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Current Management and Future Strategies of Gastric Cancer

Joong Ho Lee, Kyung Min Kim, Jae-Ho Cheong, and Sung Hoon Noh

Department of Surgery, Yonsei University College of Medicine, Seoul, Korea.

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Co-corresponding authors: Dr. Jae-Ho Cheong, Department of Surgery, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-2094, Fax: 82-2-313-8289
E-mail: jhcheong@yuhs.ac and
Dr. Sung Hoon Noh,
Department of Surgery, Yonsei University College of Medicine, 50 Yonsei-ro, Seodaemun-gu, Seoul 120-752, Korea.
Tel: 82-2-2228-2100, Fax: 82-2-313-8289,
E-mail: sunghoonn@yuhs.ac

· The authors have no financial conflicts of interest.

The overall prognosis of gastric cancer has gradually improved over the past decades with growing awareness of potential carcinogens, surveillance programs and early diagnosis, as well as advances in surgical techniques and multimodality treatments. Nevertheless, the outcome of advanced stage disease still remains poor with currently available treatments, and a worldwide consensus on the standard management thereof has not been established. To improve prognosis and quality of life in gastric cancer patients, both standardization and individualization of managements are imperative. Diagnostic tests and surgical procedures need to be further sophisticated and standardized based on more recent evidences from ongoing and future randomized controlled trials, while comprehensive management should be individualized to each patient. Future challenges lie with how to optimize personalized therapies by deciphering biological complexity of gastric cancer and incorporating molecular biomarkers in clinical practice to forecast prognosis and to guide targeted therapeutics in adjunct to current standards of care.

Key Words: Stomach neoplasm, primary prevention, screening, gastrectomy, lymphadenectomy, biological marker, molecular therapeutics

INTRODUCTION

Gastric cancer remains a major health issue and a leading cause of cancer death worldwide, although the prevalence and mortality of the disease have gradually decreased.[1,2] In Eastern Asia, including Korea and Japan, the incidence of gastric cancer is still high despite advances in treatment and subsequent improvement in prognosis. On the contrary, in the West, where the incidence has continuously decreased, the overall and stage-specific survival is worse than that in Eastern Asia.[3] Although the geographical differences in terms of incidence and prognosis have not yet been clearly elucidated, they are probably attributable to various factors in gastric carcinogenesis as well as in diagnostic and therapeutic strategies.

To conquer gastric cancer, primary prevention would be the best measure. Practically, however, a cure for gastric cancer can only be expected by both loco-regional and systemic control of the disease with early diagnosis, and the quality of life (QoL) of individual patients, particularly in perioperative periods, has also become an important component of comprehensive quality care. Nevertheless, management patterns vary worldwide and the survival gain from currently available

multimodality treatments seems to reach a plateau.

This article will review the current management of gastric cancer in depth, discussing gastric carcinogenesis in relation to the prevention of the disease, early detection with effective screening, and surgical treatment as the current standard of management, as well as a multidisciplinary approach for advanced disease. Furthermore, the current status of molecular biomarkers and targeted therapy will be discussed as the future strategy for the tailored management of gastric cancer patients.

PRIMARY PREVENTION AND GASTRIC CARCINOGENESIS

According to the World Health Organization (WHO)'s Fight Against Cancer report,[4] 40% of all cancer deaths can be prevented. At the forefront of the health care system, primary care physicians play a critical role in cancer prevention by counseling individual patients on behaviors related to certain types of cancer.[5]

Tobacco smoking and the high consumption of salted and smoked foods are well known lifestyle and environmental causes of gastric cancer.[6] Overweight and obesity are also associated with increased risk of gastric cancer.[7] Although previous studies showed an inconsistent correlation between gastric cancer and alcohol, a recent meta-analysis[8] found a significant positive association between heavy alcohol intake and gastric cancer. On the other hand, there has been consistent evidence that vegetables and fruit are protective against gastric cancer.[9] Following general cancer prevention guidelines, lifestyle modification, avoiding the aforementioned risk factors, seems to be the most effective and easiest way to reduce the incidence and mortality of gastric cancer.

Furthermore, *Helicobacter pylori (H. pylori)* has been classified as a class I carcinogen in humans by WHO since 1994,[10] based mainly on epidemiological evidence of its role in the pathogenesis of gastric carcinoma. Independent meta-analyses have led to an overall consensus that *H. pylori* infection is associated with approximately a two-fold increased risk of developing gastric cancer,[11] and this association has been reported to be stronger for patients younger than 30 years of age.[12] Beyond the epidemiologic evidence of *H. pylori*, several studies have also reported that the *H. pylori* infection directly affects the carcinogenic mechanisms of gastric cancer. For example, *H. pylori* plays a critical role in the well-known human model of gastric carcinogenesis proposed by Correa.[13] Chronic inflammatory gastritis, associated with *H. pylori* infection, is thought to form the initial lesion that induces progressive histopathological changes in gastric mucosa, towards chronic atrophic gastritis, intestinal metaplasia, dysplasia, and finally, intestinal-type adenocarcinoma. Recently, more attention has also been given to a role of stem cells in the gastric carcinogenesis initiated by *H. pylori* infection. Chronic damages to gastric mucosa alter the maturation process of epithelial stem cells and thus recruit bone marrow-derived stem cells which potentiate the carcinogenic process.[14] However, the relationship between *H. pylori* and gastric cancer still lacks evidence of a true causal relationship and its carcinogenic mechanism remains to be further elucidated.

A recent meta-analysis of seven randomized trials[15] mostly conducted in Asia, where the infection rate of *H. pylori* is substantially high, demonstrated that eradication of *H. pylori* has the potential to prevent gastric cancer. Accordingly, updated Japanese guidelines for the management of *H. pylori* and related diseases[16] have finally indicated that eradication of *H. pylori* is useful for the prevention of gastric cancer. Several antimicrobial regimens for *H. pylori* infection have been very successful, achieving eradication rates higher than 90%.[17] It seems that earlier eradication thereof would accomplish a more significant decrease in gastric cancer risk.[18] Nevertheless, identifying individuals with *H. pylori* infection is difficult because there is no specific symptom. Moreover, considering the high prevalence rates in epidemic regions like Eastern Asia, providing proper diagnostic tests and antibiotic treatment to all infected individuals would be overwhelming.[19] Consequently, research into developing a vaccine against *H. pylori* in humans is ongoing, as application of a prophylactic vaccine in clinical practice offers the best strategy to prevent *H. pylori* infection and to reduce the risk of developing gastric cancer.[20]

SECONDARY PREVENTION: EARLY DETECTION

To improve survival in gastric cancer patients, early detection and subsequent surveillance programs are essential,[21] and currently available screening tools include radiologic imaging and endoscopy with biopsy. Nationwide mass screening programs in Korea and Japan, where gastric can-

cer is the most common malignancy, has made it possible to detect the disease in earlier stages and to improve the overall survival rates of gastric cancer patients.[22] However, most nations, except for Korea and Japan, have no national guidelines or recommendations for gastric cancer screening,[23] as there are no screening tools applicable to low risk populations with respect to acceptable accuracy, minimal invasiveness, and low cost.[24]

The National Cancer Screening Program in Korea recommends that men and women older than 40 years of age receive gastric cancer screening every other year with either direct upper-gastrointestinal series or endoscopy.[25] In Japan, gastric cancer screening for all residents aged 40 years and over is performed by annual photofluorography and further investigation by endoscopy on positive findings of photofluorography.[26] In recent years, however, endoscopy has been performed instead of photofluorography as the initial mass screening method in several cities in Japan, and a cohort analysis showed that endoscopic mass screening was superior in cost-effectiveness for screening gastric cancer patients.[27] Indeed, endoscopy has been considered as the best diagnostic method of gastric cancer with advantages of direct visualization of gastric mucosa and collection of mucosal specimens for histopathological evaluation. It is useful in detecting minute lesions in early gastric cancer (EGC) in particular, which is difficult to detect by upper-gastrointestinal series alone. Accordingly, endoscopy would be the best screening tool in Korea and Japan, where the incidence of EGC is substantially high and endoscopy is readily performed by experienced endoscopists at acceptable cost.

However, mass screening by endoscopy in other nations may not be the most practical approach, considering that endoscopy is an invasive procedure carrying potential complications, and moreover, it is expensive in low-risk populations.[23,24] Therefore, there is high demand for cost-effective and non-invasive tools for gastric cancer screening to detect premalignant lesions, and two serologic makers, serum pepsinogen and gastrin-17, have been reported by several studies. Human serum pepsinogens are proenzymes of pepsin, an endoproteinase of gastric juice. In a pooled meta-analysis of Japanese studies assessing approximately 300,000 people,[28] the sensitivity and specificity of serum pepsinogen testing for gastric cancer screening were 77% and 73%, respectively. Subsequently, generalized cancer screening programs in Japan have accepted the measurement of serum pepsinogen as a non-invasive serological screening test of gastric cancer. Gastrin-17 is secreted from antral G cells and its concentrations depend on the intragastric acidity and number of G cells; therefore, measuring its serum level might predict the severity of atrophic gastritis.[29] However, as it only correlates with distal stomach status, serum gastrin-17 cannot be used as a single serum marker for gastric cancer screening.[23]

In summary, a safe and effective screening strategy should be established to improve the prognosis of gastric cancer, in consideration of the incidence of the disease as well as the availability and cost-effectiveness of the screening method.

PRESENT STATUS OF GASTRIC CANCER MANAGEMENT

Radical gastrectomy with D2 lymphadenectomy

Radical (total or subtotal) gastrectomy is the gold standard of management of gastric cancer worldwide, as the complete surgical removal of macroscopic and microscopic tumors (R0 resection) confers the only chance for curing the disease. However, the extent of lymphadenectomy has been debated between the East and West. Radical gastrectomy with extended D2 lymphadenectomy is the accepted standard in Eastern Asia, whereas limited D1 resection with chemoradiotherapy is more frequently used in Western countries.[30,31]

The well-known European Phase III randomized controlled trials in the 1990s, carried out by the Medical Research Council and Dutch Gastric Cancer Group, failed to show a survival benefit of D2 over D1 resections,[32,33] with extremely high morbidity and hospital mortality in D2 group. However, it is not feasible to draw any definite conclusion of long-term survival benefit of D2 lymphadenectomy based on these trials, because they had some critical problems which inevitably lead to the substantially higher morbidity and mortality rates in D2 resections, compared to those reported by specialized high-volume centers in Korea, Japan, and Western countries as well. There was no standardized quality control of the participating surgeons and hospitals prior to these trials and routine resection of the distal pancreas and spleen in total gastrectomy was defined as a part of D2 dissections in the trial protocol. To the contrary, splenectomy and distal pancreatectomy for removal of station 10 (parasplenic) and station 11 (parapancreatic) lymph nodes are no longer advocated as a routine adjunctive procedure during D2 resections.[34] Furthermore, it should be noted that the fifteen-year

follow-up of the Dutch trial[35] recently reported that D2 lymphadenectomy was associated with lower locoregional recurrence and gastric cancer related death rates than D1 surgery after a median follow-up of 15 years. Also, the author suggested that spleen-preserving D2 resection is recommended as a standard management of resectable gastric cancer at high-volume specialized centers. Likewise, the interim report of a randomized controlled trial by the Italian Gastric Cancer Study Group showed no significant difference in postoperative mortality and overall morbidity between D1 and pancreas-preserving D2 gastrectomy,[36] suggesting that D2 resection is a safe option of radical gastrectomy in specialized centers of Western nations as well, although the final report of long-term survival is still awaited.

Historically, a more extended lymph node dissection, such as D3 or para-aortic lymph node dissection (PAND), was once practiced in the hope of improving survival in patients with advanced diseases. PAND, however, is no longer performed as a standard procedure, because the prospective randomized Japan Clinical Oncology Group (JCOG) study 9501 failed to demonstrate the survival benefit of D2 plus PAND over D2 alone.[37,38] Also, lymph node station 14v (along the superior mesenteric vein) has been excluded from D2, even for distal tumors, in the new treatment guidelines set forth by the Japanese Gastric Cancer Association (JGCA),[39] which is consistent with the findings of retrospective study from our own institution in which 14v-positive gastric cancer demonstrated poor prognosis, similar to that of metastatic disease.[40,41]

Bursectomy is a procedure dissecting the peritoneal lining covering the pancreas and the anterior leaf of the transverse mesocolon, and is commonly performed as a standard treatment with radical gastrectomy for advanced cancer in Eastern Asia.[42] According to the Japanese Gastric Cancer Treatment Guidelines,[39] bursectomy is recommended for tumors penetrating the serosa of the posterior gastric wall, in order to remove microscopic tumor deposits in the lesser sac. However, no evidence from large-scale randomized controlled trials has come forth to support that bursectomy improves survival by reducing peritoneal or local recurrence. The JCOG 1001 trial is currently ongoing to prospectively compare the clinical benefit of bursectomy in patients with clinical T3 (SS) and T4a (SE) tumor.[43]

Minimally invasive management of EGC

Endoscopic mucosal resection (EMR) is a treatment option of EGC with an extremely low possibility of lymph node metastasis, and endoscopic submucosal dissection (ESD) has also recently become another treatment option with advances in endoscopic instrumentation and techniques.[44] Considering the benefits of ESD with minimal invasiveness of the procedure, it has the potential to extend its indication. Currently, however, a long-term oncological outcome has not been established despite its extensive use. Thus, while awaiting large scale oncologic safety data, surgical resection with appropriate lymph node dissection is the standard treatment of EGC beyond conventional EMR criteria that is only limited to differentiated adenocarcinoma of less than 2 cm in diameter without ulceration and lymphovascular invasion.[39]

In recent years, minimally invasive surgery has been adopted and widely used in Korea and Japan for EGC with low risk of lymph node metastasis, since laparoscopy-assisted distal gastrectomy (LADG) with lymph node dissection was first reported in 1994 by Kitano, et al.[45] However, it still remains an investigational treatment due to the lack of solid evidence in long-term oncologic outcomes from large-scale randomized controlled trials. Even though several short-term benefits with the laparoscopic approach to gastric resection have been proposed, few have reported on the long-term QoL benefits of LADG over open distal gastrectomy (ODG). Yasuda, et al.[46] conducted a retrospective comparison study of long-term QoL after LADG over ODG for EGC, and reported that QoL benefit of LADG in the early postoperative period was lost in the long-term follow up of 99 months.

Currently, phase III multicenter trials are ongoing both in Korea (KLASS trial) and Japan (JCOG 0912) to compare the outcomes of LADG and ODG in the stage I gastric cancer, and the interim report of the KLASS trial demonstrated that LADG for early cancer is equivalent to ODG in terms of short-term outcomes, assessed by operative morbidity and mortality, but the long-term outcomes of final survival results are still awaited.[47,48]

The application of laparoscopic techniques in advanced gastric cancer (AGC) still remains controversial and needs more compelling evidence by well-designed prospective clinical trials prior to expanding its indications. The KLASS II trial has recently commenced in Korea and will provide answers on the technical feasibility and oncological safety of laparoscopic techniques in AGC, when the final results are reported.

Perioperative quality management

In the surgical management of cancer patients, QoL should

be considered in regards to minimizing unnecessary procedures carrying morbidities and facilitating postoperative recovery, if it does not violate oncologic principles. There are a couple of simple methods for improving QoL in gastric cancer patients without having to perform additional procedure or pay additional costs.

For example, the length of conventional midline incision for laparotomy can be shortened by approximately 10 cm without sacrificing a good surgical field. At our institution, a small upper midline incision above the umbilicus is made for radical gastrectomy with D2 lymphadenectomy in order to reduce surgical stress. Also, an electrosurgical device is able to replace the traditional clamp-and-tie technique in the trimming of the lesser and greater curvature of the stomach and is superior in reducing operation time and the number of intra-abdominal foreign body like suture materials in gastric cancer surgery, while remaining cost-effective.[49] In order to avoid the placement of nasogastric tubes which cause significant patient discomfort, intraoperative needle decompression of the stomach and transverse colon is a simple and safe alternative method for achieving optimal gastrointestinal decompression for a good surgical field.[50,51] Also, an intra-abdominal drain should not be routinely placed during the operation, as a prospective randomized trial from our institution showed that the prophylactic use of intra-abdominal drain does not offer any additional benefit to decrease surgical complications, including intraabdominal fluid collection or abscess, but rather increases morbidities.[52] All of these efforts improve the QoL of gastric cancer patients and have cost-effectively led to lower postoperative morbidity and shorter hospital stay.

Adjuvant chemotherapy

Although curative D2 resection is the standard treatment of operable gastric cancer, 40-60% of patients with locally advanced cancer experience recurrence after surgery.[53,54] Adjuvant chemotherapy, suspected to reduce this recurrence, had shown limited and inconsistent efficacy in previous trials. However, a recent large meta-analysis (GASTRIC group), in which 3,838 individual patients from 17 trials were evaluated, reported a small but significant benefit of adjuvant chemotherapy after curative resection of gastric cancer [hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.76-0.90; $p<0.001$].[55] The authors suggested that postoperative adjuvant chemotherapy based on fluorouracil regimens was associated with a reduced risk of death in gastric cancer, compared with surgery alone.

In Japan, adjuvant S-1 therapy has become the standard treatment of choice for patients with AGC after D2 resections based on the positive results of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC).[56] One year after enrollment and randomization of 1,059 patients, the first interim analysis showed that both overall survival and relapse-free survival were significantly higher in the S-1 group, and the trial was discontinued following the recommendation of the monitoring committee. Subsequently, the updated data of 5-year outcomes reconfirmed the survival benefit of adjuvant S-1 therapy; the overall survival rates at 5-years in the S-1 group and in the surgery-only group were 71.7% and 61.1% (HR 0.669; 95% CI 0.540-0.828), and the relapse-free survival rates in the S-1 and surgery-only group were 65.4% and 53.1% (HR 0.653; 95% CI 0.537-0.793), respectively.[57] Accordingly, new JGCA treatment guidelines[39] recommend adjuvant S-1 chemotherapy as a standard treatment for patients of stage II-III, except for T1 andT3/N0, during the first year after R0 gastrectomy with D2 lymphadenectomy.

Recently, interim analysis of international (Korea, China, and Taiwan), multicenter, randomized, phase III trials (CLASSIC) was reported as an abstract,[58] comparing capecitabine plus oxaliplatin (CapOX) adjuvant chemotherapy group with an observation group following D2 resections in a total of 1,035 patients with locally advanced cancer. After the median follow-up of 34.4 months, 3-year disease-free survival was significantly higher in the CapOX group (74% vs. 60%; HR=0.56, 95% CI 0.44-0.72; $p<0.0001$), although a difference in overall survival has not yet been observed. Grade 3 or 4 adverse events occurred in 49% of patients in the CapOX group with serious toxicity reported in 7% of them, which was consistent with well-known safety profiles of CapOX. The final overall survival results of the CLASSIC trial assessing the clinical benefits of adjuvant chemotherapy following D2 resection are still awaited, although the preplanned interim analysis met its primary endpoint of 3-year disease-free survival.

Based on the results of the two randomized trials (ACTS-GC and CLASSIC), therefore, it is strongly suggested that 5FU-derivative based chemotherapy in an adjuvant setting following D2 resections would invariably deliver the best current clinical benefits to the patients with resectable gastric cancer.

Postoperative radiochemotherapy

With the positive results of the intergroup 0116 trial (South-

west Oncology Group 9008),[30] adjuvant radiochemotherapy with limited (D0 or D1) lymphadenectomy has been frequently used in the United States. Macdonald, et al. reported promising results of the adjuvant radiochemotherapy after surgery with curative intent in patients with adenocarcinoma of the stomach or gastroesophageal junction, demonstrating the significant superiority of radiochemotherapy over surgery alone in terms of relapse free survival and overall survival.[30,31]

Nonetheless it is crucial to consider that more than 50% of patients in this trial underwent gastric resection without any lymph node dissection (D0), and the limited (D1) and extended (D2) lymphadenectomy were performed in only 36% and 10% of cases, respectively. Therefore, most resections performed were insufficient and inadequate to achieve loco-regional control which was thereafter improved by adjuvant radiotherapy. In Korea and Japan, however, prophylactic D2 lymphadenectomy achieves good loco-regional control with much lower morbidity and mortality than those of radiotherapy, and the benefit of adjuvant radiochemotherapy following D2 resection has yet to be established[59] by ongoing randomized controlled trials in Europe and Korea.

Neoadjuvant therapy

Neoadjuvant chemotherapy has been frequently used for locally advanced gastric carcinoma in the United States and Western Europe, ever since the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial (MAGIC trial) reported their first positive results. The MAGIC trial in patients with gastric and gastroesophageal junction cancer demonstrated that the perioperative chemotherapy group, compared to the surgery alone group, showed significant improvement in resectability, as well as disease-free and overall survival.[60] Likewise, a recent phase III randomized trial by the Fédération Nationale des Centres de Luttecontre le Cancer and the Fédération Francophone de Cancérologie Digestive in 28 French centers also reported positive results similar to the MAGIC trial.[61]

Despite their promising results, however, limitations prevent the application thereof as a standard treatment of gastric cancer, because both trials included high proportions of distal esophagus and gastroesophageal junction tumors, and less than 50% of the patients completed postoperative chemotherapy as initially planned, and most importantly there were no standard preoperative staging systems. Moreover, without hazard ratio analysis on the extent of surgery, the benefit of neoadjuvant chemotherapy in addition to D2 resection remains unclear.

FUTURE STRATEGY FOR GASTRIC CANCER

Sentinel lymph node navigation and individualized resection

Radical gastrectomy with D2 lymphadenectomy is now universally accepted as the standard surgical treatment of AGC in specialized high-volume centers. This does not imply, however, that extended resection is the only option for surgical management of gastric cancer regardless of stage. Individualized resection and lymphadenectomy along with accurate prediction of primary tumor status and regional lymph nodes prior to surgery are needed for the tailored management and better QoL of gastric cancer patients. Widely used in breast cancer and melanoma, sentinel lymph node (SN) biopsy could be utilized to determine the extent of lymph node dissection required in gastric cancer as well, and indeed, the efficacy of lymphatic basin dissection in EGC navigated by SN identification has been recently studied in many centers. However, as methodologies vary widely in terms of SN identification, lymph node mapping, and intraoperative diagnosis of metastatic lymph nodes,[62] the accuracy and validity of a standardized technique need to be established first prior to its clinical application in the future.

Molecular biomarkers and targeted therapy

The prognosis of patients with AGC is still dismal even with marked advances in chemotherapeutic agents over the past decades. Moreover, treatment responses and prognosis are highly variable even within the same stage. Therefore, a thorough understanding of cancer biology is essential for better management of gastric cancer in the future. Cancer is basically a disease of genetics, and underlying molecular aberrations dictate the clinical behaviors of tumors, such as therapy resistance, recurrence, and metastasis, that eventually lead to death. Therefore, elucidation of underlying biological mechanisms will help identify potential diagnostic markers and more importantly therapeutic targets. The best studied molecular targets so far in gastric cancer include epidermal growth factor receptors (EGFR) as well as vascular endothelial growth factor (VEGF) and its receptors.

EGFR overexpression has been observed in many tumors

including gastric cancer and is generally thought to correlate with increased tumor invasion, more poorly differentiated histology, and a worse prognosis.[63] Trastuzumab (Herceptin®) is a humanized monoclonal antibody that interferes with human EGFR type 2 (HER-2/neu, ErbB-2). The HER family proteins regulate cell growth, survival, adhesion, migration, and differentiation, which are amplified or weakened in cancer cells.[64]

The trastuzumab for Gastric Cancer (ToGA) trial, a pivotal randomized clinical trial of patients with HER-2 positive advanced, mostly metastatic, gastric cancer, proved the efficacy of trastuzumab in combination with chemotherapy.[65] The median overall survival was significantly prolonged in the trastuzumab-containing arm (13.8 vs. 11.1 months; HR 0.74; p=0.0046) without unexpected toxicity including cardiac events. Furthermore, the survival benefit was most pronounced in the subgroup of high HER-2/neu protein overexpression (median overall survival of 16 months). Indeed, recent success in the ToGA trial suggested that other biological pathways could be utilized to develop new therapeutic agents if we appropriately identify patients with target pathways that drive tumor behavior. The implications of the ToGA trial are tremendous in that the results provide a couple of crucial points that should be considered when planning and conducting biomarker based targeted therapy.

First of all, companion diagnostics are essential to successfully identifying subgroups of patients who will benefit from a given targeted drug. Patients with high levels of HER-2 expression upon immunohistochemistry staining showed clinical benefits with trastuzumab. Therefore, it should be noted that robust clinical molecular testing is paramount for successful targeted therapeutics development. Secondly, the target should be dominant in cancer biology, and its modulation should alter the clinical behavior of cancer. The inhibition of HER-2, which is associated with poor prognosis, with trastuzumab improved clinical outcomes, prolonging survival rates. Lastly, HER-2 and trastuzumab exemplify the type of diagnostic markers or targetable biomarkers fundamental to the cancer biological therapy. HER-2 itself is a predictive marker and simultaneously a therapeutic target; thus, simple HER-2 testing is able to generate critical information to aid clinical decision making in order to treat patients properly.

Furthermore, understanding genetic and molecular differences between Asian and Western gastric cancer would help establish refined treatment strategies. The clinical and pathological manifestations of gastric cancer between the two topographic regions are different and this distinction should be taken into account when global multicenter trials are planned. Actually, this geographical difference was confirmed in the subgroup analysis of the recently published the Avastin in Gastric Cancer (AVAGAST) trial.[66]

Bevacizumab (Avastin®) is a humanized monoclonal antibody against VEGF, which is an endothelial cell-specific mitogen and the most potent driver of angiogenesis in tumorigenesis as it increases microvascular permeability. The inhibition of VEGF by bevacizumab has had a positive impact on patient outcomes in several malignancies including colorectal, lung, and renal cell carcinoma, as well as recurrent glioblastoma.[67] In gastroesophageal cancer, VEGF is overexpressed by up to 60%, a much higher rate than HER-2/neu, and its overexpression correlates with advanced stage, higher risk of recurrence, and poor survival.[68]

AVAGAST was a multinational, randomized, double-blind, placebo-controlled phase III clinical trial which set out to evaluate the anti-angiogenic agent bevacizumab combined with chemotherapy (capecitabine plus cisplatin) as a first-line therapy in patients with unresectable far advanced gastric carcinoma.[66] Although AVAGAST did not reach its primary endpoint with no significant difference in overall survival (12.1 months in bevacizumab plus chemotherapy vs. 10.1 months in placebo plus chemotherapy; HR 0.87; p=0.1002), both progression-free survival (6.7 vs. 5.3 months; HR 0.80; p=0.0037) and overall response rate (46.0% vs. 37.4%; p= 0.0315) were improved significantly in the bevacizumab-arm. It must be noted that preplanned subgroup analysis demonstrated regional differences in the efficacy of the bevacizumab, as patients enrolled only in Pan-America demonstrated a significant survival benefit with the addition of bevacizumab (median survival 11.5 vs. 6.8 months; HR 0.63; 95% CI 0.43 to 0.94). It is not clear whether the discrepancy came from genetic differences in ethnicity or from differences in treatment patterns such as palliative resection and second-line chemotherapy. Regardless, it surely provides a direction to investigate further in future research and clinical trials.

CONCLUDING REMARKS

The overall survival of gastric cancer has gradually improved over the past few decades with advances in surgical techniques, the evolution of multimodality treatments, and ear-

lier detection of the disease. However, gastric cancer, the second most common cause of cancer-related death worldwide, still represents a global health care burden. According to the WHO Global Action Plan Against Cancer, monitoring of cancer patients is an essential part of cancer control and should be delivered as part of the continuum of primary prevention, early diagnosis, treatment, and palliative care, by the cooperative efforts of primary physicians, specialists in oncology, local communities, governments, and international bodies.

Primary prevention is the first step to decrease the incidence of gastric cancer by educating the general public on avoiding exposure to potential environmental risk factors such as salty diet, smoking, and heavy alcohol consumption, as well as by eradicating *H. pylori* infections with antimicrobials. In the regions with high incidences of the disease, including Latin America, Eastern Europe, and especially Eastern Asia, effective screening and surveillance programs should be established to include upper endoscopy or fluorography of stomach. For EGC with minimal risk of lymph node metastasis, less invasive procedures such as EMR/ESD or minimally invasive surgery can be applied if the clinical stage and histopathological features of the disease meet the conventional criteria. However, the long-term oncologic outcomes of endoscopic and laparoscopic procedures still need to be proven by prospective, randomized controlled trials. At present, radical gastrectomy with lymphadenectomy is the gold standard of gastric cancer treatment, and extended D2 lymphadenectomy is advocated in Eastern Asia for AGC (cT2-T4) and EGC with clinically positive nodes (cT1N+). On the other hand, adjuvant radiotherapy has been frequently used in North America to compensate for the suboptimal loco-regional control with limited lymphadenectomy. However, it is noteworthy that recently revised National Comprehensive Cancer Network® Guidelines also recommend D2 dissection for gastric cancer if the procedure is performed by experienced surgeons in high volume centers.

Recent trials of multiple agent chemotherapy regimens have shown positive results in improving overall and progression-free survival. Nevertheless, prognosis of advanced stage disease is still poor and responses to conventional chemotherapeutics are heterogeneous even within the same pathologic stage. In order to overcome the limitations of currently available treatments and deliver tailored therapy to individual patients, molecular strategies are pivotal, as suggested in the recent trials of trastuzumab and bevacizumab in AGC, and further investigation of molecular biomarkers specific to gastric cancer is warranted for use not only as prognostic indicators but also as therapeutic targets.

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