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Gastric Cancer: A Mini Review

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1. Abstract

Gastric cancer is the fourth most common cancer-related death and the fifth most prevalent cancer across the world. It can have a variable clinical presentation and often can be diagnosed at an advanced stage with associated poor prognosis. Clinicians need to be aware even in the developed countries regarding this devastating upper gastrointestinal malignancy.

2. Introduction

With almost one million new cases of gastric cancer reported every year, the World Health Organization identified this as a public health problem. It ranks as the fourth most common cancer-related death and the fifth most prevalent cancer across the world [1]. Especially among older males, gastric cancer (GC) is a frequent malignancy with a high case fatality rate [1]. The total number of GC cases diagnosed has increased despite a decline in the global incidence of the disease. Younger people are much more likely to acquire GC, consistent with a bimodal presentation distribution [2]. (J Natl Cancer Inst. 2018 Jun; 110(6): 608–615)[3]. Overall incidence and deaths are declining due to better surveillance, detection, and treatment. Despite significant declines in incidence and death, stomach cancer continues to contribute to the overall burden of cancer worldwide [4]. H. pylori infection, gastric intestinal metaplasia, and, to some extent, the EBV virus are major risk factors for gastric cancer. Geographic location, age, sex, socioeconomic status, smoking, eating salty meats, and heredity are other risk factors [5]. To develop more specialized, focused preventative strategies, many of the risk variables still need to be studied further. This review article provides a brief overview of the epidemiology and risk factors, pathogenesis, clinical features, diagnosis, and management. Clinicians need to be aware of this malignancy given its high fatality.

3. Epidemiology

3.1. Global Trends

In 2020, stomach cancer-related deaths worldwide were 800,000, and new cases were approximately 1.1 million, according to GLOBOCAN [6]. Stomach cancer is predicted to be the fifth most common cancer (accounting for 7.7% of cancer deaths), liver cancer at 8.3%, colorectal cancer at 9.4%, and lung cancer at 18% of all cancer deaths, with a 7.6% incidence rate of stomach cancer in males and a 7.0% incidence rate in females. Significant variances between the sexes and across numerous nations and regions occur. In men, stomach cancer is projected to be the fourth most common cancer in 2020 [6-7]. However, there are also significant country-level variations in the development of GC. While studies show that GC is the fourth time more frequently diagnosed cancer in men, geographical variations in incidence are everywhere. There were 22.4 stomach cancer cases per 100000 in Eastern Asia in 2020, followed by 11.3 cases in Central and Eastern Europe, 9.2 cases in South America, and 8.6 cases in Western Asia [7]. Southern Africa has the lowest rate (3.3 per 100000 persons). Asia contributes to more than 75% (819944; 85.3%) of all cases of stomach cancer. Most stomach cancer cases (86.7%; 944591 cases) impacted those who lived in more developed areas [7]. Gastric cancer cases were the lowest in Micronesia and Polynesia. There are noticeable regional differences in the incidence and mortality rate of GC in 2020 [2]. Eastern Asian nations, includ-

ing Mongolia, Japan, and the Republic of Korea, had the greatest incidence rates. In contrast, western Asian nations had the highest death rates (Tajikistan, Kyrgyzstan, Iran). Incidence and fatality rates for stomach cancer were lowest in various African nations, Australia/New Zealand, North America, and Northern Europe. [7]. There are over 85% of stomach cancer cases in countries with extremely high and high Human Development Index (699000 and 360000 cases, respectively) [8]. Most stomach cancer cases (nearly 820,000 new cases and 582,000 deaths) occur in Asia (mainly in China). The estimated five-year survival rate is lower than 20%.[8]. Since highly virulent H. pylori strains are found in Southeastern and Eastern Asia, regions with high Human Development Index levels, which shows the prevalence of gastric cancer in adults 76% vs. 58% in developed countries in 2020, environmental factors, particularly H. pylori infection, most likely explain this [9].

In a recent North American Study utilizing Central Cancer Tumor Registries, there were 137 447 non-cardia gastric cancers in 4.4 billion person-years of observation. Non-Hispanic whites, the rate was 2.2 per 100 000 person-years, with an estimated annual percentage change of –2.3% (95% CI = –2.0% to –2.6%). Although overall percentage has declined, for the age <50 years, annual percentage rose 1.3% (95% CI = 0.6% to 2.1%) and fell –2.6% (95% CI = –2.4% to –2.9%) for age >50 years. (J Natl Cancer Inst. 2018 Jun; 110(6): 608–615) [3].

3.2. Risk Factors

There are several risk factors that are implicated in the pathogenesis of gastric cancer including diet, use of tobacco products, alcohol, infections. Being able to identify some of these risk factors and counselling patients on elimination or eradication is important especially in those with high-risk family history.

3.3. Diet

Gastric cancer development has been extensively studied for associations with dietary factors. Multiple research studies have concluded that vegetables and fruits protect from GC, while braised, grilled meat, salt-preserved foods, and smoked foods are likely to accelerate the progression of GC [10]. Food contaminants may react with gastric epithelial cells and cause alterations in the expression of genes. The stomach mucosa was reportedly destroyed by excessive sodium chloride consumption in animal models, promoting cell death and regenerating cell growth [11]. N-nitroso compounds have been shown to dramatically increase the chance of developing gastrointestinal cancer, mainly in non-cardia GCs, whether consumed or produced internally.

3.4. Smoking and Alcohol

Since smoking and alcohol consumption are implicated in GC development, the influence of these activities has been investigated. According to research, GC risk is 80% more prevalent in non-drinkers who smoke than in those who don't. In addition, GC risk is also higher among heavy drinkers; a group of smokers is estimated to have a GC risk of 80% in addition to smoking [12]. Four hundred forty-four patients were studied in the prospective cohort study. Alcohol consumption was directly associated with GC risk, whereas a lower frequency wasn't [13]. Cancer of the intestinal non-cardia was related to alcohol consumption. A study involving the Korean population with the ALDH2 genotype to determine whether alcohol intake contributed to GC development. Compared to patients who never or rarely drank, those who were currently/ex-drinkers had a higher likelihood of developing cancer. In this study, patients with ALDH2 polymorphisms who drank alcohol had a higher risk of developing GC [14].

3.5. Infections

Since 1994, the Gram-negative bacteria Helicobacter pylori (H. pylori) is identified as a class I GC development factor by World Health Organization. Two basic mechanisms are identified to explain how H. pylori affects the oncogenesis process: a direct epigenetic influence on gastric epithelial cells and an indirect inflammatory response to the gastric mucosa [15]. The chance of developing GC due to tissue inflammation along with preinvasive lesion in the distal stomach rise with many H. pylori virulence factors, such as CagA or VacA [16-17]. In addition, infection degrades the microenvironment of gastric mucosa, increasing the epithelial-mesenchymal transition (EMT) to progress into GC [18]. The Epstein-Barr virus (EBV) being a pervasive infectious agent is the second most linked infection to the development of GC after H. pylori infection. Tumor cells and these cells express the transforming EBV proteins [19]. Although it has been estimated that 10% of GCs are EBV-positive, there needs to be more proof to conclude that EBV plays a specific etiological role in developing GCs [20]. EBV-positive gastric carcinomas vary depending on the patient's features, such as sex, age, or anatomic subsite. Patients with EBV-positive gastric cancer were diagnosed at average age was 58 years old, and 71% of them are men and occurred mostly in the proximal stomach. (Helicobacter (2016) 21(2):153–7. 10.1111/hel.12249) [21].

3.6. Pathogenesis

Like other malignancies, the pathogenesis of gastric cancer (GC) is the consequence of the interaction of several risk factors and preventive factors. The genesis of the illness is likely to be influenced by environmental and genetic factors as well. The most frequent environmental culprits associated with the pathogenesis of GC are nutrition and Helicobacter pylori infection. Numerous research studies on the epidemiology and pathogenesis have revealed that the sequential stages of gastric carcinogenesis are chronic gastritis, atrophy, intestinal metaplasia, and dysplasia (Image 1). Gastric adenocarcinoma arising in the background of intestinal metaplasia). Excessive salt consumption and H. pylori infection have been connected to the early stages [22-23]. As a peptide hormone, gastrin can only directly influence cells with a gastrin receptor, making it a key player in the development of gastric cancer. Gastrin encourages the ECL cell's

growth and histamine release. Every disease that causes a state of chronic hypergastrinemia in humans and animals puts them at risk of developing stomach cancer [24]. Since Helicobacter pylori infection occurs exclusively in the antrum, it is possible to rule out a direct carcinogenic impact of Helicobacter pylori on the stomach mucosa as it protects against gastric cancer. Atrophic gastritis must have formed for the propensity to gastric cancer, even with the inflammation of the oxyntic mucosa; studies revealed that tumors would start across the whole stomach, not just in the oxyntic mucosa from gastric hypoacidity. People are predisposed to developing gastric cancer through secondary microbiological infections. As a result, hypergastrinemia may be a pathogenic factor for developing cancer due to Helicobacter pylori infection. [25]. If true, gastric carcinogenesis must include the Enterochromaffin cell (ECL cell), the only identified target cell for gastrin. This has been a topic of odd disagreement. Studies even asserted that the ECL cell does not multiply in humans [26]. However, it has been well demonstrated that this cell does so in rats [27]. It was challenging to comprehend the resistance to accepting that the ECL cell did divide since the ECL cells appear in clusters in hypergastrinemic individuals. Since then, it has been acknowledged that the ECL cell multiplies and gives birth to neuroendocrine stomach tumors (NETs). Except for NE carcinomas, the involvement of ECL cells in gastric carcinogenesis has been refuted. In addition, immunohistochemistry was able to detect NE markers with greater sensitivity in gastric carcinomas in patients with pernicious anemia and individuals with autoimmune gastritis [28]. We may deduce from extensive research on gastric cancers that a significant number could be labeled NE tumors, especially those that Laurén defined as diffuse [29]. The signet ring subgroup of diffuse-type gastric carcinomas has notably high levels of NE differentiation. Although these carcinomas are PAS-positive, they lack mucin expression indicators [30]. Genetic factors significantly influence the development of gastric cancer. These factors either cause defective genes to be overexpressed or normal genes to be expressed improperly, giving the malignant phenotype. Several genetic changes have been identified, most notably intestinal changes; their formation is likely to be a multi-step process. The loss of heterozygosity of tumor suppressor genes, notably of the p53 or "Adenomatous Polyposis Coli" gene, is one of the most frequent genetic anomalies in gastric cancer [31]. The latter causes gastric oncogenesis by altering the E-cadherin-catenin complex, essential for maintaining healthy tissue architecture. Cell-cell adhesion is lost when one of its components is mutated, contributing to neoplasia. Families with a hereditary propensity to diffuse gastric cancer have been shown to have germline mutations in the CDH1/E-cadherin gene. GC has also been linked to putative trophic factor amplification or overexpression. Serial analysis on gene expression (SAGE) was applied to compare the gene expression profiles of typical gastric cancer tissues with those of normal gastric tissue and to precisely identify the down-regulated genes. They chose roughly 60 genes in their gastric cancer libraries. They used real-time polymerase chain reactions to evaluate how these genes were expressed in healthy human tissues. [32] This knowledge of gene polymorphism will be helpful for cancer prevention whose expression is significantly changed in people with cancer and may be a novel risk factor.

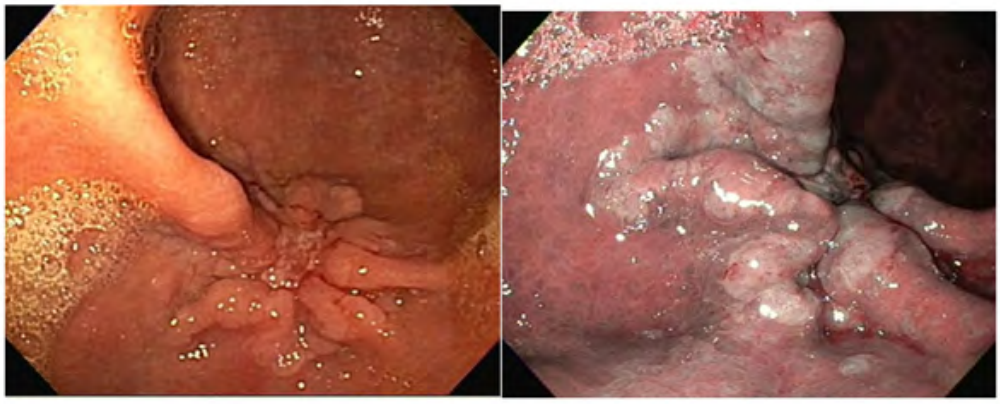
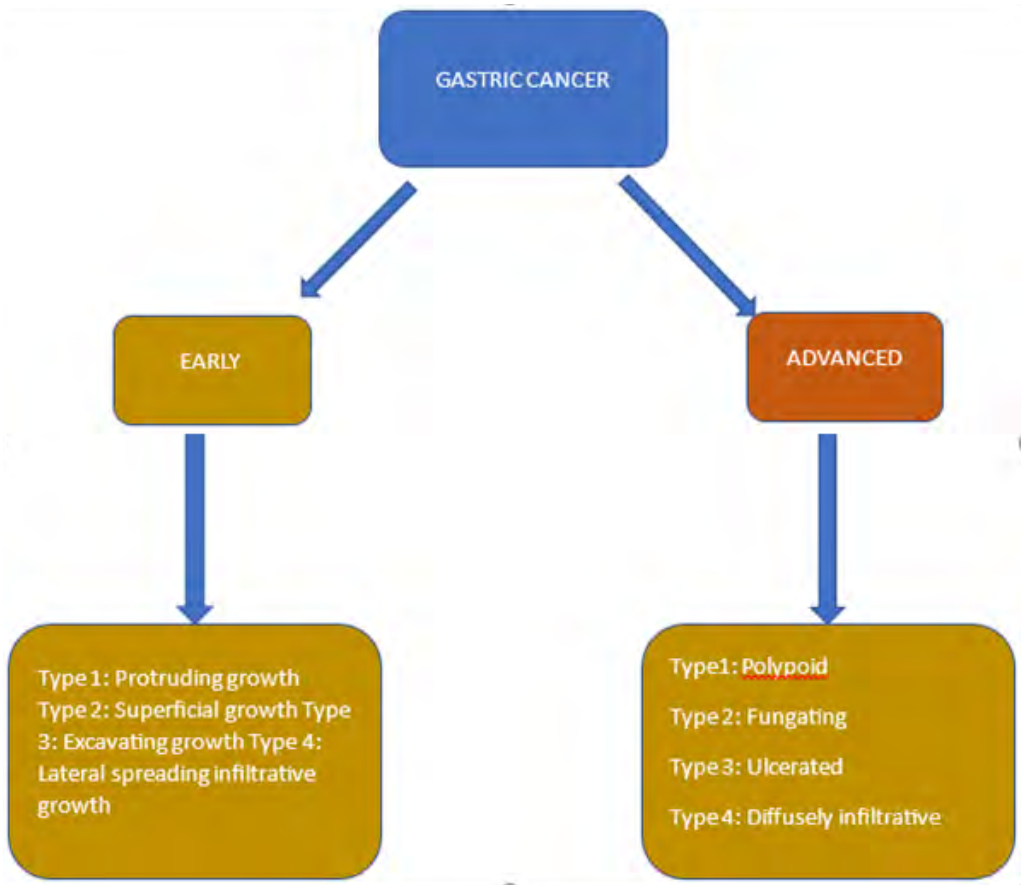


Figure 1: Gastric adenocarcinoma (Advanced, Type 3) arising in the background of gastric intestinal metaplasia. A. High definition wight light endoscopy B. Virtual chromoendoscopy with narrow band imaging.



4. Types of Gastric Cancer

Over the years, several classification systems for gastric cancer have been proposed. In 1965, Lauren in their landmark paper proposed two major histomorphological types of gastric cancer – intestinal type and diffuse type [33]. Those tumors with unclear histology were classified as indeterminate. Both the major subtypes are characterized by distinct epidemiology, prognosis, pathogenesis, and gross morphology.

4.1. Intestinal Type: The cells form glandular arrangements and adhere to each other, like adenocarcinomas. They are commonly found in the elderly with a male preponderance and lend a better prognosis [33].

4.2. Diffuse Type: There is a lack of gland formation and cohesiveness among the cancerous cells which allows the tumor to diffusely invade the gastric wall. This type has a nearly equal prevalence in both genders, affects a younger demographic, and bestows a poorer prognosis as compared to the intestinal type [34]. The Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC) proposed the tumor, node, metastasis (TNM) staging system that is universally accepted and provides prognostication of the malignancy [35]. It was most recently revised in 2017, where they differentiated between esophageal cancers and gastric cancers based on tumor epicenter location and involvement of the gastroesophageal junction. The World Health Organization (WHO) classification system of gastric cancers issued in 2010 and revised in 2019 gives a detailed categorization of the types of gastric malignancy based on the histological features and molecular phenotype [36]. Some of the major histological subtypes described include papillary, tubular (well, moderately, and poorly differentiated), poorly cohesive signet-ring, and other phenotypes, mucinous and mixed. It also goes on to describe certain rarer histological subtypes such as adenosquamous, hepatoid, undifferentiated, and varied adenocarcinomas. The early and advanced gastric carcinoma classification first originated in Japan and is widely used by multiple cancer societies and international groups.

4.3. Early Gastric Cancer: This is an invasive tumor that is restricted to the mucosa or submucosa without lymph nodal metastasis, irrespective of the size of the tumor. It has an excellent prognosis when compared to advanced cancers with a 5-year rate of survival nearing 90% [37]. The Japanese Endoscopic society has proposed a further sub-classification of early gastric cancers (EGC) into protruding growth (type 1), superficial growth (type 2), excavating growth (type 3), and lateral spreading infiltrative growth (type 4). In general, most EGCs can be adequately managed surgically.

4.4. Advanced Gastric Cancer: These cancers invade beyond the submucosa into the muscularis propria and the deeper tissues. In contrast to EGC, advanced gastric cancers (AGC) have a very poor prognosis with a 5-year survival of about 60% [38]. Based on Bormann's classification, they are sub-classified based on tumor morphology in 4 types which are polypoid, fungating, ulcerated, and diffusely infiltrative [39].

5. Clinical Features

Gastric cancer can be asymptomatic in the early stages but presents with several signs and symptoms in the more advanced stages. Weight loss, anorexia, indigestion, and abdominal pain are some of the most commonly associated symptoms of gastric cancer [40]. Early satiety and nausea result from the tumor mass occupying the gastric cavity or by causing a gastric outlet obstruction in the antrum. This reduced food and caloric intake and increased catabolic demands in turn lead to cachexia. The abdominal pain is typically epigastric and worsens in intensity as the cancer progresses. When located at the gastroesophageal junction (GEJ) or in the proximal stomach, dysphagia is common in addition to indigestion and acid reflux. Gastric cancers can also present as upper gastrointestinal bleeds which may be occult or overt (melena and hematochezia) and may or may not result in iron deficiency anemia [41]. Distant metastasis of gastric cancer can have a few varied presentations depending on the location. Peritoneal carcinomatosis usually presents as ascites or a Krukenberg tumor on the ovary [42]. Liver metastasis can be focal or diffuse and presents as an elevation in the serum alkaline phosphatase levels with or without a palpable liver mass. Clinical evidence of hepatic dysfunction is seen with advanced liver metastatic disease and indicates a very poor prognosis. On physical exam, a palpable epigastric mass is the most common finding but is suggestive of advanced cancer. In those with the lymphatic spread of cancer, palpable lymph nodes may be discovered in the left supraclavicular area (Virchow's node) [43], left axillary (Irish node), or periumbilical nodule (Sister Mary Joseph's node) [44]. In rare cases, gastric cancer is associated with paraneoplastic syndromes but is not typically seen on initial presentation. Leser-Trélat sign is a dermatological manifestation characterized by the abrupt onset of severe seborrheic keratoses which are darkly pigmented patches seen with gastric cancer but is also associated with other gastrointestinal malignancies [45]. Some of the other paraneoplastic manifestations include hemolytic anemia and a hypercoagulable state leading to thrombosis (Trousseau's syndrome) [46]. An important consideration in metastatic gastric cancers is to distinguish them from other primary cancer that metastasizes to the stomach. This distinction can be made on endoscopic appearance or biopsy and is essential for the early diagnosis and appropriate therapy for malignancy [47].

6. Diagnosis

The early diagnosis of gastric cancer is essential for prompt treatment initiation and to improve survival as evidenced by an improved prognosis of early gastric cancers when compared to advanced disease [48]. Upper gastrointestinal endoscopy remains the most effective method for the initial diagnosis [49]. It enables visualization of the morphological features of the tumor, localization, and tissue biopsy for a histopathological diagnosis. Recent studies have also demonstrated the use of narrow-band imaging in the improved detection of EGC and pre-malignant lesions [50]. Grossly, gastric tumor commonly has an ulcerated friable appearance. Malignant ulcers often have irregular, thickened, and overhanging margins (Image 1). Endoscopy may be non-diagnostic for linitus plastica which is a particularly aggressive gastric malignancy characterized by extensive infiltration of the submucosal and muscularis propria, such that the mucosa appears normal [51]. An important condition to be cognizant of would be Menetrier's disease, a pre-malignant condition that results in the thickening of the stomach wall [52]. Biopsy for tissue diagnosis should be obtained from suspicious and smaller benign appearing gastric lesions since 5% of malignant ulcers can appear benign [53]. Obtaining multiple biopsies increases the sensitivity of tissue diagnosis to 98% [53]. When there is a high suspicion of diffuse gastric cancer, a combination of bite and strip biopsy must be employed to ensure adequate deeper tissue specimens of histopathological studies [54]. Contrast-enhanced computed tomography (CT) abdominal imaging is the preferred non-invasive modality for the evaluation of the extent and location of the primary tumor. In all patients with a suspected or confirmed gastric malignancy, a CT with oral and intravenous contrast of the chest, abdomen, pelvis, and head detects signs of metastasis like hepatic lesions, ascites, peritoneal metastases, adnexal spread, and lymph nodal disease [55]. Endoscopic ultrasound, although an invasive imaging modality, is the most reliable non-surgical method for the evaluation of the depth of invasion. It can distinguish T1 tumors limited to the submucosa, T2 tumors penetrating the muscularis propria, and the more advanced T3 and T4 tumors with high sensitivity and specificity [56]. All patients must be staged according to the AJCC/UICC method to determine the appropriate treatment options. A positron emission tomography-CT scan can detect occult metastases and is used to determine treatment response and disease recurrence or progression [57].

7. Management

Studies have shown that a combination of surgical and non-surgical therapy is the most effective for non-metastatic gastric cancer. Specific modalities include endoscopic surgery, gastrectomy, antibiotic therapy for H.pylori eradication, and adjuvant therapies like chemotherapy, radiation therapy, and immunotherapy.

8. Endoscopic Resection

It is considered the first-line therapy for the majority of early gastric cancers and is considered the definitive treatment unless there is a substantial risk of locoregional nodal metastasis [58]. Some of the standard criteria for endoscopic resection include the absence of lymphovascular invasion, differentiated histology, a size smaller than 20 mm in diameter, and a mucosal tumor without ulceration [59]. Endoscopic mucosal resection (EMR): There are a variety of modified techniques such as cold snare-EMR, injection-assisted-EMR, and cap-assisted-EMR for the resection of the lesion, either en-bloc or in a piecemeal manner [60]. It has a short learning curve and is technically reproducible with reliable results. Studies have shown higher cure rates and improved survival in patients who undergo EMR for early gastric cancers [60]. Endoscopic mucosal dissection (ESD): This is a more specialized technique employing a needle-knife for

dissecting the lesion through the submucosa that has a steeper learning curve and is technically more challenging compared to EMR [61-62]. It includes marking of the tumor, submucosal injection to raise the lesion, mucosal incision, and then submucosal dissection of the tumor followed by en-bloc retrieval of the tumor. Even though ESD requires longer procedure times, endoscopic expertise, and a higher complication rate it is more likely to result in total resection of the tumor with lower fewer local recurrences [61-62].

9. Gastrectomy

For gastric malignancy with lymph nodal spread and without distant metastasis, surgical resection is the mainstay of treatment with lymph node resection combined with peri-operative or adjuvant chemotherapy [63]. Gastrectomy can either be complete (resection of the entire stomach with anastomosis of the small bowel to the esophagus), or partial (resection of the distal two-thirds of the stomach with anastomosis or the proximal stomach to the small intestine) [63]. The procedures that preserve the pylorus result in a lower incidence of complications like dumping syndrome and weight loss while also providing acceptable outcomes for T1 cancers that are not amenable to endoscopic resection [63].

10. Helicobacter Pylori Eradication

H.pylori is a well-established risk factor for gastritis, gastric ulcers, and gastric cancer. Established regimens for treatment include triple therapy with clarithromycin, amoxicillin, and proton pump inhibitor (PPI) or quadruple therapy (bismuth subsalicylate, tetracycline, metronidazole, and PPI) for 14 days. The eradication of H.pylori after endoscopic resection was associated with a lower occurrence of gastric cancer [64]. Hence, treatment is recommended for all cases of early gastric malignancy with concomitant H.pylori infection.

11. Chemotherapy

11.1. Peri-Operative or Neoadjuvant Chemotherapy

Chemotherapy prior to surgical resection for patients with locoregional disease of T2N0 and greater results in greater curative rates after resection, elimination of micro-metastasis, downstaging of the tumor prior to surgery, and better assessment of prognostication for those who have progression of the malignancy during chemotherapy [65]. The MAGIC trial by the UK Medical Research Council demonstrated improved 5-year-survival in those with resectable stage 2 and 3 cancers undergoing 6 cycles of chemotherapy with epirubicin, cisplatin and 5-fluorouracil (ECF) in comparison to surgery alone (36% vs 23%) [66]. Recently, the FLOT regimen with 5-fluorouracil, folinic acid, oxaliplatin, and docetaxel has shown improved overall survival, higher resection rates, and better pathological response compared to the ECF regimen in randomized control trials (RCT). This has made it the standard of care for those with locally advanced early gastric malignancy who are able to tolerate this regimen [67]. The generally recommended duration of pre-operative and post-operative chemotherapy is 2 to 3 months [68].

11.2. Post-Operative Chemotherapy

There has been mixed evidence on the benefit of postoperative chemotherapy in locally advanced malignancy with N1 disease and all patients with T3-4N0 disease. Although the evidence from several RCTs indicated mixed results when overall survival was measured as a primary endpoint, meta-analyses have shown there is a considerable improvement in overall survival and disease-free survival in those that received postoperative chemotherapy with platinum or 5-fluorouracil-based regimens [69]. Most studies suggest a higher benefit in eastern populations compared to western populations.

11.3. Radiation Therapy

Evidence of adjuvant chemoradiation therapy for the use of gastric cancer is limited and the role is uncertain. The National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant chemoradiation after microscopic (R1) or macroscopic (R2) residual cancer and as adjuvant therapy for T3-T4 pathology, or lymph node disease is when less than D2 lymph nodal dissection is performed [70].

11.4. Immunotherapy

In the past few years, promising advances in the immunologic therapy of gastric cancer that target specific molecular signaling mechanisms have been made. The programmed cell death-ligand 1 (PD-L1) pathway is the most studied among the immune checkpoint inhibitors. It is an accepted line of therapy for gastric cancer that has progressed even after treatment with at least 2 lines of chemotherapy. Pembrolizumab and nivolumab are two monoclonal antibodies to PD-1 that have been studied in RCTs for the treatment of gastric cancer. The KEYNOTE-062 trial showed pembrolizumab to be non-inferior to chemotherapy in those with gastric cancer positive for PD-L1 [71]. The ATTRACTION-2 demonstrated improved overall survival in Asian patients treated with nivolumab in comparison to placebo plus supportive care [72]. Further trials are underway to assess the utility of these agents in gastric cancer therapy. HER2 overexpression is seen in about 15 to 20% of advanced gastric adenocarcinomas, commonly in the intestinal type of cancer and those located at the gastroesophageal junction [65]. The humanized monoclonal antibody against the HER2 receptor, Trastuzumab, inhibits the downstream signaling leading to antibody-induced cellular toxicity. The 3toGA trial has established trastuzumab in addition to chemotherapy as the standard of care for the treatment of HER2-positive gastric malignancy by demonstrating improved overall survival in those with trastuzumab with chemotherapy in comparison to chemotherapy only [73]. Ramucirumab is a monoclonal antibody targeting VEGF-2 that has shown a survival advantage as the second-line therapy of gastric cancer, in combination with paclitaxel and as monotherapy [74].

12. Conclusion

Gastric cancer is an important disease with high morbidity and mortality worldwide. There have been profound advances in the classification, diagnosis, and treatment modalities that are available. Es-

pecially in recent years, endoscopic surgery has improved outcomes and reduced complications in patients with resectable early cancers. With the identification of newer molecular markers and immunotherapeutic agents, there is a lot of promise for future systemic therapy with metastatic disease. Numerous randomized controlled clinical trials are underway to assess the best combination of chemotherapy, immunotherapy, and radiation for both surgically and non-surgically treatable cancers.

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