Gastric Cancer Working Group Report

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Epidemiology: Gastric cancer is the second most common cancer in Asia, more than half of the world’s gastric cancer cases arise in Eastern Asia, and the majority of Asia’s cases still occur in the distal part of the stomach.

Etiology and Prevention: The etiology of gastric cancer consists of genetic susceptibility, Helicobacter pylori infection and environmental risk factors. Helicobacter pylori eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and non-steroidal anti-inflammatory drugs seem to reduce the risk of gastric cancer.

Endoscopy and Diagnosis: Screening for gastric cancer is cost-effective in countries with high incidence. Risk stratification may increase the cost-effectiveness of screening in populations at moderate risk. Endoscopic resection is curative in a subset of patients with early cancer.

Surgery and Adjuvant Treatment: R0 resection with D2 lymph node dissection has produced the best survival data. Some kind of post-operative adjuvant chemotherapy including S-1 is recommended after D2 surgery.

Chemotherapy for Advanced Gastric Cancer: As chemotherapy for gastric cancer, fluorouracils plus platinum are the most widely accepted first-line regimens, whereas taxanes or irinotecan are mostly used in second- and third-line settings. Differences in the approval and medical insurance systems may influence the status of these regimens. Trastuzumab in combination with fluorouracils/platinum will be a standard regimen for HER2-positive gastric cancer. Many new targeting agents are currently under investigation, and Asian countries are playing important roles in investigation and development of new and better treatments for this malignancy.

Key words: gastric cancer – Helicobacter pylori – D2 lymphadenectomy – adjuvant chemotherapy – endoscopic treatment – chemotherapy
most frequent, whereas the proximal gastric cancer is more common in Western countries (Fig. 4) (2).

In conclusion, gastric cancer is the second most common cancer in Asia, more than half of the world’s gastric cancer cases still arise in Eastern Asia, and the majority of those cases still occur in the distal part of the stomach. An increased trend for EC-junction adenocarcinoma is suggested in Western countries, but there is no evidence of such a trend in Asia.

ETIOLOGY AND PREVENTION

Three major factors are involved in the development of gastric cancer: *Helicobacter pylori* infection, genetic
susceptibility (CDH1 etc.) and environmental factors (such as smoking, a high-salt diet and low vegetable consumption) (3). *Helicobacter pylori* infection is the most important. A study by Dr Uemura et al. (4), published in the *New England Journal of Medicine*, found no development of gastric cancer in cases without *H. pylori* infection, whereas...
2.9% of 1246 cases with H. pylori infection developed gastric cancer over a period of 7.8 years. A randomized controlled study in China also showed that H. pylori eradication was more effective in patients without atrophic gastritis than those with it (5). Dr Fukase in Japan reported that in a randomized controlled study comparing eradication of H. pylori with no eradication after endoscopic mucosal resection (EMR) of early gastric cancer at the 3-year follow-up point significantly reduced the number (9 versus 24) of metachronous gastric cancer developed in the eradication group compared with the control group. It was concluded that prophylactic eradication of H. pylori after EMR for early gastric cancer should be performed to prevent the development of metachronous gastric cancers (Fig. 5) (6). These results suggested that it was never too late to eradicate H. pylori for prevention of gastric cancer. An Italian group performed a meta-analysis of the published data regarding whether H. pylori eradication treatment can reduce the risk of gastric cancer. It was concluded that 1.1% of treated patients would develop gastric cancer, in contrast to 1.7% of untreated patients. In six studies with about 6700 participants followed for 4–10 years, the relative risk was 0.65, and it was concluded that H. pylori eradication treatment seemed to reduce gastric cancer (7). In Taiwan, a nationwide cohort study followed 80,000 patients with H. pylori-infected peptic ulcers for 10 years. These patients were divided into early- and late-eradication cohorts. It was concluded that early H. pylori eradication showed no significant difference in the gastric cancer risk compared with the general population, but late eradication was associated with an increased risk of gastric cancer. Older age, male gender, gastric ulcer, no regular NSAIDs use and late H. pylori eradication represented independent risk factors for gastric cancer development (Fig. 6) (8).

Fock et al. concluded that fruits and vegetables are associated with a reduced risk of gastric cancer in his paper in the Journal of Gastroenterology and Hepatology. Supplementation of vitamins and minerals may be unnecessary, at least in healthy subjects with no nutritional deficiencies (9). In a meta-analysis study, all studies proved that both aspirin and NSAIDs are useful for preventing cardia and non-cardia gastric cancer (10). There is insufficient evidence for any benefit from green tea, vitamins and antioxidants. The biological behaviors of distal and proximal gastric cancers are quite different, but the prevention regimens have been the same, centered on eradication of H. pylori infection.

The Working Group concluded that the etiology of gastric cancer consists of genetic susceptibility, H. pylori infection and environmental risk factors. Helicobacter pylori eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and NSAIDs (11) seem to reduce the risk of gastric cancer.

**ENDOSCOPY AND DIAGNOSIS**

Experience in Japan has shown that access to screening and early endoscopy increased the proportion of early-stage
gastric cancers, leading to improved survival (12). Cost is a major barrier to screening. Screening is considered to be cost-effective in high-incidence countries, but perhaps not where the incidence of gastric cancer is moderate or low. Risk stratification may help to focus limited resources on patients at greatest risk, and thereby increase the cost-effectiveness of screening (13). Serum pepsinogen-based tests may help to identify a subset of patients with atrophic gastritis, who are especially at a high risk. In a country with high incidence of gastric cancer, such as Japan, it is still very cost-effective to screen even if the cost of endoscopy is high. Singapore and some other countries in East Asia have a moderate incidence of gastric cancer, and screening these populations could be cost-effective if the cost were moderate (13). In Japan, the government-supported screening program has been based on barium, and although very successful, it accounts for less than 10% of all cancers that are diagnosed by screening. Most are detected due to early or easy access to endoscopy, either through outpatient clinics or through health screening outside of the government’s screening program (14).

High-quality endoscopy is important and may be facilitated by endoscope preparation, such as lens cleaning, and by patient preparation ahead of endoscopy by the use of defoaming agents, mucolytics and antispasmodics, which make the field of interest much clearer. Techniques such as adequate air insufflation, systematic examination of the entire stomach, use of contrast agents, image enhancement and cognitive training may also help improve yield rates.

Accurate specimen collection and recording of endoscopic findings are important. There is some discordance between Western- and Japanese-trained pathologists in the biopsy definition of early gastric cancer. In the West, the gold standard for diagnosing cancer is to detect invasion of tumor cells into the lamina propria, muscularis mucosae or submucosal layer, whereas in Japan, it is more important to detect cellular atypia or structural atypia, regardless of invasion, when making a diagnosis of cancer. The revised Vienna classification has helped resolve some of these differences and may be a good starting point for consensus between Western and Japanese pathologists (15).

Gotoda et al. (16) reported that there is a clearly defined subgroup of patients with early gastric cancer that has a virtually negligible risk of nodal metastasis. Such patients could be treated definitively by local resection, with the expected long-term outcome equivalent to radical surgery. Further development led to the expanded criteria for endoscopic therapy of early gastric cancer, with en bloc resection being the primary goal (17). Endoscopic resection can be considered curative if the lesion shows differentiated histopathology, is limited to the mucosal layer or <500 μm submucosal invasion, with clear vertical and lateral margins, and no lymphovascular involvement. EMR has the advantages of short procedure time and low risk of perforation, which make it an attractive option for small lesions. EMR for differentiated, non-ulcerated early cancer <20 mm in diameter is associated with an excellent 10-year survival rate of 99% (18). Endoscopic submucosal dissection (ESD) is associated with a lower local recurrence rate than EMR because the technique permits en bloc resection without size limitation. Procedure times for ESD are longer, however, with higher delayed bleeding and perforation risk (19). A recent long-term follow-up study showed that ESD for early gastric cancer, which met the expanded criteria, resulted in 5-year overall and disease-specific survival rates of 97% and 100%, respectively (20). Training opportunities in ESD for endoscopists from outside Japan and Korea, however, remain limited.

In conclusion, screening for gastric cancer is cost-effective in countries with high incidence. Risk stratification may increase the cost-effectiveness of screening in populations at moderate risk. Barium meal-based screening is government-funded in Japan, but is less accurate than gastroscopy. Gastroscopic screening is desirable in high-risk populations. High-quality endoscopy may increase diagnostic yield in early cancer. Endoscopic resection is curative in a subset of patients with early cancer as defined by the expanded criteria. EMR has shown long-term outcomes comparable with surgery in patients with small lesions, and similar outcomes with ESD for larger lesions in experienced hands. Standardization between Western- and Japanese-trained pathologists in diagnosing gastric cancer is urgently needed. Structured training programs for ESD should be set up in high-volume centers and made accessible to suitable regional candidates.

**SURGERY AND ADJUVANT TREATMENT**

For gastric cancer, so-called D1, or perigastric lymph node, dissection is common in Western countries, whereas in high-incidence countries like Japan and Korea, so-called D2 dissection is considered to be the standard (Fig. 7) (21,22).

An RCT from UK comparing D1 versus D2 found very high mortality but failed to show a difference (23,24). The trial was flawed due to the very high mortality, inclusion of a large proportion of stage I and absence of any description regarding the quality of lymph node dissection. A Dutch trial started 20 years ago also showed much higher mortality for D2 compared with D1 dissection and demonstrated no survival benefit (25,26). These two trials were closed before reaching the plateau of the learning curve, and the high postoperative mortality offset the effect of the D2. D2 dissections should be carried out in specialized centers.

An RCT in Taiwan compared D1 and D2 showed survival benefit of D2 dissection with reasonable morbidity and mortality (Fig. 8) (27).

To investigate even more extensive dissection of gastric cancer, a Japanese group compared D2 with D2 plus para-aortic nodal dissection (28,29). The results showed slightly higher morbidity, but without increase in mortality. These morbidity and mortality results were acceptable. However,
no survival difference was observed, and D2 was thus the optimal surgery in that RCT. Comparison of reports from various countries reveals that the mortality is higher when the volume is lower, again demonstrating that D2 dissection should be performed in high-volume and/or specialized centers.

Regarding the role of adjuvant treatment, a major trial in Europe showed survival benefit from perioperative chemotherapy, but less than half of the patients underwent D2 dissection and the study also included esophageal cancer cases (30).

An RCT performed in the USA investigated the role of post-operative chemoradiotherapy and also showed significant survival benefit (31,32). However, only 10% of the patients underwent D2 dissection, there was a very high rate of local recurrence, and the surgery was not standardized among the participating hospitals. Subgroup analysis found survival benefit only in D0 or D1, but not in the D2-dissected group. The study thus showed that D0/D1 dissection was insufficient treatment.

In a Japanese randomized trial, curative D2 dissection alone was compared with D2 followed by post-operative chemotherapy by oral S-1 (33). In contrast to the Western studies, almost all of the cases in this study underwent D2 dissection, and the 3-year survival rate showed a 10% improvement (Fig. 9). A clinical trial of adjuvant treatment is being conducted in Korea, China and Taiwan, and 1024 cases have been enrolled. The results will be available within a few years. A Japanese group and a Korean group are working together to assess, for the first time, the role of reductive gastrectomy in Stage IV gastric cancer treatment (34). The chemotherapy applied in both arms is S-1 plus cisplatin. Although a very difficult project, it is very important, and it is hoped that other Asian countries will join this collaboration in the future.

In conclusion, with regard to the extent of surgery, R0 resection with D2 lymph node dissection has produced the best survival data. Some kind of post-operative adjuvant chemotherapy including S-1 is recommended after D2 surgery. In areas with a high incidence of gastric cancer, the quality of treatment can be kept very high, with both endoscopic treatment and surgery. At the moment, at least in Asia, D2 dissection should be considered as the standard.

CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

There are now four active cytotoxic agents for advanced gastric cancer, consisting of fluorouracils, platinum, taxanes and irinotecan. The fluorouracils include 5-FU, S-1 and capecitabine, and the platinum include cisplatin and oxaliplatin. During the last decade, various randomized trials investigated the optimal combination of these four chemotherapy drug groups in Japan, Korea and China (Table 1). Capecitabine plus platinum was at least non-inferior to 5-FU plus cisplatin in terms of survival (35,36). S-1 plus cisplatin showed a comparable median time to progression to those in capecitabine or 5-FU plus cisplatin in Western studies (37,38), whereas the Japanese studies yielded relatively longer survival than the Western studies. These favorable survival in Japanese studies compared with the Westerns might be caused by longer survival after failure of the first-line therapy associated with higher rates of subsequent therapy than in the Western studies (Fig. 10).
The approval status of active agents for gastric cancer differs among four East Asian countries. Capecitabine and oxaliplatin are not yet available in Japan, and S-1 and oxaliplatin are not available in Taiwan (Table 2). In Japan, approval is always associated with medical reimbursement, but that is not always the case in other countries. The differences caused by the medical insurance systems may affect the survival results larger than by ethnic differences in biology or pharmacokinetics. In countries with limitations on medical reimbursement for second- or further line chemotherapy, such as Western countries and Asian countries other than Japan, triplet regimen such as docetaxel + cisplatin + 5-FU is becoming more popular. However, in Japan, all agents that have been approved are covered by medical reimbursement at any line of chemotherapy, which cause that FUs plus platinum are the most popular first-line

### Table 1. Results of randomized trials using newer regimens: advanced gastric cancer

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<th>RR (%)</th>
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aTest for superiority in OS.
bPFS.

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regimens followed by taxane or irinotecan. In conclusion, no global standard regimen has been established yet as the first-line standard chemotherapy for metastatic cancer. In Asian countries, FU and platinum combinations are the most widely used regimens, with median progression-free survivals of 5–6 months. Differences in the approval and medical insurance systems may influence the status of these regimens.

The ToGA study compared the cytotoxic combination (5-FU or capcitabine + cisplatin) with and without trastuzumab in patients with HER2-positive gastric cancer (Fig. 11) (39). This is a global randomized trial, but more than half of the patients have been recruited from East Asian countries, including Korea, Japan and China. Trastuzumab showed a significant survival advantage compared with the cytotoxic agent combinations, with a hazard ratio of 0.74. From the Asian point of view, the ToGA trial indicates that trastuzumab in combination with FU/platinum will be a new option for HER2-positive gastric cancer. Moreover, the HER2-positive population will become an independent entity, as in breast cancer, although further studies are needed. Regional differences, such as the HER2-positive rate, may be clarified by further analyses. Five of seven ongoing global RCTs for metastatic gastric cancer are led mainly by Japan and Korea. Asian countries are playing a major role in the development of new agents for gastric cancer (Table 3) (40).

In conclusion, FU plus platinum are the most widely accepted first-line regimens for gastric cancer, whereas taxanes or irinotecan are mostly used in second- and third-line settings. Differences in the approval and medical insurance systems may influence the status of these regimens, and the improvement in these status is hopefully done in many countries. Trastuzumab in combination with FU/platinum will be a standard regimen for HER2-positive gastric cancer, and the recent phase II/III trials showed favorable median survival times exceeding 1 year. Many new targeting agents are currently under investigation and the roles of Asian countries in the development of new agents will become important.
Conflict of interest statement
None declared.

References

