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REVIEW ARTICLE

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Review: Prevention and management of gastric cancer

Marino Venerito[1] | Alexander C. Ford[2,3] | Theodoros Rokkas[4] | Peter Malfertheiner[1,5]

[1]Department of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital, Magdeburg, Germany

[2]Leeds Gastroenterology Institute, St. James's University Hospital, Leeds, UK

[3]Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK

[4]Gastroenterology Clinic, Henry Dunant Hospital, Athens, Greece

[5]Department of Internal Medicine II, Ludwig Maximilians University Hospital of Munich, Munich, Germany

Correspondence
Marino Venerito, DepartCapacitive Deionizationment of Gastroenterology, Hepatology and Infectious Diseases, Otto-von-Guericke University Hospital, 39120 Magdeburg, Germany.
Email: m.venerito@med.ovgu.de

Abstract

Gastric cancer (GC) is still the fifth most frequently diagnosed cancer and the third leading cause of cancer deaths in both sexes worldwide. Although the incidence of GC is predicted to continue declining in a growing number of countries in the future, on a global scale the number of newly diagnosed GC cases will remain high, or increase even further, due to changes in population size and increasing risks observed in younger generations. In a retrospective cohort study, collecting data from the Veterans Health Administration, treatment of *Helicobacter pylori* infection decreased GC risk only if eradication was successful. In a German case-control study, among GC patients with autoimmune gastritis, pernicious anemia was associated with earlier detection of GC, which translated into a significantly better 5-year survival. In an updated meta-analysis, *H. pylori* eradication therapy in healthy individuals significantly reduced both GC incidence and mortality from GC with a number needed to treat of 72 and 135, respectively. In Korea, successful *H. pylori* eradication substantially reduced GC incidence in first-degree relatives of GC patients as well. A meta-analysis of four trials including 1,556 patients with resectable GC reported that the patient subgroup tumors with high microsatellite instability undergoing surgery did not benefit from perioperative or adjuvant chemotherapy.

KEYWORDS

autoimmune gastritis, epidemiology, gastric cancer, *Helicobacter pylori*, prevention, therapy

1 | INTRODUCTION

Helicobacter pylori infection is the principal risk factor for gastric cancer (GC). During the past year, new important epidemiological data indicated that the prevalence of GC is changing. Retrospective studies and randomized controlled trials (RCTs) stressed the importance of the success of *H. pylori* eradication for effective GC prevention. Microsatellite instability (MSI)-high status is gaining attention for its role as a prognostic, and possibly predictive biomarker in patients with GC. This review summarizes recent epidemiological aspects and clinical advances in the field of GC prevention and therapy published between April 2019 and March 2020.

2 | METHODS

The authors performed an independent search on PubMed on April 2020 for publications on GC during the previous year. The only filter applied to the searches was the "custom date range" for articles published between April 2019 and March 2020. The Boolean operator 'AND" was used to narrow the search results. The following search term combinations were used: "gastric cancer" [All Fields] AND "epidemiology" [All Fields]; "gastric cancer" [All Fields] AND "prevention" [All Fields]; "gastric cancer" [All Fields] AND "therapy" [All Fields]. Studies included and discussed in the present review were selected by the authors for their relevance and importance to the field of GC.

3 | EPIDEMIOLOGICAL ASPECTS

GC still ranks as the fifth most frequently diagnosed cancer and is the third leading cause of cancer death in both sexes worldwide. However, GC incidence is steadily decreasing globally, and in some populations is now regarded as a rare disease.

In a registry-based study, Arnold *et al* extracted data on GC incidence by year of diagnosis, sex, and age from 92 cancer registries in 34 countries, based on the International Classification of Diseases, 10th revision: C16.[1] The numbers of new cases and age-standardized incidence rates per 10,000 by country, sex, and age, beginning in 2012, were extrapolated to 2035 and fitted to recent trends using a log-linear age-period-cohort model that levels off exponential growth and limits linear trend projection. According to their analysis, overall GC incidence rates will fall further in both high- and low-incidence countries (*ie*, Japan and Australia, respectively). They also predict that, by 2035, GC incidence rates will fall below the rare disease threshold (defined as 6 per 100 000 person-years) in 16 out of the 34 evaluated countries. In contrast, alarming incidence increases will be observed in younger age groups (below 50 years of age) in both low-incidence and high-incidence populations. On a global scale, they predicted that the number of newly diagnosed cases will remain high or increase even further. Changes in the population size and structure, as well as in the prevalence of risk factors, especially in those aged below 50 years, are likely to explain this development. Thus, while in some regions GC will become a rare disease, in others it will remain a major public health challenge.

Helicobacter pylori infection is the most well-known risk factor for GC. Based on a cohort of 371,813 patients (median age 62 years; 92.3% male) from the Veterans Health Administration in the United States, who received a diagnosis of *H. pylori* infection from 1994 to 2018, Kumar *et al* aimed to calculate the incidence of and risk factors for non-cardia gastric adenocarcinoma after detection of *H. pylori* and to identify how treatment and eradication affect cancer risk using a time to event (*ie*, diagnosis of cancer) with competing risk analysis (with death before cancer as a competing risk).[2]

Patients with *H. pylori* infection were identified based on results of endoscopic pathology, stool antigen test, urea breath test, prescription for one of 11 accepted *H. pylori* eradication regimens, as recommended by the American College of Gastroenterology, or *H. pylori*-associated International Classification of Diseases (ICD), Revision 9/10 codes. For patients with multiple criteria, the criterion with the earliest date was used. Patients with non-cardia GC were identified using the Veterans Affairs Central Cancer Registry and/or ICD 9/10 codes.

With respect to non-cardia GC, the cumulative incidence of cancer was 0.37% at 5 years and increased to 0.5% and 0.65% after 10 and 20 years post-detection of *H. pylori* infection, respectively. Older age and a history of smoking both slightly increased the cancer risk, with a sub-hazard ratio [SHR] and 95% confidence interval [CI], of 1.13 (1.11-1.15) and 1.38 (1.25-1.52), respectively. The risk of GC was roughly doubled in racial and ethnic minorities, with a SHR and respective 95% CI of 2.52 (1.64-3.89), 2.00 (1.80-2.22), and 1.59 (CI, 1.34-1.87) in Asian, African American, and Hispanic, or Latino ethnic groups, respectively. The non-cardia GC risk was still slightly increased in patients who received *H. pylori* eradication treatment (SHR: 1.16; 95% CI: 0.74-1.83) but substantially reduced in the subgroup of patients with successfully confirmed *H. pylori* eradication (SHR: 0.24; 95% CI: 0.15-0.41).

H. pylori infection increases the risk of non-cardia GC unequivocally, whereas its protective role against esophageal adenocarcinoma and proximal GC is debatable. In a retrospective study, Kumar *et al* aimed to identify, in the aforementioned Veterans Health Administration cohort of patients with previously diagnosed *H. pylori*, the risk factors for future esophageal adenocarcinoma and cardia GC.[3] Compared with whites as the reference population, the risk of future esophageal adenocarcinoma or cardia GC was similar among African Americans (SHR: 0.87, 95% CI: 0.57-1.43) and American Indians (SHR 1.31; 95% CI, 0.18-9.60) but substantially reduced in Asians (no cases among 213 *H. pylori*-positive) or native Hawaiian origin (no cases among 295 *H. pylori*-positive). Increasing age and smoking were confirmed as risk factors for esophageal adenocarcinoma and cardia GC (SHR: 1.17, 95% CI: 1.09-1.25 and SHR: 2.06, 95% CI: 1.33-3.18, respectively). Neither prescription of *H. pylori* treatment, nor eradication status, were associated with future esophageal adenocarcinoma or cardia GC.

Although *H. pylori* gastritis is the main risk factor for GC, patients with autoimmune gastritis (AIG) may develop GC as well. In a case-control study from the German centers of the staR project on GC research, Weise *et al* assessed the characteristics and outcomes of GC patients with AIG.[4] From 2013 through 2017, they recruited 759 patients with GC and documented presenting symptoms using a self-administered questionnaire. Histological assessment of gastric mucosa was available for 572 of 759 GC patients. Overall, 28 (4.9%) GC patients had AIG (mean age 67.9 years, female-to-male ratio 1.3:1). Patients with AIG were matched in a 1:2 fashion for age and gender to GC patients with no AIG. Paraffin-embedded specimens of gastric mucosa from GC patients with and without AIG were assessed centrally by a reference gastrointestinal (GI) pathologist. In patients with AIG, GC was more likely to be localized in the proximal stomach (*ie*, cardia, fundus, corpus) (OR: 2.7, 95% CI: 1.0-7.1). In GC patients with AIG, pernicious anemia was the leading clinical sign (OR: 22.0, 95% CI: 2.6-187.2) and represented the most common indication for esophagogastroduodenoscopy (OR: 29.0, 95% CI: 7.2-116.4). GC patients with AIG were more likely to present without distant metastases (OR: 6.2, 95% CI: 1.3-28.8) and to be treated with curative intention (OR: 3.0, 95% CI: 1.0-9.0). The 5-year survival rates with 95% CI in GC patients with and without AIG were 84.7% (83.8%–85.6%) and 53.5% (50.9%–56.1%), respectively (OR: 0.25, 95% CI: 0.08-0.75, $P = .001$). The authors concluded that in AIG patients, pernicious anemia was associated with earlier detection of GC, which was associated with significantly better clinical outcomes.

4 | PREVENTION STRATEGIES

New data have accumulated on the effect of *H. pylori* eradication in preventing GC in *H. pylori*-positive healthy individuals and in patients

with gastric neoplasia undergoing endoscopic mucosal resection. In an updated meta-analysis, with a literature search date through to February 2020, Ford *et al* identified 10 RCTs, comparing the effect of *H. pylori* eradication therapy vs. placebo or no treatment on future GC incidence.[5] Participants were comprised of 8,323 healthy *H. pylori*-positive adults and 1,841 *H. pylori*-positive patients with gastric neoplasia undergoing endoscopic mucosal resection. All but one of the trials were conducted in East Asia. Follow-up lasted 2 years or longer. In the pooled analysis, *H. pylori* eradication therapy reduced GC incidence (RR = 0.54; 95% CI: 0.40-0.72) with 72 as the number of healthy individuals needed to treat (NNT) to prevent one GC. Mortality from GC was also reduced (RR = 0.61; 95% CI: 0.40-0.92, NNT = 135), whereas all-cause mortality was not affected. According to these data, 8 743 815 disability-adjusted life years (DALYs) would be gained if population screening and treatment were implemented globally (95% CI: 5 646 173-11 847 456), with the highest and lowest impact expected in East Asia and Australasia, respectively. A significant reduction in future GC incidence was also demonstrated in patients already harboring gastric neoplasia (RR = 0.49; 95% CI: 0.34-0.70, NNT = 21) but undergoing *H. pylori* eradication therapy after endoscopic mucosal resection.

First-degree relatives of GC patients with *H. pylori* infection are themselves at increased risk of developing GC. In a single-center, double-blind RCT, Choi *et al* demonstrated that successful *H. pylori* eradication therapy reduced GC risk among first-degree relatives of patients with GC. They randomly assigned *H. pylori*-infected first-degree relatives of patients with GC to receive either eradication therapy (lansoprazole (30 mg), amoxicillin (1000 mg), and clarithromycin (500 mg), each taken twice daily for 7 days) or placebo.[6] Overall, 1,676 participants were included in the modified intention-to-treat population. During a median follow-up of 9.2 years, GC developed in 10 participants (1.2%) in the treatment group and in 23 (2.7%) in the placebo group (HR: 0.45; 95% CI: 0.21-0.94; $P = .03$ by log-rank test). In the treatment group, five out of the 10 participants in whom GC developed (50.0%) had persistent *H. pylori* infection. Thus, GC developed in 0.8% of participants (5 of 608) with confirmed *H. pylori* eradication and in 2.9% of participants (28 of 979) with persistent infection (HR: 0.27; 95% CI: 0.10-0.70).

5 | TREATMENT

Mismatch repair deficiency (dMMR)-/microsatellite instability (MSI)-high status is gaining attention for its possible role as a prognostic and possibly predictive biomarker in patients with GC. However, GCs with dMMR-/MSI-high status represent only 9% to 22% of all diagnosed GC cases, and thus large data sets are needed to draw robust evidence concerning its prognostic/predictive value.

In an individual patient data meta-analysis of four prospective trials, Pietrantonio *et al* investigated the value of MSI as a biomarker in 1,556 patients with resectable GC.[7] Briefly, in the MAGIC and CLASSIC trials, patients were randomized to receive or not receive perioperative or adjuvant chemotherapy, respectively, whereas in the ITACA-S and ARTIST trials, patients were randomized to receive two different schedules of adjuvant chemotherapy and chemotherapy, with or without concurrent irradiation, respectively. The 5-year overall survival (OS) of patients with MSI-high tumors was significantly higher compared with patients with MSI-low/microsatellite stable (MSS) tumors (77.5% vs. 59.3%, respectively). A 9% increase in 5-year OS was confirmed in the subgroup of MSI-low/MSS GC patients receiving

TABLE 1 Biomarker-driven approved strategies for patients with advanced inoperable or metastatic gastric/esophagogastric junction cancer*

	Group 1 HER-2 negative, MMRp/MSS, PD-L1 CPS < 1	Group 2 HER-2 positive, MMRp/MSS, PD-L1 CPS < 1	Group 3 MMRd/MSI-H or PD-L1 CPS ≥ 1
First-line	• FP + Platin (doublet), or • FP + Irinotecan (doublet), or • FP + Platin +Docetaxel (triplet)	• FP + Cisplatin +Trastuzumab	• Treatment depending on HER-2 status (refer to group 1 or 2) • Pembrolizumab[a,b]
Second-line	• Paclitaxel + Ramucirumab, or • Docetaxel, or • Irinotecan, or • Paclitaxel, or • Ramucirumab	• Treatment as in group 1	• Treatment as in group 1 • Pembrolizumab[a,b]
Third-line	• Trifluridine/tipiracil, or • Irinotecan (if not received in previous lines) • Nivolumab[b]	• Treatment as in group 1	• Pembrolizumab[b] or treatment as in group 1

Abbreviations: CPS: combined positive score, defined as the number of PD-L-1-positive cells (tumor cells, lymphocytes and macrophages) out of the total number of tumor cells x 100;FP, fluoropyrimidine (infusional 5-FU, capecitabine or S-1); HER-2, human epidermal growth factor receptor 2 (also HER2/neu or ERBB2); MMRp/MMRd, mismatch repair proficient/deficient; MSS/MSI-H, microsatellite stability/high microsatellite instability; PD-L-1: programmed cell death 1 ligand 1.

[a]For patients who have no satisfactory alternative treatment options.

[b]Application for healthy insurance reimbursement may be required. Studies with pembrolizumab in earlier treatment lines are ongoing.

*Approval status may differ according to regulatory authorities for drug safety.

chemotherapy plus surgery, compared with surgery alone (62% versus 53%, respectively, HR: 0.75, 95% CI: 0.60 - 0.94). Conversely, patients with MSI-high GC did not benefit from chemotherapy (5-year OS: 75% versus 83%, respectively). Thus, for patients undergoing surgery with curative intention for GC, MSI is a robust prognostic marker that should be adopted as a stratification factor in future trials. Prospective trials investigating the role of perioperative chemotherapy omission and/or immune checkpoint blockade in MSI-high GCs are warranted.

No new treatment emerged for patients with advanced non-resectable GC in the last year (Table 1).[8,9]

6 | CONCLUSIONS

Although in the near future GC incidence rates will fall below the rare disease threshold in many countries, on a global scale the number of newly diagnosed GC cases will remain high, or increase even further, due to changes in population size and increasing risks observed in younger generations. Successful eradication of *H. pylori* is the key to GC prevention. Accumulating evidence suggests that, in patients with MSI-high resectable GC, chemotherapy may be omitted. Precision oncology has become the standard of care for a selected group of patients, but no advances were made in systemic therapy for the majority of patients with advanced GC during the last year, and thus, more efforts in this field are warranted.

CONFLICT OF INTEREST

MV is involved in speakers' bureau or consulting: Nordic Pharma, Merck Serono, Bayer Vital, Lilly, and Sirtex and is a member of the advisory boards of Ipsen, Lilly, Nordic Pharma, BMS, MSD, Eisai, and Amgen. PM is involved in speakers' bureau or consulting: Biocodex, Biohit, Danone, Mayoly-Spindler. AC F. and TR declare no conflict of interest.

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