assess the local disease process and evaluate potential areas of spread

   v.   Endoscopic ultrasonography (EUS): Staging tool for more precise preoperative assessment of the tumor stage

Biopsy

Biopsy of any ulcerated lesion should include at least six specimens taken from around the lesion because of variable malignant transformation. In selected cases, endoscopic ultrasonography may be helpful in assessing depth of penetration of the tumor or involvement of adjacent structures.

Histologically, the frequency of different gastric malignancies is as follows [3]:

   a)   Adenocarcinoma - 90-95%

   b)   Lymphomas - 1-5%

   c)   Gastrointestinal stromal tumors (formerly classified as either leiomyomas or leiomyosarcomas) -2%

   d)   Carcinoids -1%

   e)   Adenoacanthomas -1%

   f)   Squamous cell carcinomas -1%

Management

Guidelines in Europe and the US have been proposed for management of GC depending on location, stage, and surgical candidacy. GC screening in countries with high-risk populations is effective in identifying EGC, which can be treated endoscopically. Accurate pretreatment staging is critical in identifying EGC patients with disease that is limited to the mucosa and sub mucosa (stage T1) and who are candidates for endoscopic mucosal resection of most lesions and is the preferred technique (ESD). ESD permits en bloc resection of most lesions and is the preferred technique for resecting EGC in Asia, with a complete en bloc resection rate of 87.7% and low complication rates. ESD has been reported to outperform EMR for en bloc, complete, and curative resection with lower recurrence rate. In the US, ESD is rarely performed outside referral centers with expertise in this technique. Depending on the size and location of the primary tumor, the preferred means of therapy is surgical resection with total or subtotal gastrectomy. Early Gastric cancer (EGC) is defined as a cancer confined to the mucosa and sub mucosa independently of the nodal status. The incidence of EGC in countries where there is mass screening for gastric cancer is around 53% and 5-year survival rates are above 90% in well-differentiated, mucosal lesions without nodal involvement [12].

Patients with a family history of non hereditary gastric cancer have a higher risk of developing gastric cancer. E-cadher in mutations occur in approximately 25% of families with the autosomal dominant form of hereditary diffuse gastric cancer (HDGC)

EGC is defined as tumors confined to the mucosa or sub mucosa independently of the nodal status.

EMR and ESD are comparable techniques to radical surgery in the treatment of EGC that met the strict criteria for endoscopic treatments based on large Level II-3 data source. There no randomized trials comparing EMR and gastrectomy. Radical surgery with limited lymphadenectomy (Modified) gastrectomy type A (MGA) or type B [MGB] for EGC that do not meet the criteria for endoscopic procedures should be offered as the standard of care. Gastrectomy type A [MGA] or type B [MGB] for EGC that do not meet the criteria for endoscopic procedures should be offered as the standard of care.

Treatment of Advance Gastric Cancer

The primary goal of this therapy is to improve progression-free survival (PFS) and overall survival (OS). The MAGIC trial used preoperative and postoperative epirubicin, cisplatin and 5-fluorouracil (ECF) combination chemotherapy. The role of neo adjuvant chemo radiation therapy in patients with potentially respectable esophageal and cardiac adenocarcinomas was supported in a sentinel study by Walsh et al. [13]. The extent of gastric tomy and lymphadenectomy should be tailored according to the stage of the tumor. A subtotal gastric tomy should be sufficient provided that an RO resection can be achieved. An MGA or MGB is recommended for EGC. For advanced gastric cancers expert opinion would favor radical gastric tomy with a D2 lymphadenectomy, but the best evidence currently supports gastric tomy with D1 lymphadenectomy in western patients. Extended lymphadenectomy (D3-D4) and routine pancreatictomy and/or spleenectomy are not supported by the data. A minimum of 15 lymph nodes should be harvested for adequate staging of advanced gastric cancers. There is insufficient data to recommended adjuvant therapy for node negative T1 and T2 gastric cancers. In node positive and advanced gastric cancers, adjuvant chemo radiation therapy should be offered due to the high loco regional and systemic recurrence rate. And acceptable minimal alternative after adequate R0 resection of advanced gastric cancers would be 5-fluorouracial or S-1 based chemotherapy. The high incidence of recurrence after R0 resection of advanced gastric cancer makes it imperative to recommend adjuvant therapy to optimize survival probability. Stage IV gastric patients should be offered chemotherapy as first-line therapy to prolong survival and palliation of symptoms. In highly selected group of patients, with good performance status surgery can be considered. In the presence of gastric outlet obstruction, GJJ should be offered in patients with a life expectancy of 2 months or longer.

Although several targeted therapies have been studied, only 2 targeted GC treatments have been approved for use in the US. Inhibition of human growth factor receptor 2 (HER2) has been tested as a targeted therapy for several cancers, including GC, Trastuzumab is a monoclonal antibody that targets HER2-dependent tumors. The trastuzumab for gastric cancer (ToGA) trial, a phase III international study evaluating the efficacy of trastuzumab in combination with conventional therapy (cisplatin plus 5-fluorouracil or capecitabine), showed improvement in the overall survival compared with chemotherapy alone. Ramucirumab, a human monoclonal antibody against the vascular endothelial growth factor receptor 2 (an important signaling pathway in GC and gastroesophageal cancer), is the first biologic therapy approved by the US Food and Drug Administration used as a single agent that demonstrates survival benefit in patients with advanced GC or gastroesophageal cancer who have progressed after first-line treatment.

National Comprehensive Cancer Network (NCCN) guidelines for treatment of early-stage (Tis, or T1) gastric cancer are as follows [4]:

a. Endoscopic mucosal resection or surgery are the standard treatment options

b. Complete surgical resection offers the potential for long-term survival

c. No further treatment is necessary if there is no residual disease

The NCCN guidelines for treatment of stage IB to IIIC gastric cancer are as follows [4]:

a) For medically fit patients with potentially resettable tumors, preoperative chemotherapy (category 1 recommendation) or chemo radiotherapy followed by surgery is appropriate

b) Postoperative chemo radiation or chemotherapy is indicated for patients who have undergone primary D2 lymph node dissection

c) For patients with unresettable tumors, treatment with fluoropyrimidine or taxane-based chemo radiotherapy (category 1 recommendation) or chemotherapy is acceptable.

The European Society for Medical Oncology/ European Society of Surgical Oncology/ European Society for Therapeutic Radiology and Oncology (ESMO-ESSO-ESTRO) recommendations for treatment are as follows:

1) Multidisciplinary treatment planning is mandatory; the management team should include surgeons, medical and radiation oncologists, gastroenterologists, radiologists, and pathologists plus, if available, dieticians and nurse specialists

2) T1a gastric cancers may be amenable to endoscopic resection if they are well-differentiated, ≤2cm, confined to the mucosa, and not ulcerated

3) With T1 tumors that do not meet the criteria for endoscopic therapy, lymph node dissection during open surgery can be limited to peri gastric nodes and include local N2 nodes

4) The preferred treatment for operable gastric cancers beyond stage T1N0 is surgery with both preoperative and postoperative chemotherapy

5) For patients with stage IB disease or higher who do not receive preoperative chemotherapy, the treatment options include either chemo radiotherapy or chemotherapy in the adjuvant setting.

6) Radical gastrictomy is indicated for resettable stage IB–III disease, although subtotal gastrectomy may be performed if a macroscopic proximal margin of 5cm can be achieved between the tumor and the esophagogastric junction (8cm for diffuse-type cancers)

7) For medically fit patients, D2 lymph node dissection should be standard

8) For inoperable or metastatic gastric cancer, treatment is with palliative chemotherapy, or best supportive care if the patient is unfit for treatment

9) In HER-2 negative disease, combination regimens based upon a platinum–fluoropyrimidine doublet are generally used; triplet regimens are controversial, but the addition of an anthracycline (e.g. epirubicin) has demonstrated benefit

10) In HER-2 positive disease, recommended chemotherapy is with trastuzumab plus c is platin and either 5-fluorouracil or capecitabine

11) Second-line chemotherapy options include irinotecan and docetaxel or paclitaxel

Palliative Surgical Treatment

The best palliation in GC whenever possible is still surgical resection. In fact, morbidity and mortality of palliative surgery without resection (laparotomy alone or by-pass procedures) is extremely high and should be avoided. Perhaps a better pre-operative evaluation by CT scan (heliscan) and/or laparoscopic staging indicated in selected patients could decrease the number of explanatory laparotomy in unresettable GC. Although, 25% of the patients with diagnosed GC can benefit from palliative procedures [3]. There are two different types of the palliative treatment of GC: resection of the tumor and surgical by-pass procedures without resection. Actual pre-operative investigations can not always predict the type of operative procedure as exactly as during operative exploration. Laparoscopic staging could be indicated in these conditions. Mostly, in many cases, the possibility of tumoral resection appears to surgeons as a perioperative finding, and per-operative manual exploration may find hepatic metastasis, wide or localized peritoneal implants. In these conditions, palliative surgery depends on local anatomy and preoperative clinical symptoms. A bleeding tumor is more to be resected than an obstructive one for which a by-pass might be

recommended. In a general manner, oncologic rules of resections must respect the followings: little free margin on surrounding organs, inutility of lymph node dissections, unless it is required to obtain a free margin. There is a lower mortality and morbidity in palliative resections rather than in by-pass without resections. However, by-pass procedures can still be indicated when resection risk appears to be too high (morbidity and mortality) and/or in case of biliary and/or digestive obstruction. Then, a gastroenterostomy and/or a biliary diversion may be realized.

Non Operative Treatment

Non surgical treatment represents 30% of diagnosed GC [3] and is indicated in case of diffuse hepatic, peritoneal and/or extra-abdominal metastasis without obstructive symptoms, sub-clavicular lymph nodes and/or the presence of severe physiological disorders and/or undernutrition. Treatment in these cases is difficult and varies from abstention to endoscopic des obstruction (endoscopic laser therapy, argon beam, heater probe coagulation therapy, endoscopic stent). Chemotherapy can be indicated only in phase II protocols.

Progress in Treatment of Advanced Gastric Cancer

Cancer immune therapy agents have gained great attention over the past several years for their exciting results across various types of cancer. Immunotherapies have been tested in melanoma, breast, prostate, kidney, and lung cancers, and are now being studied in advanced gastric cancers. Two monoclonal antibody agents, pembrolizumab (Keytruda) and nivolumab (Opdivo) have already shown promising results for their antitumor activity in PD-L1-positive advanced and metastatic gastric and gastro esophageal junction cancers [10].

Pembrolizumab

Pembrolizumab is an anti-PD-1 antibody tested in the treatment of several types of advanced cancer. The FDA has approved the use of pembrolizumab for the treatment of metastatic melanoma and advanced non–small cell lung cancer, and it has provided the drug with breakthrough status for relapsed or refractory classical Hodgkin lymphoma.

Pembrolizumab was studied in the treatment of PD-L1-positive recurrent or metastatic adenocarcinoma of the stomach or gastroesophageal junction in the phase Ib Keynote-012 study. Findings from the study were presented at the 2015 ASCO Annual Meeting.

The study was completed across 13 cancer research centers in the United States, Israel, Japan, South Korea, and Taiwan, to compare the results of patients from the Asian Pacific-where gastric cancers are more common-to patients from the rest of the world.

Archival tumor samples from 162 patients were screened for PD-L1 expression using a prototype immune histochemistry assay with the 22C3 antibody. Sixty-five patients (40%) were found to be eligible, of which 39 patients enrolled in the study and 36 of 39 were evaluable for assessment.

At baseline, there were 19 Asian patients and 20 patients from elsewhere in the world. Of these, the primary tumor site for the 19 patients from Asia was the stomach compared with 9 of the patients from the rest of the world. The gastro esophageal junction was the primary site for the remaining patients (n=11). At least 2 prior therapies for advanced disease were received by 67% of all patients.

Patients were given pembrolizumab intravenously at 10mg/kg every 2 weeks for up to 24 months with responses tested every 8 weeks. As of the 12-month mark, 42% of the patients were still alive. Objective response rate (ORR) was 22% (95% CI, 10%-39%) according to central review and 33% (95% CI, 19%-50%) by investigator review. Partial response (PR) was experienced by 8 patients and 5 patients had stable disease (SD). No complete responses were observed.

Thirty-three patients (85%) discontinued treatment on pembrolizumab, 32 due to progressive disease and 1 due to an unrelated adverse event (AE). According to the investigator review, 26 patients (67%) had at least 1 treatment-related AE, including mostly grade 1/2 fatigue (13%), decreased appetite (13%), pruritus (13%), hypothyroidism (10%), and arthralgia (10%). Five patients (13%) experienced grade 3/4 AEs including 2 cases of grade 3 fatigue, grade 3 pemphigoid, grade 3 peripheral sensory neuropathy, grade 3 hypothyroidism, and 1 grade 4 pneumonitis. Four patients (10%) temporarily stopped treatment due to immune-mediated toxic effects and 2 of these patients were unable to continue, 1 due to progressive disease. One treatment-related death was noted in the abstract for the 2015 ASCO Annual Meeting but not in the final report.

Pembrolizumab is also being tested in additional clinical trials for gastric cancer treatment, including one phase III trial of pembrolizumab versus paclitaxel for treatment of progressive disease after previous platinum and fluoro pyrimidine-based chemotherapy treatment.

Nivolumab

Nivolumab is a fully human immunoglobulin G4 monoclonal antibody that has already received FDA approval for the treatment of advanced renal cell carcinoma, non-small cell lung cancer, Hodgkin lymphoma, and unresectable or metastatic melanoma. The therapy has also received a breakthrough therapy designation for recurrent or metastatic squamous cell carcinoma of the head and neck. In the phase I/II CheckMate-032 study patients with advanced or metastatic gastric or gastroesophageal junction cancer were treated with nivolumab or nivolumab plus ipilimumab. A majority of the patients (83%) had already received 2 or more prior treatments for gastric cancers. Patients were enrolled into the study regardless of their PD-L1 expression but responses were tested for both PD-L1-positive and -negative tumors. According to findings to be presented at the 2016

Gastrointestinal Cancers Symposium, single-agent nivolumab was well tolerated by pretreated patients. ORR was 12% with 1 complete response and 6 partial responses out of 58 patients, and 12 patients (21%) had stable disease. The median duration of response among responders was 7.1 months (95% CI, 3.0-13.2). The median overall survival duration was 6.8 months (95% CI, 3.3-12.4), with a 1-year survival rate of 38% (95% CI, 23.2-52.7). Patients with PD-L1-positive (39%) and -negative (61%) tumors had ORRs of 18% and 12%, respectively. At the time of the analysis, 10 patients were still on active treatment and 49 had discontinued, 40 due to progressive disease, 4 from unrelated AEs, and 2 from treatment-related AEs. Overall, treatment-related AEs occurred in 66% of patients, mostly low-grade, yet 14% experienced grade 3/4 AEs including pneumonitis, fatigue, diarrhea, vomiting, hypothyroidism, and increased aspartate, alanine aminotransferase, and alkaline phosphatase levels. No treatment-related deaths occurred. Findings are yet to be released for the patients that were treated with both nivolumab and ipilimumab. The nivolumab/ ipilimumab combination is FDA-approved for advanced metastatic melanoma.

Further clinical trials for the treatment of gastric cancer are ongoing. While these are just the first steps in immunotherapy research for gastric cancer, further research could result in increased survival rates for patients with advanced gastric cancers. Although substantial improvements in the management of gastric cancer have been made over the past several decades, overall out comes remain disappointing with unsatisfactory cure rates in all but the earliest-stage patients. The optimal treatment paradigm for most patients with gastric cancer remains unclear and may vary with tumor histology and location. Furthermore, it appears that the traditional pillars of oncology are approaching their limits, and that future innovations are sorely needed. Targeted agents, novel radio sensitizers, and even new modalities may be necessary to improve upon the successes of the past half-century. However, radiotherapy continues to play a crucial role for many patients, particularly those who did preoperative therapy, are found to have positive lymph nodes, retain residual disease following surgery, or are unresettable at diagnosis. The role of a trimodality approach in the neoadjuvant setting is promising, but its use is still investigational [14-21].

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