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Evolution of Gastric Cancer Treatment: From the Golden Age of Surgery to an Era of Precision Medicine

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Gastric cancer imposes a global health burden. Although multimodal therapies have proven to benefit patients with advanced diseases after curative surgery, the prognosis of most advanced cancer patients still needs to be improved. Surgical extirpation is the mainstay of gastric cancer treatment. Indeed, without curative surgery, variations and combinations of chemotherapy and/or radiation cannot bring clinically meaningful success. Centered around D2 surgery, adjuvant and peri-operative multimodal therapies have improved survival in a certain group of gastric cancer patients. Moving toward a personalized cancer therapy era, molecular targeted strategies have been tested in clinical trials for gastric cancer. With some success and failures, we have learned valuable lessons regarding the biology of gastric cancer and the clinical relevance of biological therapies in addition to conventional treatments. Future treatment of gastric cancer will be shifted to molecularly tailored and genome information-based personalized therapy. Collaboration across disciplines and actively adopting emerging anti-cancer strategies, along with in-depth understanding of molecular and genetic underpinnings of tumor development and progression, are imperative to realizing personalized therapy for gastric cancer. Although many challenges remain to be overcome, we envision that the era of precision cancer medicine for gastric cancer has already arrived and anticipate that current knowledge and discoveries will be transformed into near-future clinical practice for managing gastric cancer patients.

Key Words: Gastric cancer, precision medicine, treatment

INTRODUCTION

Although the overall incidence of gastric cancer has been decreasing, it is still one of the most common malignances and the leading cause of cancer-related death worldwide: there were almost 1000000 new cases and over 720000 deaths in 2012.[1] Geographically, nearly two-thirds of cases are concentrated in Eastern Asia, especially, Korea, Japan, and China. Over the last couple of decades, efforts to improve the clinical outcomes of gastric cancer, including early detection, based on nationwide mass screening program,[2,3] and to develop strategies, such as radical surgery, chemotherapy, and radiotherapy, against gastric cancer have led to improved prognosis of the disease.[4] However, as populations continue to age, it is expected that the incidence of gastric cancer will rise and that the global burden related to gastric cancer will steadily increase.[5] In addition, unlike early gastric cancer (EGC), which harbors a favorable prognosis, advanced gastric cancer (AGC) is still challenging; over 50% of patients with AGC experience cancer recurrence in their life-time.[6,7] There are numerous unsolved issues yet to be adequately addressed, and recent progress in molecular biology research with cutting-edge biotechnology, such as next generation sequencing, is expected to guide personalized therapy and precision medicine in the field of gastric cancer.

This review focuses on changes in treatment strategies for gastric cancer and recent efforts towards precision medicine, which is one of the most fascinating key words throughout the medical field. We hope that this review can provide insights on

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the future direction of gastric cancer treatment and translational research.

SURGICAL TREATMENT OF GASTRIC CANCER: THE GOLDEN AGE OF SURGERY

Radical surgery, a complete surgical resection of macro/microscopic tumors (R0 resection), is the gold standard for the treatment of most solid tumors. In gastric cancer, gastrectomy with adequate resection margin and systematic lymphadenectomy is considered to be the only curative treatment. Before 2000, as several clinical trials failed to show the benefit of additional chemotherapy after surgery,[8-11] gastric cancer was considered as refractory to chemotherapy. Therefore, surgery alone was accepted internationally as standard treatment for resectable gastric cancer.[12] Thus, the main strategy against gastric cancer has been surgical treatment for a long time.

Debate for the extent for lymphadenectomy: what is the adequate range of lymphadenectomy for gastric cancer?

In Japan, where gastric cancer is endemic, the Japanese Research Society for Gastric Cancer (former Japanese Gastric Cancer Association) defined and recommended D2 lymphadenectomy for gastric cancer in reference to long-term experience with gastric cancer surgery. Based on a large case review, they mapped the location of metastatic lymph nodes according to the primary tumor site, and classified metastatic lymph nodes into three groups.[13,14] Briefly, group 1 indicates perigastric lymph nodes; group 2 includes lymph nodes around major vessels in the vicinity of the pancreas and splenic hilum; and group 3 indicates lymph nodes beyond group 2. D1 lymphadenectomy represents the resection of lymph nodes in group 1, and D2 lymphadenectomy refers to the dissection of all lymph nodes in group 2, including group 1. This guideline[15] has recommended D2 lymphadenectomy for AGC, and a randomized controlled trial (RCT) from Taiwan proved the benefit of D2 over D1 lymphadenectomy [5-yr overall survival (OS) was 59.5% in D2 and 53.6% in D1, p=0.041] in gastric cancer.[16] With belief that a greater extent of surgery can improve the prognosis of gastric cancer (and maybe because there was no additional option for further improving survival of GC at that time), D3 lymphadenectomy (D2+para-aortic lymph node dissection) was widely applied in Japan and Korea. However, a RCT, which compared the outcomes of D2 vs. D3, showed that D3 surgery was related to a tendency toward increased operative complications (20.9% in D2 vs. 28.1% in D3, p=0.07) with no improvement in the prognosis of gastric cancer [5-yr OS was 69.2% in D2 and 70.3% in D3; hazard ratio (HR) of D3 compared to D2 was 1.03, p=0.85].[17,18] Thus, the extent of lymphadenectomy for gastric cancer was decided at a level of D2, and it has remained standard surgical procedure in East Asia.[19]

On the other hand, in the West, limited lymphadenectomy had been considered as standard surgery because two RCTs, MRC trial and Dutch Gastric Cancer trial, failed to show the survival benefits of D2 over D1 lymphadenectomy.[20,21] Even worse, D2 surgery was related to un-acceptably high mortality (10–13%) and morbidity (43–46%) in these trials.[22,23] Consequently, compared to outcomes from East, which reported a mortality of less than 1% after D2 surgery,[17,24] mortality over 10% would be difficult to accept in practice. However, 15-year follow-up results of Dutch Gastric Cancer trial showed that despite no benefit to OS for D2 surgery, loco-regional recurrence (41% in D1 vs. 25% in D2) and lower gastric-cancer-related death (48% in D1 vs. 37% in D2) were lower for D2 surgery than D1 surgery.[25] Moreover, there have been reports[26,27] that D2 surgery can be performed safely (mortality rate was 1.7% to 3.6%) if it is conducted by experienced-hands in high-volume centers, even in the West. Consequently, now D2 surgery for gastric cancer is recommended in both East and West guidelines with a precondition of being performed at specialized, high-volume centers where it can be performed safely.[15,28,29]

Evolution of total gastrectomy: pancreas and spleen preserving gastrectomy

Historically, pancreatico-splenectomy was standard surgery for total gastrectomy when cancer is located in the proximal stomach. This was because the extent of D2 lymphadenectomy for total gastrectomy includes lymph nodes around the supra-pancreatic and splenic hilar area; thus, for removing these lymph nodes completely, distal pancreatectomy with splenectomy was thought to be mandatory.[30] However, a substantial number of intraperitoneal abscess and pancreatic fistula occurred as unpleasant operative sequels after distal pancreatectomy accompanying total gastrectomy. Maruyama, et al.[31] reported the necessity of pancreas-preserving (PP) total gastrectomy with results showing that pancreas preserving total gastrectomy was superior to pancreas resection (PR) in terms of morbidity (39.4% in PR vs. 19.6% in PP), mortality (0.9% in PR vs. 0.3% in PP), 5-yr OS (54.5% in PR vs. 70.5% in PP for stage II, and 36.7% in PR vs. 54.1% in PP for stage II), and newly developed diabetes mellitus (37% in PR vs. 0% in PP). Following results from a RCT supported the advantages of total gastrectomy with PP: distal pancreatectomy with splenectomy for gastric cancer was related to high morbidity and poor prognosis.[22] Thus, pancreas preserving total gastrectomy became a standard procedure for advanced proximal gastric cancer.

The next question was whether spleen should be removed as part of lymphadenectomy in total gastrectomy for proximal gastric cancer. Noh, et al. presented the technical feasibility of total gastrectomy with spleen preserving hilar lymph node dissection at the Second International Gastric Cancer Congress.[32] His data showed that splenectomy during total gastrectomy is related to increased morbidity, while providing no survival gain.[33,34] Following studies supported the results: a study from

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U.S. reported that splenectomy is related to high operative morbidity and mortality after total gastrectomy;[35] a RCT from Korea reported that prophylactic splenectomy to remove lymph nodes around spleen hilum for proximal gastric cancer is not recommended because it offers no prognostic advantages.[36] The incidence of lymph node metastasis at the spleen hilum reportedly ranges from 9.8% to 15.4%,[37-39] and prophylactic splenectomy may not be mandatory, except when the primary tumor directly invades the spleen or definite gross lymph node metastases is present at the spleen hilum. Nevertheless, organ preserving surgery should not mean that necessary lymph node dissection can be omitted during radical surgery. Spleen preserving total gastrectomy should represent total gastrectomy with D2 lymphadenectomy, including splenic hilar lymph node dissection, while preserving the spleen. We anticipate that an ongoing RCT, the Japan Clinical Oncology Group (JCOG) 0110-MF trial, will provide more concrete evidence for the oncologic feasibility of spleen preserving gastrectomy.[40]

Increasing proportion of early gastric cancer: the propagation of minimally invasive surgery

Minimally invasive surgery (MIS) including laparoscopic and robotic surgery is now considered a standard operation in most of surgical fields not only for benign surgery but also for cancer surgery. In the field of gastric cancer surgery, Kitano, et al.[41] reported the first laparoscopic distal gastrectomy for gastric cancer, and this procedure has been widely propagated for gastric cancer surgery. In the beginning of laparoscopic surgery for gastric cancer, conservative surgeons criticized that it would be impossible to perform adequate lymphadenectomy through laparoscopic devices, so its indication was limited to very early stage gastric cancer, in which the extent of lymphadenectomy is more limited, compared to AGC. However, cumulative experience with better laparoscopic surgical devices has shortened the gap in surgical quality between conventional open surgery and laparoscopic surgery. And its potential advantages [cosmetic benefit due to smaller incision size, better quality of life (QOL), and less pain with shorter hospital stay] and increasing incidence of EGC through nationwide mass screening in Korea and Japan has bolstered the popularity of laparoscopic surgery for gastric cancer. At present, even though RCTs[42,43] into the oncologic outcomes of laparoscopic surgery for EGC compared to open surgery have not been published yet (KLASS and JCOG0912 trial), laparoscopic gastrectomy is considered as a possible option for clinical EGC, based on the long term result of a large-scale Korean multicenter study.[44] However, the question about whether laparoscopic surgery can be applied for AGC requiring D2 surgery remains unanswered. Although reports[45,46] have demonstrated the possibility of laparoscopic surgery, even for AGC (similar short and long term outcomes compared to open surgery), concerns about its potential risks and whether similar quality of surgery can be achieved by laparoscopic gastrectomy compared to that of open surgery or not (because D2 surgery for AGC is still difficult to perform even through an open technique) are still under debate. In an effort to diminish those concerns and to expand the indication of laparoscopic surgery from EGC to AGC, a multicenter RCT (KLASS II, NCT01456598) is ongoing.

Robotic surgery systems were introduced into the field of gastric cancer surgery in 2005 and have propagated, especially in Korea, because of their potential advantages over laparoscopic surgery: robot systems provide a better three-dimensional view and facilitate fine movements with tremor filtering and articular movement.[47,48] Most robotic surgeries have been performed by experienced laparoscopic surgeons, and it was expected that robotic surgery systems would help overcome technical difficulties in laparoscopic surgery.[49] A meta-analysis,[50] which compared the short-term outcomes of robotic surgery to laparoscopic and open surgery for gastric cancer, showed that morbidity and mortality were similar and that robotic surgery offers practical advantages of less blood loss and hospital stay, compared to open surgery, although operative time was longer than other modalities. Even though its high cost was criticized, some surgeons have suggested that robotic surgery would have advantages over laparoscopic surgery in technically difficult and complicated cases (e.g., far advanced cancer in which combined resection should be performed for R0 resection). Now, its indication in gastric cancer surgery are similar to those of laparoscopic surgery,[50,51] although concerns remain high for whether this expensive approach can be justified over equivalent but cheaper laparoscopic surgery.

Efforts to decrease the extent of surgery: more minimum to minimum

As the proportion of EGCs has increased and its prognosis is quite good,[52] enough to be considered as cured in most cases after surgery, physicians have now began to focus on improving QOL of patients with EGC. Consequently, questions of whether prophylactic lymphadenectomy for EGC is mandatory have been raised. If there are no metastatic lymph nodes around the stomach in EGC, surgeons may be able to spare the lymph nodes from surgery and resect only the primary tumor.

A greater extent of lymphadenectomy leads to more surgical morbidity and mortality,[22,23] and gastrectomy itself can decrease QOL of patients. If metastatic lymph nodes could be identified before or during an operation, surgeons could spare lymph nodes that are noncancerous. Thereby, segmental gastrectomy with a safe margin would be possible and would improve QOL of patients without compromising prognosis. Sentinel lymph node biopsy has been widely applied in surgery for breast cancer and melanoma. There have also been attempts to adapt sentinel lymph node biopsy for gastric cancer surgery. Even though the JCOG0302 trial was terminated in the midst of enrollment because of its unexpectedly high false negative rate,[53] another phase II trial from Japan showed the practical possibility of sentinel lymph node mapping for gastric cancer.[54]

Based on the lessons learned from both Japanese trials, a new phase III clinical trial (SENORITA trial, NCT01804998) of using both Tc 99m and indocyanine green injection around tumors through intra-operative endoscopy was initiated in Korea after a quality control study (NCT01544413).[55] The result of this trial will guide the possibility of tailored and limited surgery for EGC.

In Japan, endoscopic mucosal resection (EMR) has been accepted for treating EGC with a very low probability of lymph node metastasis and adopted into practice.[56] Gotoda, et al.[57] reviewed a large cohort (over 5000 cases) of EGC patients who underwent gastrectomy and found that some subgroups show a low incidence of lymph node metastasis. Accordingly, the authors proposed expansion of criteria for local treatment. Development of endoscopic devices has made endoscopic submucosal dissection (ESD) possible, and this new procedure has shown better outcomes in en-block resection with a complete resection rate, although with more complications of bleeding and perforation.[58] Nowadays, EMR and ESD have become viable treatment options for EGC within their indications and widely adopted across Japan and Korea. Its oncologic outcomes, however, compared to surgical resection with lymphadenectomy, have yet to reach consensus.[59]

ADDITIONAL STRATEGIES FOR AGC: THE AGE OF CHEMOTHERAPY AND RADIOTHERAPY

Unlike the favorable prognosis of EGC, many patients with AGC experience tumor recurrence during their lifetime, even after radical surgery.[6,7,18] Thus, additional strategies are required to improve the survival of patients with AGC. However, numerous trials have failed to show an added benefit for chemotherapy[8-11] to surgery.

Different strategies against advanced gastric cancer for different continents

Macdonald, et al.[60] applied combined two strategies, chemotherapy and radiation therapy (fluorouracil and leucovorin with total 4500 cGy of radiation), after surgical resection of gastric cancer for AGC and compared the outcomes thereof with those of surgery alone. A total of 556 patients with resectable gastric cancer or gastro-esophageal junction cancer were enrolled in this RCT [intergroup 0116 (INT-0116) trial], and the results were promising: improved median survival (27 months for surgery alone vs. 36 months for additional chemoradiotherapy group), OS (HR of surgery alone was 1.35, 1.09 to 1.66, p=0.005), and relapse-free survival (HR of surgery alone was 1.52, 1.23 to 1.86, p<0.001) with acceptable incidence of toxic effect from chemoradiotherapy. However, only 10 % of the patients underwent D2 surgery, and 54% of patients received less than D1 surgery, igniting a fierce debate over the clinical utility of the treatment when D2 surgery is completed. Regardless, based on the results, post-operative chemoradiotherapy has become standard treatment for resectable gastric cancer in the United States.

Another RCT from the United Kingdom, the Medical Research Council Adjuvant Gastric Infusional Chemotherapy trial (MAGIC), enrolled 503 patients with resectable stomach cancer, gastroesophageal junction cancer, and lower esophageal adenocarcinoma and compared the outcomes of peri-operative chemotherapy (epirubicin, cisplatin, and infused fluorouracil) in conjunction with surgery with those of surgery alone.[61] The results showed the benefit of peri-operative chemotherapy over surgery alone: better OS (HR of chemotherapy group was 0.75, 0.60 to 0.93, p=0.009) and progression-free survival (HR of chemotherapy group was 0.66, 0.53 to 0.81, p<0.001) with similar postoperative complications (46% in chemotherapy group vs. 45% in surgery alone). However, only 67.8% of patients received curative intent surgery, 24.1% received gastrectomy including esophagectomy and 41.4% of patients underwent D2 surgery. Again, similar debates as with the INT-0116[60] were raised regarding the clinical utility thereof after D2 surgery. Based on the results, however, peri-operative chemotherapy has been applied a standard strategy for AGC in Europe.

Although these two RCTs showed the benefits of additional post-operative chemoradiotherapy and peri-operative chemotherapy for AGC over surgery alone, the 5-year OS thereof was much lower than that of surgery alone in East Asia.[18] Thus, a question of whether chemotherapy provides additional benefits even after radical surgery (D2 surgery) or not was raised in East Asia, where radical D2 surgery is a standard surgery for AGC. To answer to this question, two landmark phase III RCTs were conducted to compare the outcomes of chemotherapy as adjuvant treatment after radical surgery to those of surgery alone. The first study to demonstrate the benefits of adjuvant chemotherapy after D2 surgery for AGC was the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) in Japan.[62,63] A total of 1059 patients with stage II and III disease were enrolled in over 100 centers after D2 surgery in this trial. The results showed that the prognosis of S-1 monotherapy after D2 surgery was better than that of D2 surgery alone regarding 5-year OS (71.7% in S-1 group vs. 61.1% in surgery only, HR of S-1 group was 0.669, 0.540 to 0.828) and 5-year RFS (65.4% in S-1 group vs. 53.1% in surgery only, HR of S-1 group was 0.653, 0.537 to 0.793) with acceptable toxicity (less than 6% of over grade 3 toxicity).

Thereafter, the CLASSIC trial (Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer), which was conducted at 37 centers throughout Korea, China, and Taiwan, further supported the benefits of adjuvant chemotherapy after D2 surgery.[6,64] In this study, 1035 patients with stage II and III gastric cancer who underwent D2 surgery were enrolled, and capecitabine and oxaliplatin (XELOX) were applied as an adjuvant con-

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cept to the XELOX group. The results revealed that adjuvant XELOX improved the prognosis of the patients: estimated 5-year OS was 78% in the XELOX group versus 69% in the surgery alone (HR of XELOX group was 0.66, 0.51 to 0.85, p=0.0015) and estimated 5-year DFS was 68% in the XELOX group versus 53% in surgery alone (HR of XELOX group was 0.58, 0.47 to 0.72, p<0.001). In addition, the results of a meta-analysis conducted by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group supported the benefits of adjuvant chemotherapy (pooled HR of chemotherapy for OS was 0.82, 0.76 to 0.90, p<0.01 and that of DFS was 0.82, 0.75 to 0.90, p<0.01).[65] Taken all together, all doubts of whether adjuvant chemotherapy after D2 lymphadenectomy is needed or not were resolved,[66] and adjuvant chemotherapy has become a standard treatment for resectable AGC in East Asia.

The role of radiotherapy in gastric cancer: is it still effective after radical D2 surgery?

The results of the INT- 0116 trial, which showed the benefits of chemoradiotherapy, suggested the potential benefits of radiation therapy in gastric cancer, and additional results showed that adjuvant chemotherapy improves the survival of AGC patients. The next question facing clinicians is whether radiation could save more patients if added to D2 surgery with adjuvant chemotherapy. To address this, the ARTIST trial (Adjuvant Chemoradiation Therapy in Stomach Cancer) was conducted in Korea.[67,68] This RCT assigned 458 patients who underwent D2 surgery into two groups: XP group (treated by six cycles of capecitabine and cisplatin) and XPRT group (treated by two cycles of XP, followed by chemoradiation therapy with capecitabine, and then two additional cycles of XP). After 7 years of follow up, the results revealed no significant benefits of additional radiation therapy (HR of XPRT for OS was 1.130, 0.775 to 1.647, p=0.5272, and HR of XPRT for DFS was 0.740, 0.520 to 1.050, p=0.0922). It is has been argued that radiation therapy is a loco-regional treatment rather than systematic treatment, and D2 surgery would be enough for loco-regional control of gastric cancer. Therefore, the addition of radiation therapy to D2 surgery would have no further benefit. Interestingly, subgroup analyses showed a possible benefit of XPRT over XP regarding DFS in lymph node positive and intestinal-type gastric cancer. The ARTIST-II successor trial is currently evaluating the benefits of adjuvant XPRT in patients with lymph node metastasis after D2 surgery.

Target therapy for gastric cancer: its successes and failures

One of the problems of traditional chemotherapy is that it acts against all actively proliferating cells, normal and cancerous, causing serious collateral damage. Thus, treatments against targets specific to cancer cells could spare normal cells. Although understanding of the molecular genetic underpinnings of gastric cancer has lagged behind that for other solid cancers, recent efforts to better understand gastric cancer biology has led to the discovery of a handful of genetic alterations specific to cancer cells: overexpressed proteins are present in cancer cells but not in normal cells, and specific mutant proteins drive cancer growth and survival.

The precedent success of target therapy by trastuzumab, a humanized monoclonal antibody interferes human epidermal growth factor receptor type 2 (HER2/neu/ErbB2), for HER2 positive breast cancer encouraged the expanding of its indications to gastric cancer. The Trastuzumab for Gastric Cancer (ToGA) trial, a RCT of patients with HER2 positive mostly metastatic gastric/gastro-esophageal cancer, was conducted in 122 centers in 24 countries.[7] A total of 549 patients were randomly assigned into two groups: trastuzumab with chemotherapy and chemotherapy alone. The results showed that trastuzumab improves the prognosis of HER2 positive gastric cancer; the median OS of trastuzumab with chemotherapy was 13.8 months versus 11.1 months in chemotherapy alone (HR of trastuzumab with chemotherapy was 0.74, 0.60 to 0.91, p=0.0046). The success of the ToGA trial suggested that cancer biology-driven target therapies could be possible in gastric cancer and encouraged investigations into additional candidate targets for AGC.

The next target evaluated was vascular endothelial growth factor (VEGF), which is known to be related to angiogenesis in tumorigenesis. Treatment with bevacizumab, a humanized monoclonal antibody that inhibits VEGF, exhibited a positive impact among patients with several types of cancers, such as colorectum,[69] lung,[70] and recurrent glioblastoma.[71] Also, a phase II trial to evaluate the safety and efficacy of bevacizumab with conventional chemotherapy (doxetaxel, cisplatin, and fluorouracil) for advanced gastro-esophageal cancer seems to have been successful.[72] Expecting continued success, the Avastin in Gastric Cancer (AVAGAST) trial for evaluating the efficacy of additional bevacizumab to chemotherapy (capecitabine and cisplatin) as the first-line treatment for unresectable AGC was conducted.[73] This double blind, placebo-controlled phase III RCT enrolled 774 patients. The primary endpoint of improving OS, however, was not satisfied (median OS was 12.1 months in adding bevacizumab group vs. 10.1 months in placebo plus chemotherapy group; HR of adding bevacizumab was 0.87, 0.73 to 1.03, p=0.1002), although progression free survival and overall response rates were significantly better for adding bevacizumab over the placebo group. A subsequent biomarker evaluation study, which analyzed blood and tumor tissue samples collected for the AVAGAST trial reported that VEGF-A and tumor neurophilin-1 (NRP1) could be potential predictive biomarkers for bevacizumab efficacy.[74] The most recently reported REGARD study, an international Phase III RCT for assessing the clinical benefit of VEGF receptor 2 (VEGFR-2) inhibition in gastric and gastroesophageal cancer, showed promising results for angiogenesis blockade therapy in gastric

cancer.[75] The study showed that patients assigned to treatment with ramucirumab, a fully humanized IgG1 monoclonal antibody inhibitor of VEGFR-2, had significantly improved survival (HR 0.776, 95% CI 0.603–0.998, p=0.047), with a median survival of 5.2 months versus 3.8 months with placebo. Still, there are many questions regarding the results for the AVAGAST and REGARD trials. In AVAGAST trial, it seemed that Asian patients were less benefited from bevacizumab compared to patients in the rest of the world, and in biomarker study of the trial showed that those biomarkers, VEGF-A and NRP1 were not effective to predict responsiveness of bevacizumab. In REGARD trial, however, the proportion of Asian patients enrolled was only around 8%. This is largelry due to the practical reason: 2nd line chemotherapy is considered standard of care in Asia. Togetehr, the resutls of the two pivotal trials on anti-angiogenesis treatment for gastric cancer imply that understanding of heterogeneity in gastric cancer across the globe[76] including ethnicity could impact the biologically targeted therapies for this disease. Regardless, the data impose a significant clinical insight of targeted biological options in selected patients' subpopulations with corresponding target presence.

NECESSITY OF PERSONALIZED THERAPY IN GASTRIC CANCER TREATMENT: THE PROLOGUE OF PRECISION MEDICINE FOR GASTRIC CANCER

Despite the successes of some clinical trials, which showed the benefits of chemotherapy, the effect size of benefit was just around 10–20%,[6,18,62-65] and this number is somewhat disappointing. This implies that current standard chemotherapy is effective in only a small subgroup of patients, which might be explained by the heterogeneity of the disease. If we can predict who will and will not respond to chemotherapy, physicians can treat patients more effectively and spare some from unnecessary chemotherapy. Indeed, practicing this on a routine basis is the ultimate goal of personalized and precision cancer medicine. Precision medicine is defined by the National Academy of Sciences as "the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment".[77] This concept is not new, as Hippocrates, who is the father of modern medicine said, "It's far more important to know what person the disease has than what disease the person has."

In tradition, anatomic site and histology based classifications, such as the Lauren[78] and World Health Organization[79] classifications, have been widely used to classify gastric cancer. However, these systems are not good enough to classify prognosis and/or predicting chemo-responsiveness. Another potential candidate marker for predicting prognosis and chemo-responsiveness in gastric cancer is microsatellite instability (MSI). The loss of function of mismatch repair (MMR) genes can cause cancer, and colon cancer with MSI is known to be related to good prognosis after surgery alone and be refractory to fluorouracil-based chemotherapy.[80,81] In gastric cancer, it was reported that the characteristics of gastric cancer with MSI are similar to those of colon cancer;[82-84] however, these results need to be validated across distinct populations.

There has been numerous efforts to classify gastric cancer based on molecular characteristics over anatomical classification. Among others that have tried to define subgroups of gastric cancer,[85-87] Tan, et al.[88] described the possibility that gastric cancer could be divided into intrinsic subtypes (genomic intestinal and genomic diffuse) according to gene expression profiles and that the subtypes might be of use in predicting prognosis and customized therapy. Recently, The Cancer Genome Atlas Research Network reported the results of molecular classification of gastric cancer through integrative genomic analyses, which suggested that gastric cancer could be divided into four subtypes: 1) Epstein-Barr virus-related tumors that exhibit recurrent *PIK3CA* mutation, hypermethylation of DNA, and overexpression of PD-L1/2; 2) MSI represented by elevated mutation rates and MLH1 silencing, which is one of the main MMR genes; 3) genomically stable tumors that are strongly related with diffuse histology, *RHOA* mutations, and CLDN18-ARHGAP fusion; and 4) chromosomal instability that mainly comprise intestinal histology, *TP53* mutation, and focal amplification of receptor tyrosine kinases.[89] Further, another study reported that gastric cancer can be classified into four molecular subtypes as follows: microsatellite unstable, microsatellite stable (MSS) with/without *TP53* mutation, and MSS with epithelial-to-mesenchymal transition (EMT) type. They found that the MSS/EMT type of gastric cancer was related to poor prognosis, early-aged onset, and the highest risk of cancer recurrence.[90] These results imply that gastric cancer can be classified according to its molecular characteristics and that these classifications can indicate which types of gastric cancer will be responsive to standard treatment and which types will be refractory, potentially guiding tailored options for individual patients.

FUTURE PERSPECTIVES

Despite extraordinary efforts to improve the prognosis of gastric cancer over the last couple of decades, we still have a long way. Recent advancements in cancer biology and biotechnology, including technology of sequencing and its interpretation, have set in motion the realization of personalized and precision medicine into clinical practice.[91] In the United States, a precision medicine initiative has been announced and will be supported by more than 215 million USD. The initiative is expected to accelerate efforts to realize precision medicine, such that the genetic make-up of tumors, individual patient variations, and environmental factors can be taken into account in

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clinical care decision making processes. To realize precision medicine in gastric cancer, comprehensive characterization of molecular mechanisms and identification of driver genetic alterations for individual patients are imperative. Although these once seemed formidable challenges, we are now closer to the future of biomarker-based stratification of gastric cancer patients and application of targeted therapeutics more than ever.

Finally, immunotherapy, the next generation of anti-cancer strategies (after surgery, chemotherapy, and radiation therapy), targeting immune checkpoints of cancer, has been actively evaluated in clinical trials and applied in clinical practice for selected cancer types.[92,93] With all the old and new armamentaria, we need to continuously integrate and adopt state-of-the-art strategies across all disciplines to fight against gastric cancer. Precision medicine is at our fingertips, and we are on the verge of conquering gastric cancer.

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