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REVIEW: GASTRIC MALIGNANCIES – CLINICAL ASPECTS & PREVENTION

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Abstract – Gastric cancer is the fifth most common type of cancer and the third most common cause of cancer related mortality worldwide. Although its incidence and prevalence continue to decrease in most countries, recent large registry-based studies have shown that the incidence rate remains high in some nations and is also increasing in younger cohorts. A prospective case-cohort study in a Chinese population also confirmed the significant role played by *Helicobacter pylori* infection as the predominant risk factor for gastric carcinogenesis. Prospective and retrospective cohort studies have demonstrated that population level screening and *H. pylori* eradication therapy significantly reduced the risk of gastric cancer and provided significant economic benefits amongst high risks groups in Taiwan and Japan. Diagnosis remains multi-modal although the potential of novel blood-based genetic panels as an accurate diagnostic marker has been shown in a Korean study involving more than 100 patients. Surgical resection remains the only curative option and an updated network meta-analysis demonstrated no significant differences in the complication rates or oncological outcomes between minimally invasive and open approaches to distal gastrectomy. The recently published CheckMate 649 trial has also highlighted the potential of adjunctive immunotherapy in improving outcomes associated with unresectable gastric cancers, paving the way for future studies to explore the role of similar targeted therapies in wider cohorts.

Keywords: Gastric cancer, Gastric adenocarcinoma, *Helicobacter pylori*, Epidemiology, Prevention, Management.

INTRODUCTION

Helicobacter pylori is well recognised as a type I carcinogen and is the predominant risk factor associated with the development of gastric cancer. Gastric carcinogenesis most commonly occurs via a series of premalignant stages including atrophic gastritis, intestinal metaplasia and dysplasia in a small proportion of *H. pylori* infected individuals who also have a permissive immune response to this infection. Although the overall worldwide incidence of gastric cancer is decreasing, it remains a major global health concern. Measures to prevent its development and to improve the efficacy of treatment in patients who develop this malignancy are therefore urgently required.

In this article we have reviewed a selection of papers that were published over the last twelve months and which we considered to represent some of the major advances in our understanding of the epidemiology, prevention and clinical management of

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gastric adenocarcinoma. The article did not set out to comprehensively review the topic and we therefore apologise to the authors of many other interesting and important papers whose content we did not have the space to include.

MATERIALS AND METHODS

A PubMed literature search was performed to obtain relevant English language publications associated with gastric cancer between April 2021 and March 2022. The search terms used included: "gastric cancer", gastric adenocarcinoma", "epidemiology", "prevention", "management" and "therapy". The Boolean operator "AND" was subsequently used to derive relevant combinations and generate broad search results. Articles were screened according to their relevance, resulting in the refined selection of papers felt to be most pertinent to the review topic by the authors.

RESULTS

Epidemiology

Gastric cancer is the fifth most common type of cancer and the third most common cause of cancer related mortality worldwide[1]. Whilst globally, there has been a general reduction in incidence and prevalence, there is significant geographical variance in its epidemiology. In a comprehensive analysis of 108 cancer registries across 43 high-, middle- and low-income countries, Lin et al[2] demonstrated a persistent decreasing trend in worldwide incidence rates between 1988 and 2012. With the exception of Turkey, which demonstrated an overall increase in incidence rate (from 7.8 per 100,000 to 9.7 per 100,000), there was a 56% decrease in the global age standardised incidence rate, with an annual overall percentage decrease of approximately 2% over the study period. Despite this decrease, a number of nations continued to demonstrate relatively high incidence rates, of which Japan and Korea were the highest (Table 1). Using a Bayesian age period cohort model, the authors extrapolated their findings in order to predict the trends in gastric cancer incidence up to the year 2030. This analysis demonstrated a continued decreasing incidence in most high-, middle- and low-income nations, including high incidence countries such as Japan and Korea. However, other nations such

TABLE 1. AGE STANDARDISED INCIDENCE RATES (PER 100,000) OF SELECTED NATIONS WITH HIGHEST RATES OVER THE STUDY PERIOD OF 1988 TO 2012.

	Age standardised incidence rates per 100,000	
Nation	1988	2012
Japan	57.49	41.41
Korea	54.32	43.43
Chile	38.01	18.84
China	37.81	17.10
Costa Rica	28.57	15.75
Estonia	26.95	14.39
Italy	25.54	11.51
Colombia	24.65	16.53
Lithuania	24.14	17.67
Ecuador	24.02	19.02

Data adapted from Lin et al[2].

as Ecuador (20 per 100,000 in 2012 to >80 per 100,000 in 2030) and Lithuania (20 per 100,000 in 2012 to 55 per 100,000 in 2030) were predicted to show significant increases in gastric cancer incidence[2].

There also appears to be an increasing incidence of gastric cancer in younger age groups and this appears to be independent of geographical location. A recently published registry-based cohort study across 48 nations demonstrated that although gastric cancer incidence had reduced in patients older than 40 years in most countries (30 out of 48), it had increased in the under 40-years age group across both genders in nations including Brazil, Sweden and the United Kingdom (Table 2)[3]. Whilst such findings may be explained by the prevalence and distribution of gastric cancer risk factors amongst different populations (*i.e.*, increasing obesity, higher rates of caffeine consumption and patterns of migration amongst younger cohorts), it is also possible that the increasing use of invasive and non-invasive investigations is resulting in early detection and a perceived increase in incidence in the younger population[3].

With *H. pylori* being the predominant risk factor in many gastric cancers, Yang et al[4] recently published a prospective case-cohort study which assessed the relative and attributable risk of gastric cancer associated with *H. pylori* infection in China. This study utilised sensitive immunoblot assays to assess biomarkers of *H. pylori* as a measure of plasma seropositivity in 499 non-cardia gastric cancer patients, 436 cardia gastric cancer patients and 500 individuals who were cancer free at the time of study participation. *H. pylori* seropositivity was 94% in the non-cardia cancer group, 92% in the cardia cancer group and 76% in the non-cancer group. As such, in this population, 79% of non-cardia gastric cancers and 62% of cardia gastric cancers were attributable to *H. pylori*. Cox regression analysis demonstrated that those patients who were *H. pylori* seropositive had a 6-fold increased risk of non-cardia gastric cancer (Hazard Ratio (HR) 5.94) and a 3 times increased risk of cardia gastric cancer (HR 3.06). This increased risk of malignancy persisted even when additional risks factors were controlled for and was independent of age and gender. Extrapolation from this dataset suggested that *H. pylori* was responsible for over 330,000 cases of gastric cancer in China in 2018[4].

Gastric Cancer Prevention

A logical paradigm in gastric cancer management is to prevent it developing with prophylactic eradication of *H. pylori*. Chiang et al[5] recently assessed the incidence and prevalence rates of gastric cancer in the high risk population of Matsu Island, in whom mass screening (^{13}C-urea breath test (^{13}C-UBT)) and eradication of *H. pylori* was initiated in 2004 and has been fully implemented biennially since 2012. The overall coverage rate of the screening programme was reported to be 85%, with an average of over

TABLE 2. AVERAGE ANNUAL PERCENTAGE INCREASES IN THE INCIDENCE RATE OF GASTRIC CANCER IN INDIVIDUALS YOUNGER THAN 40 YEARS FROM SELECTED NATIONS.

Nation	Average annual percentage change in incidence rates (<40 years old)
Brazil	15.50 (95% CI -2.19 to 36.69)
Sweden	13.92 (95% CI 7.16 to 21.11)
Ecuador	4.36 (95% CI -6.87 to 16.95)
United Kingdom	4.27 (95% CI 0.15 to 8.55)
Estonia	4.29 (95% CI -14.65 to 27.21)
Slovakia	3.90 (95% CI -0.54 to 8.54)

CI: Confidence Interval. Data adapted from Wong et al[3].

2,665 participants undergoing biennial tests between 2012 and 2018. Upper gastrointestinal endoscopy was used both to identify potential cancerous lesions, and to examine the prevalence and severity of identified pre-malignant lesions over the study period. In this "before and after" style study, historical data regarding gastric cancer incidence between 1995 and the end of 2003 was used as a control. Following the initial commencement of the screening and eradication programme in 2004, the *H. pylori* prevalence rate decreased from 64% to 28% in 2012. Following full biennial implementation, this reduced further to 15.7% in 2018. Over the same time period (2004-2018), the prevalence of pre-cancerous lesions in the stomach also reduced significantly with atrophic gastritis and intestinal metaplasia falling from 56% to 16% and 32% to 21%, respectively. When compared to the historical control cohort, there was a 53% reduction in the gastric cancer incidence rate as a result of the screening programme and a reduction in the actual observed cases from 96 per 100,000 to 16 per 100,000 between 2004 and 2018[5]. This suggests that in a region with a high prevalence of *H. pylori* and high incidence of gastric adenocarcinoma, a screening programme with a high participation rate (85%) utilising an accurate screening test (^{13}C-UBT), with an associated high participation rate of treatment (93%) and eradication (97%) can significantly reduce the burden of gastric cancer.

The economic feasibility of a population wide preventive approach has also recently been evaluated. Kowada et al[6] examined the economic and health benefits of *H. pylori* eradiation in Japanese patients with chronic gastritis, where such a strategy has been in place since 2013. Using a transition model assessing the costs, quality adjusted life years (QALYs) and gastric cancer cases over a lifetime, they demonstrated that from 2013 to 2019, *H. pylori* eradication in over 8 million patients resulted in savings of over 3.5 billion US dollars, an increase of over 11 million QALYs, and prevented 284,188 cases of gastric cancer. In the 35 million patients who did not receive *H. pylori* eradication treatment, they calculated a potential savings of over 14 billion US dollars and prevention of over 1 million gastric cancer cases.6 Taken together, these studies suggest that in a high risk/high incidence area of the world such as Japan, population-based screening and *H. pylori* eradication can be effective in reducing the risk of gastric adenocarcinoma. Whether such a strategy has similar merits in low risk/low incidence countries or in high-risk individuals within those countries, however, remains to be shown.

Diagnosis of Gastric Cancer

Multi-modal investigations including upper gastrointestinal endoscopy, endoscopic ultrasound, computed tomography and staging laparoscopy with peritoneal washing are the most common current methods of diagnosis and staging in gastric cancer. Given that earlier diagnosis and treatment can lead to improved outcomes, studies have continued to explore the utility of adding novel, non-invasive biomarkers to the diagnostic armamentarium for patients with suspected gastric cancer.

For example, Lee et al[7] performed biomarker discovery and validation of selected candidate genes as a blood-based signature of gastric cancer in their Korean cohort of gastric adenocarcinoma patients. They firstly analysed three publicly available genomic datasets (GSE29272, GSE62254 & GSE66222) containing genome wide expression data of matched gastric cancer and adjacent normal tissue. One hundred four separate matched gastric cancer and adjacent normal tissue samples were analysed using multiple random forest with 10-fold cross validation to identify 9 candidate genes (Table 3). The selected genes were subsequently validated in tissue samples taken from 82 patients who had resected diffuse type gastric cancers. Using qPCR to assess gene expression, their regression analysis validated the utility of this gene panel to successfully distinguish gastric cancer from non-cancerous tissue (area under the curve (AUC) 0.914 95% CI 0.862-0.953). To translate these findings into a potential non-invasive serological marker, the expression of this 9 gene panel was also analysed in serum taken from 54 gastric cancer patients and 31 healthy volunteers. This identified five genes which were upregulated in patients who had gastric cancer, of which three were statistically significant (Table 3). Regression

TABLE 3. GENE PANELS INITIALLY IDENTIFIED THROUGH SCREENING OF PUBLIC DATABASES WITH SUBSEQUENT VALIDATION IN A CLINICAL COHORT IN TISSUE AND IN SERUM.

Genes derived from expression databases	Gene panel validated in tissue	Gene panel validated in serum
ALDOB	ALDOB	HBB*
CEACAM6	CEACAM6	ISG15*
HBB	HBB	KRT7
ISG15	ISG15	PLA2G2A
KRT7	KRT7	UBD*
MSMB	MSMB	
PLA2G2A	PLA2G2A	
TNFRSF17	TNFRSF17	
UBD	UBD	

*Statistically significant upregulation in isolation. Data adapted from Lee et al[7].

analysis using a bootstrapping algorithm confirmed the utility of this five gene panel for distinguishing gastric cancer patients from healthy volunteers (AUC 0.896; 95% CI 0.894-0.898), a finding which was confirmed by validation in an independent cohort of 35 patients and 23 healthy volunteers (AUC 0.947; 95% CI 0.946-0.949). These findings were not influenced by cancer stage, supporting the utility of the independent panel as markers in the early-stage disease7. Continued focus is now required to establish whether such findings are confirmed on a larger scale and to identify additional novel non-invasive markers of diagnosis. Future studies could also focus on the utility of novel markers such as circulating tumour cells or free DNA as markers of efficacy or prognosis in response to systemic treatment and surgery.

Surgical Treatment

Surgical resection, often in combination with peri-operative systemic oncological treatments, is the only curative option for gastric adenocarcinoma. Very early-stage neoplastic lesions confined to the mucosa (T1a) can be excised endoscopically, whilst stage IB-III cancers require surgical resection via radical gastrectomy.

In a systematic review and updated network metanalysis of randomised control trials, Aiolfi et al[8] investigated the surgical and oncological outcomes associated with the major surgical approaches for operable gastric cancer. This study analysed 17 trials encompassing over 5,900 patients and compared open, laparoscopic assisted and robotic distal gastrectomy for both early and locally advanced gastric adenocarcinoma. With regards to surgical outcomes, all 17 studies reported an overall complication rate, 15 of the 17 trials reported 30-day mortality rates, 16 reported data on anastomotic leak rates and 7 reported severe post-operative complications (Clavien-Dindo III-IV). The findings are summarised in Table 4 and demonstrated similar 30-day mortality and post-operative complication rates between the open, laparoscopic assisted and robotic approaches for early and locally advanced gastric cancers. Secondary outcomes such as intra-operative blood loss and time to first flatus were significantly improved in patients undergoing minimally invasive surgery, whilst time to first oral intake and time to ambulation were similar across the treatment arms. The length of admission was significantly reduced for laparoscopic surgery but was similar for robotic and open surgery (Table 4).

The pertinent oncological outcomes of the number of lymph nodes resected (all 17 trials, 5,909 patients), R0 tumour-free resection margin rates (8 trials, 2,420 patients) and disease-free survival (4 trials, 1,674 patients) were also compared in this network

TABLE 4. PERTINENT SURGICAL OUTCOMES FROM NETWORK METANALYSIS OF OPEN, LAPAROSCOPIC ASSISTED AND ROBOTIC DISTAL GASTRECTOMY

Post-operative variable	Number of studies reporting outcome (n= number of patients)	Meta-analysis outcome	
30-day mortality	15 (5,818)	**Laparoscopic assisted *vs.* open:** RR 1.58 (95% Crl 0.88 to 2.83)	**Robotic *vs.* open:** RR 0.93 (95% Crl 0.43 to 2.01)
Anastomotic leak rate (%)	16 (5,713)	**Laparoscopic assisted *vs.* open:** RR 1.45 (95% Crl 0.91 to 2.29)	**Robotic *vs.* open:** RR 0.87 (95% Crl 0.41 to 1.85)
Severe complication rate (%)	7 (3,076)	**Laparoscopic assisted *vs.* open:** RR 0.94 (95% Crl 0.69 to 2.29)	**Robotic *vs.* open:** RR 0.73 (95% Crl 0.41to 1.35)
Overall complication rate (%)	17 (5,909)	**Laparoscopic assisted *vs.* open:** RR 0.76 (95% Crl 0.63 to 1.45)	**Robotic *vs.* open:** RR 0.0.69 (95% Crl 0.41 to 1.22)
Intra-operative blood loss (ml)*	16 (5,713)	**Laparoscopic assisted *vs.* open:** WMD -49.1 (95% Crl -56.9 to -41.2)	**Robotic *vs.* open:** WMD -14.5 (95% Crl -38.4 to -9.4)
Time to first flatus (days)*	11 studies (4,066)	**Laparoscopic assisted *vs.* open:** WMD -0.62 (95% Crl -56.9 to -41.2)	**Robotic *vs.* open:** WMD -0.52 (95% Crl -1.11 to -0.3)
Time to oral intake (days)		**Laparoscopic assisted *vs.* open:** WMD -0.43 (95% Crl -1.90 to -1.03)	**Robotic *vs.* open:** WMD 0.03 (95% Crl -3.81 to 3.88)
Time to ambulation (days)		**Laparoscopic assisted *vs.* open**: WMD 0.07 (95% Crl -0.98 to -1.17)	**Robotic *vs.* open:** WMD -0.50 (95% Crl -2.91 to 1.91)
Length of admission (days)**		**Laparoscopic assisted *vs.* open:** WMD -0.95 (95% Crl -1.87 to -0.27)	**Robotic *vs.* open:** WMD 0.66 (95% Crl -2.03 to -3.62)

RR = relative risk, Crl = credible intervals, WMD = weighted mean difference. Data adapted from Aiolfi et al[8].
*Statistically significant differences between laparoscopic assisted vs open and robotic vs open approaches.
**Statistically significant differences between laparoscopic assisted and open approaches only.

meta-analysis. The results demonstrated that there were no statistically significant differences between the mean number of lymph nodes harvested between open and laparoscopic assisted resections (weighted mean difference 0-.261; 95% Credible Interval (CrI) -3.9 to 0.91) or between open and robotic distal gastrectomies (weighted mean difference 1.01; 95% Crl -4.6 to 6.65). The R0 resection rate was also no different between laparoscopic assisted and open surgery (Relative Risk (RR) = 1.02; 95% Crl 0.96-1.05). Subgroup analysis in patients who had locally advanced cancers (9 studies, 3,363 patients) again demonstrated no impact of tumour stage on the above outcomes. No

studies were identified which compared the R0 resection rate between robotic and open or laparoscopic surgery. There were no significant differences in the disease-free survival between laparoscopic and open gastrectomy (HR 0.99; 95% Crl 0.46-1.95). Furthermore, network analysis of the results of five trials with a total of 1,581 patients found no significant overall survival advantages between laparoscopic and open gastrectomy (HR 0.89; 95% Crl 0.58-3.71)[8]. The findings of this updated meta-analysis thus suggest that minimally invasive surgical approaches for both early and locally advanced distal gastric cancers were non inferior to open surgery with regards to oncological outcomes, and were similar to open surgery with regards to significant post-operative outcomes such as 30-day mortality, anastomotic leak and overall survival. Although minimally invasive surgery appeared to be associated with improvement of some short-term peri-operative outcomes, further evidence is still required to fully elucidate the benefits of a robotic and fully laparoscopic approach.

Systemic Treatment

Progress has also been made in the management of patients with gastric cancers that are not suitable for surgery. Whilst platinum-based systemic chemotherapy remains the first-line treatment for human epidermal growth factor (HER)-2 negative unresectable gastric cancers, the potential role of immunotherapy such as the monoclonal antibody Nivolumab, a programmed death (PD) – 1 inhibitor, has also been investigated with promising results[9].

The recently published CheckMate 649 trial examined the benefits conferred by adjunctive immunotherapy with nivolumab to chemotherapy as first-line treatment for gastric, junctional and oesophageal adenocarcinomas. This multi-centre randomised, phase III trial enrolled 1,581 subjects, of whom approximately 70% (1,110 patients) had gastric cancers. The reported analysis included patients assigned to nivolumab plus chemotherapy (XELOX or FOLFOX) or chemotherapy alone. Subgroup analysis was conducted to account for the differing levels of PD ligand expression on tumour cell and tumour associated immune cells (measured by the combined positive score), which, as expected, can impact the efficacy of Nivolumab therapy.

The results demonstrated that overall patient survival was significantly improved in patients with a combined positive score of >5 who received Nivolumab and chemotherapy versus chemotherapy alone at a median follow up of approximately 1 year (HR 0.71; 98% CI 0.59-0.86). Furthermore, adjunctive immunotherapy resulted in a 32% reduction in disease progression or disease related death in patients who had a combined positive score >5 at a median follow-up of approximately 1 year (HR 0.68; 98% CI 0.56-0.81). Of note, Nivolumab in combination with chemotherapy also improved the overall survival of patients who had a combined positive score of >1 and in all randomised patients when compared to chemotherapy alone (HR 0.77; 99% CI 0.64-0.92 and HR 0.80; 99% CI 0.68-0.94, respectively). This trial did not identify any new safety concerns and the adverse effect profiles between the comparator arms were also similar. These results would suggest that combining chemo-immunotherapy could significantly improve disease-free and overall survival in patients with gastric cancers not amenable to potentially curative surgery who would otherwise have limited treatment options. It would be interesting for future studies to investigate the potential role of immunotherapy as adjunctive treatment in combination with potentially curative surgery and identify further ligands for the development of additional targeted therapies[10].

CONCLUSIONS

Although gastric cancer incidence and prevalence continue to decrease globally, there remains significant geographical variation, with a small number of countries predicted to demonstrate increasing prevalence over the next 10 years. Furthermore, the gastric

cancer incidence rate appears to be increasing in younger cohorts in traditionally high income/low incidence rate countries such as the United Kingdom and further research is required to elucidate the factors responsible. In high risk populations, mass screening for *H. pylori* and subsequent eradication therapy has been shown to be safe, effective and economically beneficial. However its role and any potential benefits in lower risk/lower incidence rate nations remains to be ascertained. For patients undergoing potentially curative surgery, minimally invasive surgery appears to be safe and have outcomes that are oncologically equivalent to open resection, although further investigation into any potential superiority is ongoing. Recent advances have also been made with regards to systemic therapy options for gastric adenocarcinoma, with evidence supporting a role for adjunctive immunotherapy alongside chemotherapy in advanced metastatic disease. Future studies investigating the role of such targeted adjunctive treatment in larger populations and in patients who have resectable disease is warranted to continue to improve outcomes associated with gastric cancer worldwide.

Conflict of Interest

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Informed Consent

None required.

Authors' Contributions

MA performed the literature search and wrote the first draft of the article. NS, NH and DMP reviewed the manuscript for important intellectual content and supervised MA. All authors approved the final version of the manuscript and DMP is the guarantor.

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