Microb Health Dis 2021; 3: e531

European Helicobacter & Microbiota Study Group

# REVIEW – RECENT NEWS ON PREVENTION AND TREATMENT OF GASTRIC CANCER

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**Abstract:** Despite its decreasing incidence, gastric cancer (GC) is still the third leading cause of cancer death in the world. Eradication of *Helicobacter pylori* has been shown to decrease the risk of GC, without evidence of adverse consequences. Operable GC is treated with surgery, and laparoscopic gastrectomy has proven to be a valid alternative to open gastrectomy. For advanced GC, the available therapies show limited benefit in extending survival, but some new approaches are emerging, like immunotherapy using immune checkpoint inhibitors which, in combination with chemotherapy, has been shown to increase survival. In this article, we review the most relevant articles concerning GC prevention and treatment published between April 2020 and March 2021.

**Keywords:** *Helicobacter pylori*, Screening, Prevention, Immunotherapy, Laparoscopy.

## INTRODUCTION

Gastric cancer (GC) is the third leading cause of cancer death in the world, and despite a decline in its incidence, it remains a major public health problem on a global scale. The impact of massive *H. pylori* eradication on GC prevention has been debated, and recent data further confirm the efficacy of this approach. In the treatment of advanced GC, promising results have been obtained with new targeted therapies and immunotherapies using checkpoint inhibitors. The safety of laparoscopic gastrectomy has been further supported. An innovative molecular approach for the detection of residual disease after surgery based on liquid biopsy has been proposed.

This review highlights the most relevant articles concerning the clinical aspects of GC published during the last year.

The authors performed a search on PubMed for recent publications on GC, using the following search terms: "gastric cancer'' and ''prevention''/''epidemiology''/screening"/''treatment''. Only the articles published between April 2020 and March 2021 were taken into consideration. Amongst all articles published, we selected those we considered the most relevant.

## EPIDEMIOLOGY AND PREVENTION

A comprehensive review by Park and Herrero summarized recent data on GC epidemiology and prevention. The authors highlight the existing discrepancies in GC incidence in different countries

and appearance of new epidemiological trends showing an increasing incidence of GC in young individuals, especially women. Together with a poor overall survival in this deadly disease, they underline a need for global and more efficient preventive actions, which should include testing and treating *H. pylori* infection, through population-based screening programs adapted to the local context. Several ongoing prevention trials, carried out in particular in Asian and East-European countries, aim to prove the efficacy of *H. pylori* eradication in the prevention of GC.

The results of a long-term cohort study launched in 2004 in Matsu Island in Taiwan, a high GC risk area, have been published recently. The study evaluated the effectiveness of mass *H. pylori* eradication in reducing the incidence and mortality rates of GC. The program covered 85.5% of the population (over 6,500 individuals). After eradication, the prevalence rates of *H. pylori* infection declined from 64.2% in 2004 to 15% in 2008, and the incidence and mortality of GC were reduced by 53% (95%CI, 30%-69%; $p<0.001$] and 25% (95%CI, 14%-51%; $p=0.18$), respectively. This study also addressed the potential negative consequences of mass *H. pylori* eradication and showed, in particular, that non-significant changes in esophageal and colorectal cancer incidence, as well as in antibiotic resistance rates, were observed.

A population-wide *H. pylori* screening and eradication is also recommended by the recently published Taipei global consensus. This consensus resulted in 26 statements, and its major conclusions are that at the individual level, *H. pylori* eradication is indicated for all patients after curative endoscopic resection of early GC and for those with known gastric precancerous lesions (advanced gastric atrophy or intestinal metaplasia), while on the population level, the "screen and treat *H. pylori*" strategy appears to be the most effective in young adults in regions with a high GC incidence and should be performed before the development of atrophic gastritis and intestinal metaplasia.

## TREATMENT

In the field of treatment, two aspects will be addressed, GC surgery and systemic treatment.

### GC Surgery

Laparoscopic total gastrectomy has recently become an accepted surgical option for GC, but its safety and efficiency still remain to be proven. A laparoscopic approach, in particular, may be advantageous in terms of patients' convenience and an economic point of view. During the last year, the results of three separate studies addressing these issues were published.

The CLASS02 trial was a Chinese, multicenter, open-label, non-inferiority, randomized trial, to evaluate the safety of laparoscopic total gastrectomy with lymphadenectomy for the treatment of stage I GC. Two hundred twenty-seven patients were randomized for a laparoscopic total gastrectomy or an open total gastrectomy. The overall morbidity and mortality rates were not significantly different between the two groups (rate difference: -1.1%; 95%CI, -11.8% to 9.6%), and there was no significant difference in the overall postoperative complications rate (2.9% and 3.7%, respectively).

The LOGICA trial, conducted in the Netherlands, was the first European multicenter, randomized trial, comparing laparoscopic gastrectomy with open distal or total gastrectomy, in terms of duration of post-operative hospital stays and quality of life. Five hundred seventeen patients with histologically proven, resectable (cT1-4aN0-3bM0) GC, were randomly assigned to laparoscopic gastrectomy and open gastrectomy. Laparoscopic gastrectomy did not lead to a reduced hospital stay but resulted in less intraoperative blood loss and a longer operating time. Post-operative complications, R0 resection rate, lymph node yield, 1-year overall survival, and quality of life did not differ between the two groups. In this study, more than 65% of the patients received neoadjuvant therapy (vs none in the CLASS02 trial), which allows an extrapolation of these results to the Western countries where neoadjuvant therapy is usually used.

Finally, the long-term outcomes of the Klass-02-RCT randomized trial, that compared the outcome of 1,050 patients with locally advanced GC randomly assigned to laparoscopic surgery or open surgery, were published this year. These results were particularly awaited be-

cause the oncologic safety of laparoscopic surgery for advanced GC used to be questioned due to a potentially increased risk of locoregional and peritoneal recurrence. They confirm the non-inferiority of the laparoscopic approach regarding the 3-year relapse-free survival rates: 80.3% for the laparoscopy group and 81.3% for the open surgery group (hazard ration (HR): 1.035; 95%CI, 0.762 to 1.406; $p=0.827$).

Altogether, the results of these three trials support the use of laparoscopic gastrectomy as a valid alternative to open gastrectomy in GC.

## Systemic Treatments of GC

Advanced GC has a poor prognosis and systemic treatments available so far, essentially cytotoxic chemotherapy, have limited efficacy in prolonging survival. Some targeted therapies (anti-EGFR, anti-VEGF), efficient in other cancers, turned out not to be effective in GC. The only targeted treatment proven to bring some benefit in terms of survival in patients with metastatic GC is the anti-HER2 agent trastuzumab in patients with HER2 over-expressing tumors. Last year, two new approaches showed promising results: a new targeted therapy with trastuzumab-deruxtecan and immunotherapy with immune checkpoint inhibitors.

Trastuzumab-deruxtecan is a novel antibody-drug conjugate in which trastuzumab is linked with deruxtecan, an anticancer drug that interrupts DNA replication in cancer cells. In a randomized, open-label, multicenter, phase II trial, Shitara et al evaluated the effectiveness of trastuzumab-deruxtecan on objective tumor response in advanced GC. All patients had previously received fluoropyrimidine and trastuzumab and were randomly assigned in a 2:1 ratio to receive trastuzumab-deruxtecan or chemotherapy. Results of the first cohort of 187 patients (79% from Japan and Korea) with HER2+/IHC3+ or IHC2+/FISH+ tumors, were in favor of trastuzumab-deruxtecan with a significantly higher objective response (42.9% *vs.* 12.5%, $p<0.0001$), progression free survival (PFS) (5.6 *vs.* 3.5 months; HR=0.47; 95%CI,0.31-0.71) and overall survival (OS) (12.5 *vs.* 8.4 months, HR: 0.59; 95%CI, 0.39-0.88; $p=0.0097$) as compared to chemotherapy. At the European Society for Medical Oncology (ESMO) congress in 2020, the results of the second and third cohorts of patients who had a lower HER2 expression (IHC2+/ISH- and IHC1+) were presented showing that the effectiveness of trastuzumab-deruxtecan was less pronounced (objective response of 26.3% and 9.5%/PFS 4.4 months and 2.8 months/OS of 7.8 and 8.5 months, respectively).These results indicate that a high expression of HER2 is crucial for a good response to this treatment, and they also support the concept of re-challenge with anti-HER2 after a first-line failure. A phase III study, evaluating trastuzumab-deruxtecan's effectiveness is in progress in a non-Asian population (DESTINY-Gastric02). It would also be interesting to study its efficacy as a first-line treatment.

The KEYNOTE-62 study is a randomized, international phase III study evaluating the efficacy and safety of pembrolizumab alone or in combination with chemotherapy, compared to chemotherapy alone, in the first-line treatment of advanced GC, HER2- negative and with a PD-L1 CPS (combined positive score or the number of PD-L1 positive cells compared to the total number of tumor cells) ≥1. Seven hundred sixty-three patients were randomized 1:1:1 in 3 groups: pembrolizumab alone, pembrolizumab + chemotherapy, or chemotherapy + placebo. No significant benefit in OS, PFS or response rate in favor of adding pembrolizumab to chemotherapy was observed, regardless of the CPS. In contrast, pembrolizumab appeared non-inferior to chemotherapy in terms of OS in patients with CPS ≥1 (median, 10.6 vs 11.1 months; HR: 0.91; 99.2%CI, 0.69-1.18). This is appreciable since this group of patients had fewer adverse events as compared to the chemotherapy group. This is the first published phase III study evaluating an immune checkpoint inhibitor as a first-line treatment for advanced gastric adenocarcinoma and it raises the question of immunotherapy alone in some particular settings, for instance in cases of elevated PD-L1-CPS.

A combination of pembrolizumab and lenvatinib (a multi-tyrosine kinase inhibitor) was tested in patients with advanced GC in the first- or second-line setting in an open-label single arm phase II EPOC1706 trial in Japan. This combination allowed to obtain an objective response in 20 out of 29 patients (69%; 95%CI, 49-85), with manageable toxicities. A confirmatory phase 3 trial will be planned in the future.

In the phase III CheckMate 649 trial, nivolumab in combination with chemotherapy became the first PD-1 inhibitor to demonstrate superior OS and PFS as first-line treatment. This trial included 1,581 patients with HER2- negative, untreated, unresectable, advanced or metastatic GC, gastroesophageal junction cancer, and esophageal cancer. Patients were included regardless of PD-L1 expression but the dual primary endpoints, OS and PFS, was restricted to the population with a PD-L1 CPS ≥ 5 (60% of the patients). Patients were randomized into three groups: chemotherapy alone (FOLFOX or XELOX), nivolumab + chemotherapy, or nivolumab + ipilimumab (the data of this third arm are not available yet). The nivolumab + chemotherapy combination led to a better OS and a reduction of the risk of death or disease progression of 30%. Median overall survival was 14.4 months in nivolumab plus chemotherapy arm *vs.* 11.1 months in chemotherapy arm in the PD-L1 CPS ≥5 population (HR: 0.71; $p<0.0001$). The differences were also statistically significant for the PD-L1 CPS ≥1 population (HR: 0.77; $p=0.0001$) and for all randomly assigned patients (HR: 0.80; $p=0.0002$). The trial CheckMate 649 is the first phase III trial that demonstrated a benefit in OS and PFS in patients with advanced GC and may lead to a new standard of care. It should be underlined that this successful strategy is based on the combination of an immune check point inhibitor with chemotherapy and is restricted to the selected population based on biomarker (CPS score) expression.

In comparison, in phase II/III Attraction-4 trial which compared nivolumab + chemotherapy with chemotherapy alone (oxaliplatin plus S-1 or capecitabine), the median PFS was improved but overall survival was not. Unlike the Checkmate 649 trial, the Attraction 4 study was performed only in Asian patients and the primary endpoints were evaluated regardless of a specific CPS threshold.

Immunotherapy could be also an interesting approach in adjuvant setting as shown in CheckMate 577 study evaluating nivolumab in resected esophageal or gastroesophageal junction cancer. In this global, randomized, double-blind, placebo-controlled, phase III trial, 794 patients with resected esophageal or gastroesophageal junction cancer after neoadjuvant chemoradiotherapy and with residual pathological disease, were assigned in a 2:1 ratio to receive nivolumab, as adjuvant therapy, or a placebo. The primary endpoint was disease-free survival, and it was significantly longer among patients who received adjuvant nivolumab (22.4 months *vs.* 11.0 months; HR: 0.69; 96.4%CI, 0.56 to 0.86; $p<0.001$). The results were the same regardless of PD-L1 expression. Distant and locoregional recurrence were less frequent in the nivolumab group. There was no difference in quality of life between the 2 groups (EQ-D5-2L questionnaire). This is the first trial to demonstrate positive efficacy and safety of a checkpoint inhibitor in the adjuvant setting of gastroesophageal cancer.

## SUPPORTIVE CARE

Beyond the development of novel anticancer agents, it is important to explore other interventions to improve survival in patients with metastatic GC. In an open-label phase III trial, Lu et al studied the effectiveness of early integration of supportive care, such as nutritional and psychological intervention, on OS in patients with untreated metastatic gastric or gastroesophageal cancer. Patients included in the arm with a systematic meeting with a dieticien and psychologist had a significantly longer OS compared to standard care group (14.8 *vs.* 11.9 months; HR: 0.68; 95% CI, 0.51 to 0.9; $p=0.021$). The intervention group also had a lower risk of malnutrition, depression, and anxiety. This study is the first to demonstrate both the survival and the quality-of-life benefits of early interdisciplinary nutritional and psychological supportive care. It should therefore be offered to patients, where available.

## DIAGNOSTIC OF RESIDUAL DISEASE IN GC

A major challenge for resectable GC is identifying patients at high risk of recurrence after surgery because of microscopic residual disease. A new innovative approach could be provided by circulated tumor-derived DNA (or ctDNA), a type of non-encapsulated DNA (cell-free DNA or cfDNA) that is derived from a tumor and circulates in the bloodstream. Leal et al[15] showed the value of using ctDNA as a prognostic factor for predicting survival outcome by evaluating

ctDNA levels before and after treatment in 50 patients, randomly selected from CRITICS study (Phase III randomized study of perioperative treatments in patients with operable GC). They showed that the presence of ctDNA predicts a recurrence when analyzed within nine weeks after preoperative treatment: patients with high levels of ctDNA did not experience tumor regression and eventually died from recurrent disease, while patients with low ctDNA levels achieved complete or major pathologic response.

## CONCLUSIONS

GC is a frequent and deadly disease if diagnosed at an advanced stage. Successful eradication of *H. pylori* is essential in GC prevention. Laparoscopic gastrectomy is a valuable alternative to open gastrectomy, in both early and advanced GC. The efficacy and safety of a checkpoint inhibitor, nivolumab, has proven for the first time its efficacy in Western populations, in adjuvant settings as well as in advanced GC at first line. The results for pembrolizumab are promising but its efficacy is yet to be proven. A novel therapeutic approach by using antibody-drug conjugates, like trastuzumab-deruxtecan, is emerging. Finally, supportive care deserves a more central place in the management of GC.

### Conflict of interest

The authors declare to have no conflict of interests.

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