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Overview

Gastric Cancer – From Aetiology to Management: Differences Between the East and the West

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Abstract

Gastric cancers are highly prevalent in both the East and the West, although they differ in aetiology and prognostic outcome. Management of gastric cancer from screening to definitive treatment varies substantially between Eastern and Western countries and regions, owing to numerous factors, including government incentives to carry out population-wide screening programmes to detect early disease, differences in clinical and biological tumour behaviours and responsiveness to treatment, patient accessibility to effective treatment, etc. This review highlights and contrasts the differences in tumour aetiology and histology, as well as the management approaches between the East and the West, which gives important insights and inspirations on future international multicentre research collaboration to combat this dreadful malignancy.

Key words: Aetiology; chemotherapy; gastric cancer; radiation therapy; surgery; targeted therapy

Statement of Search Strategies

Searches were done with PUBMED with keywords on the topic.

Introduction

Gastric cancer is the fifth most common cancer worldwide and the third leading cause of cancer mortality [1]. There is a wide geographical variation in incidence, with the highest incidence rates in the Eastern Asian populations of Japan, Korea and China reaching up to 37.4 per 100 000; compared with incidence rates of 8.0 per 100 000 in North America. However, when considering the mortality-to-incidence ratio, Korea and Japan show a much lower ratio than Western populations [2]. In South Korea, the incidence of gastric cancer is the highest in the world, but it reports one of the lowest mortality rates (age-standardised mortality rate: 13/100 000). These significant differences in incidence and mortality between Eastern and Western populations may be explained by differences in both the inherent underlying biological characteristics of the disease, as well as differing management approaches with regards to screening and treatment strategies.

This review compares the aetiology, screening, diagnosis and management of gastric cancer between Eastern and Western populations. Differences in treatment strategies, including surgical approaches and neoadjuvant, adjuvant and palliative therapies, will also be evaluated.

Aetiology

Differences in location, histology and risk factors explain some of the differences in gastric cancer patients between the East and the West. In terms of tumour location, tumours

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located in the proximal third of the stomach are more common in Western countries. Proximal tumours are associated with more advanced stage at presentation, a larger tumour size and poorly differentiated histology. This may account for the worse survival in the West [3,4]. The incidence of proximal gastric cancer is rising and is probably related to obesity and an increasing prevalence of gastro-oesophageal reflux disease [5,6]. This phenomenon is also increasingly recognised in the East.

Environmental risk factors and pathogens also account for the differences in incidence and presentation in the East and the West. *Helicobacter pylori* infection increases cancer risk by three to six times, especially for intestinal-type distal carcinoma [7]. There is a large variation of *H. pylori* prevalence worldwide, with the highest reported in Africa (70.1%; 95% confidence interval 62.6–77.6%), South America (69.4%; 95% confidence interval 63.9–74.9%) and Western Asia (66.6%; 95% confidence interval 56.1–77.0%) and the lowest reported in Oceania (24.4%; 95% confidence interval 18.5–30.4%), Western Europe (34.3%; 95% confidence interval 31.3–37.2%) and Northern America (37.1%; 95% confidence interval 32.3–41.9%) [8]. This explains the higher incidence of gastric cancer in the East.

A high salt diet, smoked foods, nitrates, nitrites and poorly preserved foods alter the gastric milieu, resulting in the production of carcinogens such as N-nitro compounds, contributing to the increased incidence of gastric cancer in the East [9]. According to a large cohort study of 2476 Japanese subjects, a high dietary salt intake is a significant risk factor for gastric cancer and its association might be stronger in the presence of *H. pylori* infection [10]. Cigarette smoking and *H. pylori* infection are also significant synergistic risk factors [11,12]. These epidemiological factors, including diet or smoking, are universal risk factors irrespective of geography. Lifestyle modifications, including a less salty diet and smoking cessation, could be useful ways of preventing gastric cancer worldwide.

Histology

Gastric cancer is a heterogeneous disease entity. Different types of classification according to histological features have been used. The World Health Organization classifies gastric cancer into papillary, tubular, mucinous and poorly cohesive carcinomas. The Lauren classification divides gastric cancer into intestinal, diffuse and mixed types. More recently, The Cancer Genome Atlas (TCGA) research group categorised gastric cancer into four groups by comprehensive molecular characterisation [13]:

(i) Epstein-Barr virus (EBV)-positive tumours: 9% of all gastric cancer, characterised by DNA hypermethylation, high frequency of *PIK3CA* mutation, *PDL1/PDL2* overexpression;
(ii) microsatellite instable (MSI) tumours: 22% of all gastric cancer, usually with intestinal-type histology, showing a high number of mutations and DNA methylation sites, mutation in one of several different DNA mismatch repaired genes (i.e. *MLH1* or *MLH2*);
(iii) chromosome instable (CIN) tumours: 50% of all gastric cancer, mainly coding for alteration in tyrosine kinase receptors, RTK-RAS amplifications (*EGFR*, *ERRB2*, *ERRB3*, *VEGFA*, *FGFR2*, *MET*, *NRAS*/*KRAS*, *JAK2* and *PIK3CA*), amplification of cell cycle genes, *TP53* mutation;
(iv) genome stable (GS) tumours: 20% of all gastric cancer, diffuse-type histology with a lower mutation burden.

The Asian Cancer Research Group (ACRG) also developed a molecular classification with similar molecular approaches [14]. The ACRG classification included four subtypes:

(i) microsatellite stable TP53-positive (MSS/TP53+): 15.3% of all gastric cancer, frequently EBV-positive, with mutations in *ARID1A*, *APC*, *KRAS*, *PIK3CQA* and *SMAD4*;
(ii) MSI: 22.7% of all gastric cancer, usually associated with intestinal-type histology, with early stage at diagnosis and a favourable prognosis, hypermutated due to frequent loss of MLH1, frequently affected by mutations with KRAS, ALK, ARID1A, PIK3 pathway;
(iii) microsatellite stable *TP53*-negative (MSS/*TP53*−): 35.7% of all gastric cancer, TP53 mutation, amplification of RTK2
(iv) microsatellite stable/EMT (MSS/EMT): 26.3% of all gastric cancer, diffuse-type histology, low number of mutations.

The TCGA and ACRG classifications were similar and partially overlapping. Both classifications identified the MSI subgroup, characterised by a high mutation frequency, the intestinal subtype and associated with the best prognosis. Although CIN and TCGA GS subtype tumours were present across all ACRG subtypes, TCGA GS, EBV-positive and CIN subtypes were enriched in ACRG MSS/EMT, MSS/*TP53* + and MSS/*TP53*− subtypes, respectively. However, CDH1 and RHOA mutations were highly prevalent in the TCGA GS subtype but infrequent in the ACRG MSS/EMT subtype, making these two subtypes absolutely not equivalent or synonyms. Possible reasons for these differences could be related to the patient population (USA and Western Europe in TCGA and Korea in ACRG), tumour sampling (mainly diffuse in ACRG) and technology platforms (TCGA with six different molecular platforms: exome sequencing, copy number analysis, mRNA-miRNA-methylation analysis versus ACRG: only mRNA expression and targeted gene sequencing in ACRG). Another study, investigating the gene expression profiles of 1016 gastric cancers, revealed that tumour immunity signatures differ significantly between Asian and non-Asian gastric cancers [15]. Non-Asian gastric cancers were associated with the enrichment of tumour-infiltrating T-cells as well as T-cell gene expression signatures, including *CTLA-4* signalling. Also, non-Asian gastric cancers showed a significantly higher

expression of T-cell markers (*CD3*, *CD45R0*, *CD8*) and a lower expression of the immunosuppressive T-regulatory cell marker *FOXP3* compared with Asian gastric cancers. The variation in the immune checkpoint genes (e.g. *CTLA-4*, *FOXP3*) may have an impact on clinical outcome and geographic locality-specific survival.

Screening

A major difference in management approaches between the East and the West is in the institution of population-based screening programmes. Due to the high incidence of gastric cancer, population-based screening for gastric cancer has been carried out in Japan, Korea and the Matsu Island of Taiwan. Such screening may result in a 'stage-shift', i.e. cancer detection at an earlier stage where more curative intervention is possible.

A prospective Korean multicentre cohort over 10 years of follow-up showed that screening with gastroendoscopy significantly reduced the risk of gastric cancer-specific death (hazard ratio 0.58, 95% confidence interval 0.36–0.94) with a 2.24-fold higher survival rate than the unscreened group [16]. Also, the repeated screening group showed a significantly higher proportion of early gastric cancer (EGC: 96% versus 71%, $P = 0.01$), a smaller size of tumour (1.9 cm versus 3.0 cm, $P = 0.01$), a higher proportion of intramucosal cancer (81% versus 50%, $P = 0.02$) and more frequent performance of endoscopic submucosal dissection (ESD) as treatment (54% versus 23%, $P = 0.007$) compared with the infrequent screening group [17].

There has been no adoption of widespread screening in the West. The European Society of Gastrointestinal Endoscopy, a group of European gastrological societies, published guidelines for the management of precancerous conditions and lesions in the stomach (MAPS) in 2012, with a recent update in 2019 [18]. Both the original and the updated guidelines focus only on the management of precancerous lesions, including atrophy, intestinal metaplasia and dysplasia, but do not make any recommendations on general population screening.

A cost-effectiveness analysis of gastric cancer screening carried out in the USA showed that biennial gastroendoscopy was only cost-effective for non-Hispanic Black people ($80 278/quality-adjusted life years [QALY]), Hispanic people ($76 070/QALY) and Asian people ($71 451/QALY), but not for non-Hispanic White people ($122 428/QALY) [19]. According to the study model, screening should only be considered in high-risk races and ethnicities.

Surgical Approach

Endoscopic Resection

As a result of population-based screening programmes in the East, more EGC is detected. EGC is defined as a tumour confined to the mucosa (T1a) or submucosa (T1b), regardless of the status of lymph node metastases. Series of studies in the East have shown the efficacy and safety of endoscopic mucosal resection (EMR) and ESD for EGC. Nakamura *et al.* [20] reported on 1161 EGC patients treated by ESD from multiple Japanese centres. The 5-year overall survival and recurrence-free survival rates were 93.7 and 99.8%, respectively, in the absolute indication group, and 90.9 and 98.90%, respectively, in the extended indication group. Kim *et al.* [21], reporting on 514 EGC patients who were treated at 13 institutions in Korea, found a local recurrence rate of 6% and no cancer-related deaths during the median follow-up period of 39 months. The use of ESD or EMR is widely adopted in the East. Indications for ESD are well-differentiated tumours, without evidence of venous or lymphatic involvement, <3 cm in diameter and confined to the mucosa or submucosa. In Japan, about 50% of stage IA gastric cancer is treated by EMR.

The use of ESD is not so common in the West because of the lower incidence of early staged gastric cancer. However, with improvements in technology, ESD is now increasingly carried out. Petruzziello *et al.* [22] reported on 70 patients who underwent ESD in Italy. The successful en-bloc resection rate was 97% and 65.6% of patients had R0 resection [22]. Another retrospective review by Mendonça *et al.* [23] on 47 patients with adenocarcinoma of the stomach who underwent ESD in Brazil reported that the en-bloc and complete resection rates were 92.1 and 73.6%, respectively. With a median follow-up of 15.8 months (±14.3 months), the recurrence-free rate was 86.1% [23].

Gastrectomy

Surgical resection is the mainstay of curative treatment for locally advanced gastric cancer. There are several differences in the surgical approaches of the East and the West.

Resection Margins

In Japanese Gastric Cancer Association guidelines, a proximal margin of at least 3 cm is recommended for T2 or deeper tumours with an expansive growth pattern and 5 cm for those with an infiltrative growth pattern [24]. In the American National Comprehensive Cancer Network (NCCN) guidelines, a 4 cm or greater margin is the standard [25]. Subtotal gastrectomy is the preferred approach for distal gastric cancer. In the European Society for Medical Oncology (ESMO) guidelines, radical gastrectomy is indicated for stage IB–III gastric cancer [26]. Subtotal gastrectomy may be carried out if a microscopic proximal margin of 5 cm can be achieved between the tumour and the gastroesophageal junction. For diffuse tumours that are more prone to lateral spread, a wider margin of 8 cm is recommended.

D1/D2 Dissection

The extent of lymph node dissection has been extensively debated. D1 dissection involves the removal of perigastric lymph nodes, whereas more extensive D2 dissection involves the dissection of nodes along the left gastric artery, common hepatic artery, celiac artery and splenic artery. In Eastern countries, D2 dissection is routinely carried out as

the standard of care. In the Japanese Gastric Cancer Association guidelines, D2 dissection is indicated for potentially curable T2–T4 tumours, as well as for cT1N + tumours [24].

On the contrary, D1 dissection is more commonly carried out in the West. The Western preference for a limited D1 dissection or a less extensive lymph node dissection has historically been driven by two large randomised controlled trials (RCTs) carried out in the Netherlands (D1D2 trial) and the UK (Medical Research Council ST01 trial) [27,28]. Both failed to show a significant survival benefit from D2 dissection and even showed higher surgery-associated morbidity and mortality. However, long-term follow-up data from the Dutch study have now confirmed a survival benefit for D2 dissection; 15-year overall survival rates were 21 and 29%, for the D1 and D2 groups, respectively [29]. A Cochrane review involving five RCTs (three European studies and two Asian studies) compared D2 and D1 dissection and found no significant difference in overall survival (hazard ratio 0.91, 95% confidence interval 0.71–1.17) and disease-free survival (DFS; hazard ratio 0.95, 95% confidence interval 0.84–1.07) [30]. D2 dissection was associated with a better disease-specific survival (hazard ratio 0.81, 95% confidence interval 0.71–0.92) but a higher postoperative mortality rate (relative risk 2.02, 95% confidence interval 1.31–3.04). Therefore, both NCCN and ESMO guidelines now recommend that D2 dissection should be considered for physically fit patients in high-volume centres [25,26].

Multimodality Treatment for Operable Gastric Cancer

There is wide variation in the multimodality treatment of gastric cancer between the East and the West. In European countries, perioperative chemotherapy with FLOT4 for four cycles before and four cycles after surgery is the standard. In the USA, adjuvant chemoradiotherapy is commonly used. In Asian countries, like Japan, Korea and China, adjuvant chemotherapy with capecitabine and oxaliplatin (known as the XELOX regimen) or TS-1-based chemotherapy with or without docetaxel is preferred.

Perioperative Chemotherapy

Perioperative chemotherapy is the standard approach in Europe, based primarily on the MRC ST02 'MAGIC' trial [31]. The trial included 503 patients with stage II or greater adenocarcinoma of the stomach, gastroesophageal junction and lower oesophagus. The results showed that perioperative chemotherapy consisting of three cycles of pre- and three cycles of postoperative epirubicin, cisplatin and 5-fluorouracil improved overall survival (hazard ratio for death 0.75, 95% confidence interval 0.60–0.93, $P = 0.009$; 5-year survival rate: 36% versus 23%) and progression-free survival (PFS) (hazard ratio 0.66, 95% confidence interval 0.53–0.81, $P < 0.001$) compared with surgery alone. A similar benefit was seen in the contemporaneous French FFCD9703 trial [32].

FLOT4 is a randomised trial that compared four cycles of pre- and four cycles of postoperative chemotherapy using 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) with the MAGIC regimen for patients with resectable gastric or gastroesophageal junction adenocarcinoma [33]. Of 716 patients enrolled, 360 patients received epirubicin, cisplatin, 5-fluorouracil/capecitabine (the MAGIC regimen) and 356 patients received FLOT. FLOT improved the median overall survival (50 months versus 35 months, hazard ratio 0.77, $P = 0.012$) and PFS (30 months versus 18 months, hazard ratio 0.75, 95% confidence interval 0.62–0.91, $P = 0.004$) with no significant difference in perioperative complications or mortality. Since the publication of this study, FLOT has become the standard of perioperative chemotherapy for gastric cancer.

Adjuvant Chemoradiotherapy

In the USA, adjuvant chemoradiotherapy is the standard of care. In the US Intergroup INT 0116 study, 559 patients with stage ≥ T3 and/or node-positive gastric cancer were randomly assigned to observation versus chemoradiotherapy (three cycles of 5-fluorouracil/leucovorin + radiotherapy with 45 Gy in 25 fractions) after surgery [34]. The 2012 updated report showed that adjuvant chemoradiotherapy improved the median overall survival (35 months versus 27 months, hazard ratio 1.32, 95% confidence interval 1.10–1.60; $P = 0.0046$) and median PFS (27 months versus 19 months, hazard ratio 1.51, 95% confidence interval 1.25–1.83; $P < 0.001$). However, the study was criticised, as only 10% of patients had D2 dissection, 30% did not complete chemoradiotherapy due to toxicity and more than 30% of radiotherapy plans had significant errors. The use of a two-dimensional radiotherapy technique probably contributed to the high rate of toxicity in the trial.

On the contrary, the Korean ARTIST trial randomised 458 gastric cancer patients with D2 dissection to either six cycles of adjuvant chemotherapy with capecitabine and cisplatin or to two cycles of capecitabine and cisplatin followed by radiotherapy and two additional cycles of capecitabine and cisplatin [35]. There was no difference in overall survival (hazard ratio 1.130, 95% confidence interval 0.775–1.647; $P = 0.5272$) or DFS (hazard ratio 0.740, 95% confidence interval 0.520–1.050; $P = 0.0922$) with the addition of adjuvant chemoradiotherapy. Subgroup analyses showed that chemoradiotherapy improved DFS in node-positive disease and the benefit was higher in the subgroup with a ratio of metastatic lymph nodes to examined lymph nodes >25% [36]. The ARTIST-2 study is ongoing and is investigating the role of adjuvant chemoradiotherapy in node-positive patients.

Adjuvant Chemotherapy

In the East, adjuvant chemotherapy is the standard treatment after gastrectomy in stage II or more advanced gastric cancer. The CLASSIC trial is a RCT that randomised 1035 stage II–IIIB gastric cancer patients who received a D2 gastrectomy to eight cycles of adjuvant chemotherapy with XELOX versus surgery alone. The trial was carried out in 37 centres in South Korea, Taiwan and China. Adjuvant

chemotherapy with XELOX improved overall survival (5-year overall survival 78% versus 69%, $P = 0.0015$) and DFS (5-year DFS: 68% versus 58%, $P < 0.0001$) [37].

In Japan, adjuvant chemotherapy with TS-1 for 1 year is the standard of care. The ACTS-GC study, conducted in Japan, randomised 1059 patients with stage II/III gastric cancer who underwent gastrectomy with D2 dissection into 1-year oral TS-1 or surgery alone [38]. The study confirmed an improvement in overall survival (5-year overall survival: 71.7% versus 61.1%, hazard ratio 0.669, 95% confidence interval 0.540–0.828).

Adding docetaxel to TS-1 also improved outcomes, as shown in the JACCRO GC-7 study, a phase III RCT to explore the role of postoperative TS-1/docetaxel carried out in 138 Japanese institutions [39]. Patients with pathological stage III disease were randomised to either TS-1/docetaxel or TS-1 for 1 year. The 3-year recurrence-free survival of 65.9% of the TS-1/docetaxel arm was significantly superior to the 49.6% of the TS-1-alone arm (hazard ratio 0.632, 99% confidence interval 0.400–0.998; $P = 0.0007$) at the planned second interim and the independent data and safety monitoring committee recommended termination of the trial. There was a higher rate of ≥grade 3 adverse events, including leucopenia, anorexia, stomatitis and anaemia, in the TS-1/docetaxel arm. Since the announcement of the promising results of JACCRO GC-7 in ASCO 2018, TS-1 with docetaxel is the standard adjuvant chemotherapy for stage III gastric cancer in Japan.

Metastatic Disease: Palliative Treatment

Despite improvements in the multimodality management approach, the recurrence rate is still high. Even for those whose tumours are resectable upfront, the recurrence rate is still high, at round 25–60% [40,41]. Moreover, more than half of patients are already too advanced and inoperable at diagnosis.

In both the East and the West, first-line and second-line palliative chemotherapy with or without a targeted agent has become a standard treatment in patients with advanced/metastatic gastric cancer. The treatment regimens are also similar. Standard frontline therapy includes doublet chemotherapy with 5-fluorouracil and platinum agents and triplet chemotherapy with added anthracycline or a taxane group agent. In *Her-2*-positive advanced gastric cancer, as proven in the ToGA study, adding trastuzumab to platinum-based chemotherapy (cisplatin/carboplatin + 5-fluorouracil) showed a superior efficacy compared with chemotherapy alone (overall survival 13.8 months versus 11.1 months, hazard ratio 0.74; 95% confidence interval 0.60–0.91; $P = 0.0046$) [42].

Several systematic reviews and meta-analyses have also confirmed a survival advantage using second-line chemotherapy when compared with best-supportive care (BSC) alone [43–45]. In Kim *et al.*'s [43] meta-analysis, which involved 410 patients, second-line chemotherapy significantly reduced the risk of death when compared with BSC (hazard ratio 0.64, 95% confidence interval 0.52–0.79, $P < 0.0001$). Standard second-line therapies include irinotecan-based and taxane-based (docetaxel or paclitaxel) chemotherapy. Ramucirumab, a vascular endothelial growth factor receptor monoclonal antibody, has also been established as monotherapy or in combination with paclitaxel in the second-line setting [46,47].

For third-line therapy or beyond, there are wide variations in use around the world. In Eastern countries, around 21–27% of advanced gastric cancer patients are treated with third-line systemic treatment, with a median overall survival of around 4–5 months from starting third-line therapy [48,49]. On the contrary, the use of systemic treatment beyond second-line is less common in Western countries. A retrospective review of 511 cases treated at the Royal Marsden Hospital in the UK from April 2009 to November 2015 reported that 71 patients (14%) received third-line treatment. Of these 71 patients, two (3%), 26 (37%) and 42 (60%) received triplet, doublet or single-agent therapy, respectively [50]. In another multicentre retrospective study involving 2200 advanced gastric cancer patients treated from May 2000 to February 2015 in 19 Italian oncology departments, 331 patients (15.0%) received a third-line therapy [51]; 45.7% of patients received single-agent chemotherapy, whereas 49.7% received a combination regimen. Patients who had experienced a first-line PFS ≥6.9 months or a second-line PFS ≥3.5 months had a better prognosis compared with those who had achieved a shorter PFS.

A systematic review and meta-analysis on third-line systemic treatment involving six RCTs and 890 participants, of which 76.2% were Asian, showed that third-line treatment improved overall survival (hazard ratio 0.63; 95% confidence interval 0.46–0.87, corresponding to an improvement in median overall survival from 3.20 to 4.80 months) and PFS (hazard ratio 0.29; 95% confidence interval 0.18–0.45) when compared with BSC [52]. The magnitude of overall survival benefit in the Asian subgroup (hazard ratio 0.63; 95% confidence interval 0.45–0.90, corresponding to an improvement in median overall survival from 3.20 to 4.83 months) was not significantly different compared with the whole population. This evidence implied that even in Western populations, a proportion of patients could tolerate and gain benefit from a sequenced treatment approach incorporating multiple lines of therapy.

Established third-line therapies include irinotecan, taxane, TAS102, apatinib, regorafenib and checkpoint inhibitors nivolumab and pembrolizumab. There is no international consensus on the best regimen for metastatic gastric cancer in the third-line setting. In China, apatinib is the standard third-line treatment. In the phase III RCT conducted in China, apatinib showed significant clinical benefits compared with placebo in terms of overall survival (6.5 months versus 4.7 months, hazard ratio 0.709, $P = 0.0156$) and PFS (2.6 months versus 1.8 months, hazard ratio 0.444, $P < 0.001$) [53]. The Japanese Gastric Cancer Guidelines suggests the use of nivolumab or irinotecan as third-line treatment [54]. In the ATTRACTION-2 study, which was a double-blind, placebo-controlled phase III RCT conducted in Japan, South Korea and Taiwan, nivolumab was associated with a significant overall survival benefit

Table 1
Differences in clinical practices for gastric cancer between the East and the West

	East	West
Screening	National screening programmes in: • Japan: radiographic and endoscopic screening starting at age 50 years • Korea: radiographic or endoscopic screening every 2 years for ages 40–74 years • Matzu Island of Taiwan: first by carbon-urea breath test; those with positive results receive endoscopy with subsequent *Helicobacter pylori* eradication treatment	No national screening programmes
Surgery	Endoscopic resection is common for early staged cancer	The use of endoscopic resection is rising
	Routine D2 dissection	D2 dissection only in fit patients and high-volume centres
Multimodality treatment	Adjuvant chemotherapy: • Xelox × 8 cycles • TS-1 for 1 year in Japan • TS-1 + docetaxel for stage III in Japan	Europe: perioperative chemotherapy with FLOT for four cycles before surgery and FLOT for four cycles after surgery USA: adjuvant chemoradiotherapy
Palliative systemic treatment		
First line	Platinum + 5-fluorouracil-based chemotherapy (5-fluorouracil/capecitabine, whereas S-1 in Japan/Korea) If Her-2 positive, add trastuzumab on top of platinum and 5-fluorouracil	
Second line	Paclitaxel and ramucirumab Single agent: paclitaxel, docetaxel, irinotecan	
Third line	More commonly used Agents approved: • Nivolumab • Apatinib in China • Irinotecan/taxane • TAS-102	Usually in a trial setting Agents approved: •TAS-102 • Pembrolizumab in tumours that expressed PD-L1 with a combined positive score ≥ 1

FLOT, 5-fluorouracil, leucovorin, oxaliplatin and docetaxel.

versus placebo (overall survival 5.32 months versus 4.14 months, $P < 0.0001$; 12-month overall survival 26.6% versus 10.9%) [55]. The survival advantage was persistent over time with nivolumab and irrespective of PD-1/PD-L1 expression.

In the West, the NCCN recommends TAS-102 for the third-line setting and pembrolizumab for third-line or beyond treatment in adenocarcinoma of the stomach that expresses PD-L1 with a combined positive score ≥1. TAS-102 has obtained approval from the US Food and Drug Administration in the third-line setting. This is based on the international phase III TAGS study, in which TAS-102 showed a significant improvement in overall survival, corresponding to a 31% improvement relative to placebo (median overall survival: 5.7 months versus 3.6 months, $P = 0.0058$) [56]. TAS-102 also improved PFS, with a relative 43% improvement (PFS 2.0 months versus 1.8 months, hazard ratio 0.57, $P < 0.0001$).

The similarities and differences in the screening and management of gastric cancer between the East and the West are summarised in Table 1.

Conclusions

There are clear differences in the management of gastric cancer between the East and the West. The differences in aetiology, surgical approach and perioperative or adjuvant treatment may account for the differences in survival outcomes between Eastern and Western countries. Similarities in the metastatic setting show that optimal sequencing of systemic treatment could maximise benefits in both survival and quality of life. By understanding the inherent differences between the East and the West we can design better RCTs and treatment paradigms to suit the unmet need across different parts of the world.

Conflict of Interest

Ka-On Lam received grants and research support from Bayer, Roche and Taiho. He also received honoraria as an advisory board member from Amgen, Bayer, Bristol-Myers Squibb, Eli Lilly, Merck Serono, Merck Sharp & Dohme, Roche, Sanofi-Aventis and Taiho.

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