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## Towards personalized perioperative treatment for advanced gastric cancer

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### Abstract

Gastric cancer is one of the most frequently diagnosed cancers worldwide. Although the rate of gastric cancer has declined dramatically over the past decades in most developed Western countries, it has not declined in East Asia. Currently, a radical gastrectomy is still the only curative treatment for gastric cancer. Over the last twenty years, however, surgery alone has been replaced by a multimodal perioperative approach. To achieve the maximum benefit from the perioperative treatment, a thorough evaluation of the tumor must first be performed. A complete assessment of gastric cancer is divided into two parts: staging and histology. According to the stage and histology of the cancer, perioperative chemotherapy or radiochemotherapy can be implemented, and perioperative targeted therapies such as trastuzumab may also play a role in this field. However, perioperative treatment approaches have not

been widely accepted until a series of clinical trials were performed to evaluate the value of perioperative treatment. Although multimodal perioperative treatment has been widely applied in clinical practice, personalization of perioperative treatment represents the next stage in the treatment of gastric cancer. Genomic-guided treatment and efficacy prediction using molecular biomarkers in perioperative treatment are of great importance in the evolution of treatment and may become an ideal treatment method.

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**Key words:** Gastric cancer; Pre-therapeutic evaluation; Perioperative chemotherapy; Perioperative radiochemotherapy; Perioperative target therapy

**Core tip:** Multimodal perioperative treatment of advanced gastric cancer is playing an increasingly important role in patient treatment. Different strategies, including preoperative and postoperative chemotherapy and radiochemotherapy, are implemented in clinical practice and a new concept of perioperative-targeted therapy is emerging. Although many randomized clinical trials have been performed to determine the effectiveness of these therapies over surgery alone, little evidence exists regarding the comparison of the different therapies. Personalized treatment should be based on the results of randomized clinical trials as well as subgroup analyses, tailored by histology, demography, and predictors, including tumor markers and genomic profiling.

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## INTRODUCTION

Gastric cancer is one of the most frequently diagnosed cancers around the world. Until the mid-1990s, it was the first cause of cancer death in the world and now it represents the fourth most common cancer<sup>[1,2]</sup>. While gastric cancer is the 14<sup>th</sup> most common cancer in the United States, it is the 2<sup>nd</sup> most common cancer in China<sup>[3,4]</sup>. Although the effects of geography on the incidence and prognosis are still not clearly understood, factors of gastric carcinogenesis, diagnosis, and therapeutic strategies may contribute to the differences<sup>[5]</sup>.

Radical gastrectomy, the complete surgical resection of macroscopic and microscopic tumors (R0 resection), is still currently the only way to cure gastric cancer. The extent of lymphadenectomy, however, has been controversial between the East and West until recent years. Radical gastrectomy with extended D2 lymphadenectomy is considered the standard surgical practice in East Asia and has been accepted in the West. Nevertheless, limited D1 resection with radiochemotherapy is still more frequently implemented in Western countries<sup>[5-7]</sup>.

In contrast to those with early gastric cancers (EGCs), patients diagnosed with advanced gastric cancers (AGCs) typically have a poor prognosis. According to the 7<sup>th</sup> edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging of gastric cancer, the 5-year survival rate of patients with AGCs was 9.2%-45.5% in the United States<sup>[8]</sup>, and 40%-60% of patients with local AGCs experience recurrence after surgery<sup>[9]</sup>. Over the last few decades, surgery as the sole form of treatment has been replaced by different forms of multimodal treatment of AGCs around the world<sup>[10-12]</sup>. To achieve the most benefits from the perioperative treatment of AGCs, a thorough evaluation of the tumor is required. Different stages and histological types of gastric cancers have different biological behaviors and thus respond differentially to treatment, a factor that hits at the core of personalized perioperative treatment for gastric cancer.

This article will review the current strategies towards personalized perioperative treatment of gastric cancer and discuss the appropriate indications for perioperative treatment, multidisciplinary approaches for AGCs, as well as the future questions that remain in the tailored management of gastric cancer.

## PRETHERAPEUTIC EVALUATION OF AGC

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology of Gastric Cancer and other guidelines worldwide, a complete endoscopic evaluation of the esophagus, stomach, and duodenum with a biopsy of any suspicious lesion is considered the gold standard for detection and histological verification of gastric cancer<sup>[11,13,14]</sup>. Because the number and location of the biopsies are still controversial and limited evidence-based data exist to address the controversy, a variety of recommendations in national

guidelines have been suggested. Aside from verifying malignant disease histologically, the goal of biopsies is to evaluate the histological tumor type and examine the biological behavior of the tumor, if possible, by appropriate sampling. Different types of gastric cancer may respond differentially to chemotherapy or radiotherapy. For example, hepatoid adenocarcinoma, a rare form of gastric cancer, responds poorly to chemotherapy and the best strategy is to operate as early as possible<sup>[15]</sup>. However, several different histological classifications of gastric cancer currently exist and include the Lauren classification, Japanese Gastric Cancer Association classification, and World Health Organization (WHO) classification<sup>[16,17]</sup>. The lack of consensus in histological classification reveals an insufficient understanding of the biological behavior of gastric cancer. Inconsistencies between the biopsy and postoperative histology occur frequently, which limits the implementation of personalized treatment by histology alone. Therefore, TNM stage-oriented treatment is the gold standard for preoperative treatment of gastric cancer. The heterogeneity of gastric cancer greatly contributes to the personalized treatment and represents one of the main challenges in perioperative treatment.

Evaluation of the tumor infiltration stage (T-stage) is the main parameter to distinguish AGCs from EGCs. The current gold standard for T-staging is endoscopic ultrasound (EUS), which has an accuracy between 65% and 92%<sup>[18]</sup> and a sensitivity and specificity of 88% and 100% for T1, 82% and 96% for T2, 90% and 95% for T3, and 99% and 97% for T4, respectively<sup>[19]</sup>. Multi-detector computed tomography (MDCT) for T-staging is less accurate than EUS, though the sensitivity and specificity of serosa involvement are similar to EUS<sup>[18,19]</sup>. A meta-analysis involving nine studies utilizing positron emission tomography (PET) to evaluate gastric cancer reported that, despite the inability to stage gastric cancer by tumor depth, PET has a pooled primary tumor detection ratio of 80% in identifying the existence of gastric cancer<sup>[20]</sup>.

Lymph node involvement (N-stage) represents the greatest challenge in gastric cancer staging. N-staging is currently achieved by evaluating the number of metastatic lymph nodes according to the 7<sup>th</sup> AJCC TNM staging system<sup>[8]</sup>. Currently, lymph node size is the primary parameter used to define nodal involvement. Micrometastasis without lymph node enlargement is not detected by imaging methods such as MDCT or EUS. The sensitivity and specificity for N-staging with EUS is approximately 50%-60% and 85%-95%<sup>[19]</sup>, respectively, and MDCT is not superior to EUS<sup>[18,19]</sup>. PET can evaluate node metabolism using the standardized uptake value (SUV) in addition to acquiring the size of the lymph nodes. However, the mean SUV noted for N-staging can also vary, with overall values ranging from 4.5 to 6.8, and an overall accuracy of 17.7% to 79.2%<sup>[20]</sup>.

Distant metastasis (M-stage) is predominantly evaluated with thoracic, abdominal, and pelvic MDCT with a sensitivity and specificity of > 70% if performed using a biphasic protocol (including a portal venous contrast phase) and a slide thickness < 3 mm<sup>[14,21]</sup>. Thus, MDCT is

considered the gold standard approach for assaying solid organ metastasis. PET is also one of the best methods to assess the M-stage of gastric cancer with an overall accuracy of 88%<sup>[20]</sup>, but studies comparing PET with MDCT for M-staging are still lacking<sup>[20]</sup>. Because of the high prevalence of peritoneal carcinomatosis, additional attention must be paid to T3 and T4 patients<sup>[22-24]</sup>. Laparoscopic exploration should be employed to exclude liver metastasis and peritoneal carcinomatosis. Detection of free cancer cells by peritoneal lavage cytology can predict the risk of peritoneal carcinomatosis with high specificity and this patient category may also benefit from hyperthermic intraperitoneal chemotherapy (HIPEC), which has been shown to improve overall survival and decrease peritoneal local recurrence<sup>[25]</sup>. Metabolic imaging represents another advantage of PET in evaluating gastric cancer, as it may provide clues to predict treatment responses, which will be discussed later in this article.

## MOLECULAR AND RADIOLOGIC ASPECTS OF PERSONALIZED PERIOPERATIVE TREATMENT

Researchers worldwide have been working to identify the molecular subtypes of gastric cancer and their differential responses to chemotherapy. Lei and colleagues identified three subtypes of gastric adenocarcinoma: proliferative, metabolic, and mesenchymal. In the study from Lei *et al.*<sup>[26]</sup>, cancer cells from the metabolic subtype were more sensitive to and reaped greater benefits from 5-fluorouracil (5-FU) than the other subtypes. Meanwhile, tumors of the mesenchymal subtype contained cells with features of cancer stem cells, and cell lines of this subtype were particularly sensitive to phosphatidylinositol 3-kinase-AKT-mTOR inhibitors *in vitro*. This study has been touted by some experts in the field as a new direction for personalized therapy of gastric adenocarcinoma and they are finding ways to apply this information to identify tumor subsets and develop molecularly tailored, individualized therapies<sup>[27]</sup>. Although many other studies have been conducted, there is still no consensus on the molecular subtypes of gastric cancer<sup>[28-31]</sup>. Recently, several studies have focused on predicting the efficacy of chemotherapy using genome-guided chemotherapy. Molecular biomarkers including VEGFR-1 and ERCC1/TS mRNA levels<sup>[32]</sup> were reported in the 2013 International Gastric Cancer Congress<sup>[33]</sup>. While there is still a long way before these studies can be translated into clinical practice, clinical trials may provide some clues for the choice of treatment regimen in the postoperative setting.

Diffusion-weighted MRI (DW-MRI) is a promising imaging technique to evaluate cancer treatment response, as it is sensitive enough to detect the macromolecular and microstructural changes that occur at the cellular level prior to anatomical changes during therapy<sup>[34]</sup>. Studies have shown that successful treatment of many tumor types can be detected using DW-MRI to measure the

early increase in the apparent diffusion coefficient (ADC) values<sup>[35-38]</sup>. Additionally, a low pretreatment ADC value is often predictive of a better outcome<sup>[34]</sup>, which may provide an important opportunity for individualized therapy, minimizing unnecessary toxicity associated with ineffective therapies and improving overall patient health care at a lower cost. The efficacy of DW-MRI in gastric cancer, however, has only been evaluated in a few cases<sup>[39,40]</sup>.

Because of the nature of metabolic imaging, PET can provide information on the metabolic response of gastric cancers. A series of studies have been performed to assess the utility of PET in predicting the response to gastric cancer treatment<sup>[41-49]</sup>. In these studies, a metabolic response was defined as a decrease of  $\geq 35\%$  in the tumor glucose SUV after preoperative chemotherapy, which can be predicted by fluorodeoxyglucose PET. These studies suggested that the metabolic response may correlate with tumor response, ultimately translating into improved patient survival<sup>[41-48]</sup>.

## PERIOPERATIVE CHEMOTHERAPY

Over the past decades, gastric cancer treatment by surgery alone has been replaced by a multimodal treatment approach consisting of surgery and pre- or postoperative chemotherapy or radiochemotherapy. In addition to the wide clinical application of multimodal treatment, personalized perioperative treatment represents the future of gastric cancer treatment.

### Postoperative chemotherapy

The survival benefits of postoperative chemotherapy differ in clinical trials between Eastern and Western countries. In 1993, Hermans and colleagues performed a meta-analysis on 11 clinical trials from 1980 and found that postoperative chemotherapy for resectable gastric cancer did not, in general, improve survival<sup>[49]</sup>. In contrast, the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration Group conducted a meta-analysis on 17 randomized clinical trials (RCTs) including 3838 patients with resectable gastric cancer and reported that postoperative chemotherapy was associated with a statistically significant benefit in terms of overall survival (HR = 0.82, 95%CI: 0.76-0.90;  $P < 0.001$ ) and disease-free survival (HR = 0.82, 95%CI: 0.75-0.90;  $P < 0.001$ )<sup>[50]</sup>. This meta-analysis supports the utility of postoperative chemotherapy in resectable gastric cancer.

In contrast to the small benefit observed on overall survival in the Western clinical trials, favorable outcomes were observed in RCTs in the East. A large RCT from the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) in Japan randomly assigned 1059 patients with stage II or III gastric cancer who underwent gastrectomy with extended (D2) lymph node dissection to groups with or without S-1 adjuvant chemotherapy<sup>[51]</sup>. In this study, the 3-year overall survival rate was 80.1% in the S-1 group and 70.1% in the surgery-only group (HR = 0.68, 95%CI: 0.52-0.87;  $P = 0.003$ ). However, the high

overall survival rate at 3 years in both groups has not been replicated in any Western trials. The United States multicenter phase III study comparing cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma stratified more than 1000 patients to compare the overall survival between the postoperative chemotherapy regimens of cisplatin/S-1 and cisplatin/5-FU but failed to confirm the results from the ACTS-GC trial and showed that cisplatin/S-1 did not prolong overall survival of patients with advanced gastric or gastroesophageal adenocarcinoma when compared with cisplatin/5-FU<sup>[52]</sup>.

In addition to S-1, capecitabine, another form of oral fluoropyrimidine, with oxaliplatin (XELOX) was evaluated in the Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study, which was a multicenter, randomized, phase III trial occurring across 37 centers ( $n = 1035$  patients) in South Korea, China, and Taiwan<sup>[53]</sup>. The 3-year disease-free survival was 74% in the chemotherapy and surgery group in comparison to 59% in the surgery only group (HR = 0.56, 95%CI: 0.44-0.72;  $P < 0.0001$ ). A recent update of the CLASSIC trial has also been reported. After a median follow-up of 5 years, a 34% reduction in the risk of death with chemotherapy versus surgery alone was observed (HR = 0.66, 95%CI: 0.51-0.85;  $P = 0.0015$ )<sup>[54]</sup>. The 5-year overall survival rates were 78% in the XELOX group and 69% in the surgery alone group ( $P = 0.0029$ ). This update further proved the efficacy of XELOX as a treatment regimen for postoperative chemotherapy.

A meta-analysis from Janunger *et al*<sup>[55]</sup> also found that there was a significant difference in the effect of chemotherapy on AGCs between Asian and European patients. This study has raised the issue about whether there are ethnic differences between gastric cancer patients in the East and West. RCT results should always be tracked back to the population from whom the study group was sampled, which is an important principle of personalized medicine.

The results of the above clinical trials and meta-analyses indicate that 5-FU (or its derivatives) postoperative chemotherapy may bring selected patients with resectable gastric cancer a higher probability of survival, but the studies are insufficient at predicting how individuals will respond. Thus, there is still a long way to go towards achieving personalized postoperative chemotherapy.

The subgroup analysis of the ACTS-GC and CLASSIC trials highlights the future direction of personalized postoperative chemotherapy. In the ACTS-GC trial, male patients  $< 60$  years of age with stage II (6<sup>th</sup> TNM classification), stage T2 (tumor invades the muscularis propria or the subserosal connective tissue), stage N1 (1-6), and undifferentiated histological tumors may benefit most from postoperative S-1 chemotherapy, although it is important to note that the difference was not statistically significant. In a similar analysis performed in the CLASSIC trial, male patients  $< 65$  or  $\geq 65$  years of age with stage II (6<sup>th</sup> TNM classification) and stage N1 or N2 (1-15

involved nodes) respond more favorably to postoperative XELOX chemotherapy when 3-year disease-free survival was examined. A comparison between the two treatment regimens suggests that patients older than 65 years of age or with lymph node metastasis in 7-15 nodes may benefit more from the XELOX regimen than S-1. This type of comparison between different trials, however, does not provide solid evidence of one treatment having an advantage over another; RCTs are still required to provide additional evidence for personalized perioperative chemotherapy.

What is the best chemotherapy regimen and course of treatment? Dozens of clinical trials including the NCT01426646, NCT00343668, and NCT01531452 are currently being performed to address this question. It seems to be an answerless question with the increasing number of cytotoxic drugs being developed. Studies must also find a way to predict the effects of different treatments. Moreover, there is currently no way to assess how these treatments affect individuals, rather than populations.

### Preoperative chemotherapy

Preoperative chemotherapy is commonly applied in Europe and this clinical practice is based on the results of three major RCTs. The Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial, a British multicenter RCT, randomly assigned over 500 patients with histologically verified adenocarcinoma of the stomach or gastroesophageal junction to either surgery alone or surgery following chemotherapy with epirubicin, cisplatin, and 5-FU<sup>[56]</sup>. With a median follow-up of four years, the preoperative chemotherapy group had a higher likelihood of overall survival (HR = 0.75, 95%CI: 0.60-0.93;  $P = 0.009$ ; 5-year survival rate: 36% *vs* 23%) and of progression-free survival (HR = 0.66, 95%CI: 0.53-0.81;  $P < 0.001$ ). This trial was limited by the heterogeneous inclusion criteria, which included patients with gastric cancer, gastroesophageal cancers, and cancers of the distal esophagus, as well as the lack of quality control of surgical and pathological operations. Moreover, more than half of the patients in the preoperative group did not complete the chemotherapy regimen, making it difficult to evaluate the effects of preoperative chemotherapy from postoperative chemotherapy. Thus, it is important to remember that the results of the MAGIC trial are not sufficient to confirm the effects of preoperative chemotherapy on gastric cancer following curative gastrectomy with D2 lymphadenectomy.

The ACCORD07/FFCD-9703 French trial obtained similar results to the MAGIC trial<sup>[57]</sup>. Two hundred and twenty-four patients with resectable cancer of the lower esophagus, gastroesophageal junction, or stomach were enrolled to either a surgery alone group or to the preoperative chemotherapy group, which received two or three preoperative cycles of intravenous cisplatin and a continuous intravenous infusion of 5-FU for five consecutive days every 28 d and three or four postoperative cycles of the same regimen in addition to the surgery.

Compared with the surgery alone group, the preoperative chemotherapy group had better overall (38% *vs* 24%; HR = 0.69, 95%CI: 0.50-0.95;  $P = 0.02$ ) and disease-free (34% *vs* 19%; HR = 0.65, 95%CI: 0.48-0.89;  $P = 0.003$ ) 5-year survival rates. In a multivariate analysis, preoperative chemotherapy ( $P = 0.01$ ) and stomach tumor localization ( $P < 0.01$ ) were favorable prognostic factors for survival, and preoperative chemotherapy significantly improved the curative resection rate (84% *vs* 73%,  $P = 0.04$ ). The same limitation of heterogeneous inclusion criteria still exists in this trial and does not answer the remaining questions from the MAGIC trial.

To address the questions remaining in the trials mentioned above, the EORTC 40954 trial was performed<sup>[58]</sup>. This trial used stringent inclusion criteria to include only locally advanced adenocarcinoma of the stomach and gastroesophageal junction (SIEWERT II and III). Patients in this trial were randomly assigned to either undergo surgery alone or receive surgery in combination with preoperative chemotherapy consisting of cisplatin, 5-FU, and leucovorin. In contrast to the above trials, rigorous preoperative staging and quality control of surgery were applied in this trial. However, this trial was halted due to poor accrual after 144 patients were assigned. Out of the 144 included patients, 52.8% had tumors located in the proximal third of the stomach (including SIEWERT II and III) and the R0 resection rate was 81.9% after preoperative chemotherapy, as compared with 66.7% with surgery alone ( $P = 0.036$ ). After a median follow-up period of 4.4 years and 67 deaths, a survival benefit could not be shown (HR = 0.84, 95%CI: 0.52-1.35;  $P = 0.466$ ). An overall survival of 64.6 mo was observed in the chemotherapy group in comparison to 52.5 mo in the surgery alone group. This trial showed a significantly increased R0 resection rate, but failed to demonstrate a survival benefit. Possible explanations of why a survival benefit was not observed in the study include a low statistical power, a high rate of proximal gastric cancer and a better outcome than expected after radical surgery alone due to the high quality of surgery, which included resections of regional lymph nodes outside the perigastric area. Another limitation that needs to be considered is the possibility of increased morbidity and mortality of the operation after preoperative chemotherapy.

The differing results from these three trials might be associated with the quality control of the surgery. Only the EORTC 40954 trial applied the D2 lymphadenectomy and may render the negative effects of preoperative chemotherapy more apparent. The specific treatment regimen used for preoperative chemotherapy is another caveat that must be addressed. The regimens used in the three trials above are not recommended in East Asia, despite being included in the NCCN and European Society for Medical Oncology guidelines<sup>[10-12]</sup>. Clinical trials to compare different regimens have been performed worldwide. There are currently more than 50 clinical trials registered on the clinicaltrials.gov website, with a broad spectrum of regimens and drugs.

Proper imaging evaluation should be performed at the appropriate time to achieve the utmost benefit prior to surgery. Currently, the Response Evaluation Criteria In Solid Tumors 1.1 criteria, WHO criteria, and many other sets of criteria are used to evaluate the effectiveness of preoperative treatment<sup>[59]</sup>, but limitations still exist. None of these criteria can accurately predict a gastric cancer patient's response to chemotherapy. New imaging methods like diffusion weighted imaging and PET may provide clues for this problem. As to the pathology evaluation, the widely applied Tumor Regression Grade was developed from patients with rectal cancer and is still not specific enough for gastric cancer. Patients diagnosed as M1 may benefit from preoperative chemotherapy due to the free cancer cells in a peritoneal lavage cytology examination. These patients received HIPEC together with preoperative chemotherapy, which converted some patients to ypM0 when a second peritoneal lavage cytology examination was performed, giving them a potential R0 operation<sup>[24]</sup>. This modality is now being evaluated in our center (NCT01471132).

## PERIOPERATIVE RADIOCHEMOTHERAPY

Although postoperative radiochemotherapy is currently used in the United States as a standard treatment of AGCs, it is not widely accepted in other parts of the world. In 1984, a small prospective clinical trial that included 60 patients evaluated the value of postoperative radiochemotherapy for the first time, and a significant 5-year survival benefit was observed (23% *vs* 4%)<sup>[60]</sup>. Based on this small trial, the larger South West Oncology Group/Intergroup trial was established to further evaluate the utility of postoperative radiochemotherapy in the treatment of gastric cancer<sup>[61]</sup>. In this trial, a total of 556 patients with resectable adenocarcinoma of the stomach or gastroesophageal junction were randomly assigned to surgery alone or surgery plus postoperative radiochemotherapy. The postoperative treatment consisted of fluorouracil/leucovorin, followed by 4500 cGy of radiation (180 cGy for five days). The median overall survival in the surgery-only group was 27 mo, as compared with 36 mo in the radiochemotherapy group; the HR for death was 1.35 (95%CI: 1.09-1.66;  $P = 0.005$ ). The HR for relapse was 1.52 (95%CI: 1.23-1.86;  $P < 0.001$ ). The trial showed promising results for postoperative radiochemotherapy in the treatment of gastric cancer, but the quality control for surgery was still poor, with only a 10% rate of D2 lymphadenectomy. As a result, the value of postoperative radiochemotherapy after D2 lymphadenectomy remained unclear and was not fully accepted in East Asia. Based on the results of this trial, only patients with D0/D1 lymphadenectomy or non-R0 gastrectomy should be assigned to postoperative radiochemotherapy.

Preoperative radiochemotherapy is not currently used as a standard treatment for gastric cancer anywhere. The Chemoradiotherapy for Oesophageal Cancer Followed by Surgery study evaluated the utility of preoperative

radiochemotherapy for esophageal or gastroesophageal junction cancer and reported significant overall survival improvement in the preoperative radiochemotherapy group (49.4 mo *vs* 24 mo; HR = 0.65, 95%CI: 0.495-0.871;  $P = 0.003$ )<sup>[62]</sup>. This trial, however, primarily focused on esophageal cancer and does not provide strong evidence for gastric cancer. Other ongoing trials are currently evaluating the safety and utility of preoperative radiochemotherapy (NCT01924819, NCT01815853, NCT00512304, NCT01523015), but a large phase III RCT has not yet been reported. The main caveat of this treatment is the potential for radiotherapy to cause tissue damage, leading to undesirable healing of the anastomosis. Before the results of these trials are reported, administration of preoperative radiochemotherapy should be applied with additional attention and care. Based on the results from esophageal cancer studies and small trials, preoperative chemoradiation may bring a favorable survival benefit though a definitive answer requires analysis of the results from the ongoing clinical trials.

## PERIOPERATIVE TARGETED THERAPY

Recent advances in molecular therapies have developed a new weapon against AGCs through the use of anti-human epidermal growth factor 2 (HER2) therapies. Trastuzumab, a HER2 monoclonal antibody, was the first drug in the metastatic setting that showed a benefit in overall survival when combined with 5-FU chemotherapy. Assaying the HER2 status of a tumor is imperative to achieve the utmost treatment efficacy. Only HER2 positive (immunohistochemistry [IHC] +++ or fluorescence *in situ* hybridization +/IHC ++) gastric cancer is eligible for trastuzumab treatment. HER2 treatment is a good example for targeted therapy as well as personalized medicine. Although there are not any trials reporting results on the role of trastuzumab in the preoperative setting, a number of case reports with trastuzumab-containing preoperative chemotherapy regimens have been published with promising outcomes, and complete remission has been observed occasionally in these cases<sup>[63,64]</sup>. The value of perioperative-targeted therapy in clinical practice still needs to be thoroughly evaluated, in addition to the rapid development of molecular oncology.

## CONCLUSION

Perioperative treatment is playing an increasingly important role in the multimodal treatment of AGC. Current large-scale RCTs have laid a solid foundation for the utility of perioperative treatment. Several questions still remain. How do we translate these results into clinical practice? How can we present the individual patient with the best benefits and least amount of damage? How do we predict the efficacy of preoperative treatment as early as possible to reduce further damage and decrease costs? Pretreatment evaluation, consisting of a systematic review of tumor stage, location, and biological behavior, is essential to clinical decision-making. Different strategies

may be applied on different patient subsets that have been classified by stage, location, biology, and other parameters. Here, we recommend that clinical trial results should be adopted on the appropriate patients based on study inclusion criteria, with regard to age, stage, surgery, and even ethnicity. In addition to the traditional pretreatment workup, new imaging techniques such as PET, diagnostic laparoscopy and DW-MRI, can provide additional information on efficacy prediction and patient selection. Different therapies including preoperative and postoperative chemotherapy and radiochemotherapy are applied in clinical practice and new concepts of perioperative-targeted therapies are starting to play a role in this field. The core of individualized treatment is to use the appropriate strategy on the right patient. Development of molecular biomarkers, molecular and functional imaging techniques will be of great help.

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