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

Yoon Young Choi¹, Sung Hoon Noh¹², and Jae-Ho Cheong¹²³

¹Department of Surgery, Yonsei University College of Medicine, Seoul; ²Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul; ³Department of Biochemistry & Molecular Biology, Yonsei University College of Medicine, Seoul, Korea.

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,²³ 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.⁶⁷ 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
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. 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 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. 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, \( p = 0.85 \)]. 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.

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. Even worse, D2 surgery was related to unacceptably high mortality (10–13%) and morbidity (43–46%) in these trials. Consequently, compared to outcomes from East, which reported a mortality of less than 1% after D2 surgery, 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. Moreover, there have been reports 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.

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. However, a substantial number of intraperitoneal abscess and pancreatic fistula occurred as unpleasant operative sequel after distal pancreatectomy accompanying total gastrectomy. Maruyama, et al. 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. 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. His data showed that splenectomy during total gastrectomy is related to increased morbidity, while providing no survival gain. Following studies supported the results: a study from...
U.S. reported that splenectomy is related to high operative morbidity and mortality after total gastrectomy; 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 RCTs42,43 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 reports45,46 have demonstrated the possibility of laparoscopic gastrectomy, 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,51,52 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,53 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,54 another phase II trial from Japan showed the practical possibility of sentinel lymph node mapping for gastric cancer.55
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). 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. Gotoda, et al. 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. 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.

### 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. 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 to surgery.

**Different strategies against advanced gastric cancer for different continents**

Macdonald, et al. 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 perioperative chemotherapy (epirubicin, cisplatin, and infused fluorouracil) in conjunction with surgery with those of surgery alone. 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 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. 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. 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. 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-
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, \( p < 0.01 \)). Taken all together, all doubts of whether adjuvant chemotherapy after D2 lymphadenectomy is needed or not were resolved, 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. 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. 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, lung, and recurrent glioblastoma. Also, a phase II trial to evaluate the safety and efficacy of bevacizumab with conventional chemotherapy (doxorubicin, cisplatin, and fluorouracil) for advanced gastro-esophageal cancer seems to have been successful. Expecting continued success, the Avasatin 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. 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. 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.
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 largely due to the practical reason: 2nd line chemotherapy is considered standard of care in Asia. Together, the results of the two pivotal trials on anti-angiogenesis treatment for gastric cancer imply that understanding of heterogeneity in gastric cancer across the globe 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’ sub-populations 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%,6,16,62–65 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.” 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 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.60,61 In gastric cancer, it was reported that the characteristics of gastric cancer with MSI are similar to those of colon cancer;62–64 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,65–67 Tan, et al.68 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 to 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.69 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.70 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.71 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
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. 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.

ACKNOWLEDGEMENTS

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI3C2162), and the National R&D Program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (1020390, 1320360).

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136: E359-86.
2. Lee KS, Oh DK, Han MA, Lee HY, Jun JK, Choi KS, et al. Gastric cancer screening in Korea: report on the national cancer screening program in 2008. Cancer Res Treat 2011;43:83-8.
3. Hamashima C, Shibuya D, Yamazaki H, Inoue K, Fukao A, Saito H, et al. The Japanese guidelines for gastric cancer screening. Jpn J Clin Oncol 2008;38:259-67.
4. Jung KW, Won YJ, Kong HJ, Oh CM, Cho H, Lee DH, et al. Cancer statistics in Korea: incidence, mortality, survival, and prevalence in 2012. Cancer Res Treat 2015;47:127-41.
5. Jung KW, Won YJ, Oh CM, Kong HJ, Cho H, Lee DH, et al. Prediction of cancer incidence and mortality in Korea, 2015. Cancer Res Treat 2015;47:142-8.
6. Noh SH, Park SR, Yang HK, Chung HC, Chung IJ, Kim SW, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1389-96.
7. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet 2010;376:687-97.
8. Nakajima T, Nashimoto A, Kitamura M, Kito T, Iwana T, Okabayashi K, et al. Adjuvant mitomycin and fluorouracil followed by oral uracil plus tegafur in serosa-negative gastric cancer: a randomised trial. Gastric Cancer Surg Study Group. Lancet 1999;354:273-7.
9. Macdonald JS, Fleming TR, Peterson RF, Berenberg JL, McClure S, Chapman RA, et al. Adjuvant chemotherapy with 5-FU, Adriamycin, and mitomycin-C (FAM) versus surgery alone for patients with locally advanced gastric adenocarcinoma: A Southwest Oncology Group study. Ann Surg Oncol 1995;2:488-94.
10. Engstrom PF, Lavin PT, Douglass HO Jr, Brunner KW. Postoperative adjuvant 5-fluorouracil plus methyl-CCNU therapy for gastric cancer patients. Eastern Cooperative Oncology Group study (EST 3275). Cancer 1985;55:1688-73.
11. Krook JE, O’Connell MJ, Wieand HS, Beart RW Jr, Leigh JE, Kugler JW, et al. A prospective, randomized evaluation of intensive-course 5-fluorouracil plus doxorubicin as surgical adjuvant chemotherapy for resected gastric cancer. Cancer 1991;67:2454-8.
12. Cunningham D, Chua YJ. East meets west in the treatment of gastric cancer. N Engl J Med 2007;357:1863-5.
13. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma - 2nd English Edition -. Gastric Cancer 1998;1:10-24.
14. Cancer JRSIG: Japanese classification of gastric carcinoma. 1st ed (English), Tokyo: Kanehara; 1995.
15. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113-23.
16. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF; et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. Lancet Oncol 2006;7:309-15.
17. Sano T, SASAKO M, Yamamoto S, Nashimoto A, KURITA A, HIRATSUKA M, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy--Japan Clinical Oncology Group study 9501. J Clin Oncol 2004;22:2767-73.
18. SASAKO M, SANO T, YAMAMOTO S, KUROKAWA Y, NASHIMOTO A, KURITA A, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med 2008;359:453-62.
19. Hyung WJ, Kim SS, Choi WH, Cheong JH, Choi SH, Kim CB, et al. Changes in treatment outcomes of gastric cancer surgery over 45 years at a single institution. Yonsei Med J 2008;49:409-15.
20. Bonenkamp JJ, Hermans J, SASAKO M, van de Velde CJ, VELWAART K, Songun I, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med 1999;340:908-14.
21. Cuschieri A, Weeden S, Fielding I, BANCEWICZ J, CRAVEN J, JOYPAUL V, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer 1999;79:1522-30.
22. Cuschieri A, Fayers P, Fielding I, CRAVEN J, BANCEWICZ J, JOYPAUL V, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet 1996;347:995-9.
23. Bonenkamp JJ, Songun I, Hermans J, SASAKO M, VELWAART K, PUKKER JT, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet 1995;345:745-8.
24. Kim KM, AN JY, Kim HI, Cheong JH, Hyung WJ, Noh SH. Major early complications following open, laparoscopic and robotic gastrectomy. Br J Surg 2012;99:1681-7.
25. Songun I, Putter H, KRAENENBURG EM, SASAKO M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol 2010;11:439-49.
26. Martin RC 2nd, JAQUES DP, BRENNAN ME, KARPEH M. Extended local resection for advanced gastric cancer: increased survival versus increased morbidity. Ann Surg 2002;236:159-65.
27. Mansfield PF. Lymphadenectomy for gastric cancer. J Clin Oncol
distal gastrectomy with nodal dissection for clinical stage IA/IB.

Nakamura K, Katai H, Mizusawa J, Yoshikawa T, Ando M, Terashi T. Prospective, randomized Trial (KLASS Trial). Ann Surg 2010;252:653-60.

Kim HH, Hyung WJ, Noh SH. Current practice of splenectomy for lymph node dissection in gastric cancer patients: relative comparison of the benefits in subgroups of patients. Gastric Cancer 2012;15:298-304.

Lee KY, Noh SH, Hyung WJ, Lee JH, Lah KH, Choi SH, et al. Impact of splenectomy for lymph node dissection on long-term survival outcome in gastric cancer. Ann Surg Oncol 2001;8:402-6.

Bartleth EK, Roses RE, Kolz RR, Drehin JA, Fraser DL, Karakousis GC. Morbidity and mortality after total gastrectomy for gastric malignancy using the American College of Surgeons National Surgical Quality Improvement Program database. Surgery 2014;156:298-304.

Choi YY, An JY, Kim HI, Cheong JH, Hyung WJ, Noh SH. Current practice of gastric cancer treatment. Chin Med J (Engl) 2012;147:547-53.

Oh SJ, Hyung WJ, Li C, Song J, Kang W, Rha SY, et al. The effect of spleen-preserving lymphadenectomy on surgical outcomes of locally advanced proximal gastric cancer. J Surg Oncol 2009;99:275-80.

Lee KY, Noh SH, Hyung WJ, Lee JH, Lah KH, Choi SH, et al. Impact of splenectomy for lymph node dissection on long-term surgical outcome in gastric cancer. Ann Surg Oncol 2001;8:402-6.

Mönig SP, Pollet PH, Baldus SE, Schmackpfeffer K, Schröder W, Thiele J, et al. Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus. J Surg Oncol 2001;76:89-92.

Sasada S, Ninomiya M, Nishizaki M, Harano M, Ojima Y, Matsukawa H, et al. Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer. Anticancer Res 2009;29:3347-51.

Sano Y, Yamamoto S, Sasaki M: Japan Clinical Oncology Group Study LCOG 0110-MF. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan clinical oncology group study JCOG 0110-MF. Jpn J Clin Oncol 2002;32:363-4.

Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. Surg Laparosc Endosc 1994;4:146-8.

Kim HH, Hyung WJ, Cho GS, Kim MC, Han SJ, Kim W, et al. Morbidity and mortality of laparoscopic gastrectomy versus open gastrectomy for gastric cancer: an interim report—a phase III multicenter, prospective, randomized Trial (KLASS Trial). Ann Surg 2010;251:417-20.

Nakamura K, Katai H, Mizusawa J, Yoshikawa T, Ando M, Terashima M, et al. A phase III study of laparoscopy-assisted versus open distal gastrectomy with nodal dissection for clinical stage IA/IB gastric Cancer (JCOS012). Jpn J Clin Oncol 2013;43:324-7.

Kim HH, Han SJ, Kim MC, Hyung WJ, Kim W, Lee HJ, et al. Long-term results of laparoscopic gastrectomy for gastric cancer: a large-scale case-control and case-matched Korean multicenter study. J Clin Oncol 2014;32:627-33.

Choi YY, Bae JM, An JY, Hyung WJ, Noh SH. Laparoscopic gastrectomy for advanced gastric cancer: are the long-term results comparable with conventional open gastrectomy? A systematic review and meta-analysis. J Surg Oncol 2013;108:550-6.

Cai J, Wei D, Gao CF, Zhang CS, Zhang H, Zhao T. A prospective randomized study comparing open versus laparoscopy-assisted D2 radical gastrectomy in advanced gastric cancer. Dig Surg 2011;28:331-7.

Song J, Oh SJ, Kang WH, Hyung WJ, Choi SH, Noh SH. Robot-assisted gastrectomy with lymph node dissection for gastric cancer: lessons learned from an initial 100 consecutive procedures. Ann Surg 2009;249:927-32.

Park SS, Kim MC, Park MS, Hyung WJ. Rapid adaptation of robotic gastrectomy for gastric cancer by experienced laparoscopic surgeons. Surg Endosc 2012;26:60-7.

Son T, Kwon IG, Hyung WJ. Minimally invasive surgery for gastric cancer treatment: current status and future perspectives. Gut Liver 2014;8:229-36.

Marano A, Choi YY, Hyung WJ, Kim YM, Kim J, Noh SH. Robotic versus Laparoscopic versus Open Gastrectomy: A Meta-Analysis. J Gastric Cancer 2013;13:136-48.

Coratti A, Anneciachiorio M, Di Marino M, Gentile E, Coratti F, Giulianotti PC. Robot-assisted gastrectomy for gastric cancer: current status and technical considerations. World J Surg 2013;37:2771-81.

Kunisaki C, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono H, et al. Significance of long-term follow-up of early gastric cancer. Ann Surg Oncol 2006;13:363-9.

Miyashiro I. What is the problem in clinical application of sentinel node concept to gastric cancer surgery? J Gastric Cancer 2012;12:7-12.

Kitagawa Y, Takeuchi H, Takagi Y, Natsugoe S, Terashima M, Murakami N, et al. Sentinel node mapping for gastric cancer: a prospective multicenter trial in Japan. J Clin Oncol 2013;31:3704-10.

Ryu KW. The future of sentinel node oriented tailored approach in patients with early gastric cancer. J Gastric Cancer 2012;12:1-2.

Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225-9.

Gotoda T, Yanagisawa A, Sasaki M, Ono H, Nakanishi Y, Shimoda T, et al. Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. Gastric Cancer 2000;3:219-25.

Lian J, Chen S, Zhang Y, Qiu F. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. Gastrointest Endosc 2012;76:763-70.

Choi JH, Kim ES, Lee YJ, Cho KB, Park KS, Jang BK, et al. Comparison of quality of life and worry of cancer recurrence between endoscopic and surgical treatment for early gastric cancer. Gastrointest Endosc 2015 Apr 17 [Epub]. http://dx.doi.org/10.3349/ymj.2015.56.5.1177.

Macdonald JS, Malley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for resectable gastroesophageal junction. N Engl J Med 2001;345:725-30.

Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006;355:11-20.
Nashimoto A, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. N Engl J Med 2007;357:1810-20.

63. Sasako M, Sakuramoto S, Katak H, Kinoshita T, Furukawa H, Yamaguchi T, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011;29:4387-93.

64. Bang YJ, Kim YW, Yang HK, Chung HJ, Park YK, Lee KH, et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. Lancet 2012;379:315-21.

65. GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group, Paolotti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA 2010;303:1729-37.

66. Choi YY, Cheong JH, Noh SH. Advanced gastric cancer: is chemotherapy needed after surgery? Expert Rev Gastroenterol Hepatol 2013;7:673-5.

67. Lee J, Lim do H, Kim S, Park SH, Park JQ, Park YS, et al. Phase III trial comparing capecitabine plus cisplatin versus capicitabine plus cisplatin with concurrent capcitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol 2012;30:268-73.

68. Park SH, Sohn TS, Lee J, Lim DH, Hong ME, Kim KM, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol 2015 Jan 5 [Epub]. http://dx.doi.org/10.1200/JCO.2014.58.3930.

69. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2345-52.

70. Sandler A, Gray R, Perry MC, Brahmmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-50.

71. Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol 2009;27:740-5.

72. Shah MA, Jhawer M, Ilson DH, Lefkowitz RA, Robinson E, Capanu M, et al. Phase II study of modified docetaxel, cisplatin, and fluorouracil with bevacizumab in patients with metastatic gastro-esophageal adenocarcinoma. J Clin Oncol 2011;29:868-74.

73. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a randomized, double-blind, placebo-controlled phase III study. J Clin Oncol 2011;29:3968-76.

74. Van Cutsem E, de Haas S, Kang YK, Ohtsu A, Tebbutt NC, Ming Xu J, et al. Bevacizumab in combination with chemotherapy as first-line therapy in advanced gastric cancer: a biomarker evaluation from the AVAGAST randomized phase III trial. J Clin Oncol 2012; 30:2119-27.

75. Fuchs CS, Tomasek J, Yong CJ, Dumitru F, Passalacqua R, Goswami C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma ( REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet 2014;383:31-9.

76. Shah MA. Gastrointestinal cancer: targeted therapies in gastric cancer—the dawn of a new era. Nat Rev Clin Oncol 2014;11:10-1.

77. Committee on a Framework for Development a New Taxonomy of Disease, Board on Life Sciences, Division on Earth and Life Studies, National Research Council. Toward precision medicine: building a Knowledge network for biomedical research and a new taxonomy of disease. Washington, DC: The national Academies press; 2011.

78. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965;64: 31-49.

79. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: International Agency for Research on Cancer; 2010.

80. Ribe CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med 2003;349:247-57.

81. Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol 2010;28:3219-26.

82. An JY, Kim H, Cheong HJ, Hyung WJ, Kim H, Noh SH. Microsatellite instability in sporadic gastric cancer: its prognostic role and guidance for 5-FU based chemotherapy after R0 resection. Int J Cancer 2012;131:505-11.

83. Choi YY, Bae JM, An JY, Kwon IG, Cho I, Shin HB, et al. Is microsatellite instability a prognostic marker in gastric cancer? A systematic review with meta-analysis. J Surg Oncol 2014;110:129-35.

84. Kim SY, Choi YY, An JY, Shin HB, Jo A, Choi H, et al. The benefit of microsatellite instability is attenuated by chemotherapy in stage II and stage III gastric cancer: results from a large cohort with subgroup analyses. Int J Cancer 2015;137:819-25.

85. Cho JY, Lim JY, Cheong JH, Park YY, Yoon SL, Kim SM, et al. Gene expression signature-based prognostic risk score in gastric cancer. Clin Cancer Res 2011;17:1850-7.

86. Wang K, Kan J, Yuen ST, Shi ST, Chu KM, Law S, et al. Exome sequencing identifies frequent mutation of ARD1A in molecular subtypes of gastric cancer. Nat Genet 2011;43:1219-23.

87. Boussios A, Li H, Liu J, Waring P, Lade S, Holloway AJ, et al. Distinctive patterns of gene expression in premalignant gastric mucosa and gastric cancer. Cancer Res 2003;63:2569-77.

88. Tan IB, Ivanova T, Lim KH, Ong CW, Deng N, Lee J, et al. Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. Gastroenterology 2011;141:476-85, 485.e1-11.

89. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature 2014;513: 202-9.

90. Cristescu R, Lee J, Nebozhyn M, Kim KM, Ting JC, Wong SS, et al. Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. Nat Med 2015;21:449-56.

91. US Food and Drug Administration. Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development. US Department of Health And Human Services, FDA; 2013.

92. Gatterlin SN, Horn L, Gandhi L, Spigel DR, Antonia SJ, Rizvi NA, et al. Overall Survival and Long-Term Safety of Nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in Patients With Previously Treated Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2015;33:2004-12.

93. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.

http://dx.doi.org/10.3349/ymj.2015.56.5.1177