REVIEW

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Recent Strategies for Treating Stage IV Gastric Cancer: Roles of Palliative Gastrectomy, Chemotherapy, and Radiotherapy

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ABSTRACT

Recently, many strategies have been reported for the effective treatment of gastric cancer. However, the strategy for treating stage IV gastric cancer remains controversial. Conducting a prospective phase III study in stage IV cancer patients is difficult because of heterogeneous performance status, age, and degree of cancer metastasis or extension. Due to poor prognosis, the variance in physical status, and severe symptoms, it is important to determine the optimal strategy for treating each individual stage IV patient. In the past decade, many reports have addressed topics related to stage IV gastric cancer: the 7th Union for International Cancer Control (UICC) TNM staging system has altered its stage IV classification; new chemotherapy regimens have been developed through the randomized ECF for advanced and locally advanced esophagogastric cancer (REAL)-II, S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer (SPIRITS), trastuzumab for gastric cancer (ToGA), ramucirumab monotherapy for previously-treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD), and ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously-treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW) trials; and the survival efficacy of palliative gastrectomy has been denied by the reductive gastrectomy for advanced tumor in three Asian countries (REGATTA) trial. Current strategies for treating stage IV patients can be roughly divided into the following five categories: palliative gastrectomy, chemotherapy, radiotherapy, gastric stent, or bypass. In this article, we review recent publications and guidelines along with above categories in the light of individual symptoms and prognosis.

Key words: Stage IV gastric cancer – palliative gastrectomy – chemotherapy – radiotherapy – bypass.

Abbreviations: APC: argon plasma coagulation; AVAGAST: anti-angiogenic antibody bevacizumab, the avastin in gastric cancer; BSC: best supportive care; CF: cisplatin and fluorouracil; CRP: C-reactive protein; DCF: docetaxel, cisplatin, and 5-FU; FISH: fluorescent in-situ hybridization; GJ: gastrojejunostomy; GPS: Glasgow Prognostic Score; HER: human epidermal growth factor receptor; HR: hazard ratio; NLR: neutrophil-to-lymphocyte ratio; OS: overall survival; PS: performance status; QOL: quality of life; RAINBOW: ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously-treated advanced gastric or gastro-oesophageal junction adenocarcinoma; RCTs: randomized controlled trials; REAL: randomized ECF for advanced and locally advanced esophagogastric cancer; REGARD: ramucirumab monotherapy for previously-treated advanced gastric or gastro-oesophageal junction adenocarcinoma; REGATTA: reductive gastrectomy for advanced tumor in three Asian countries; SEER: Surveillance Epidemiology and End Results; SEMS: self-expandable metal stents; SPIRITS: S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer; ToGA: trastuzumab for gastric cancer; TTP: time-to-progression; VEGFR: vascular endothelial growth factor receptor.

INTRODUCTION

Gastric cancer is the fourth most common cancer and the second leading cause of cancer death in the world (738,000 deaths, 9.7% of the total) [1]. The incidence and pathology of gastric cancer vary significantly by geography, especially between the East and the West. Globally, half of the cases occur in Eastern Asia, and the stages at initial consultation, as well as location of tumor and therapeutic outcomes, are different [2]. For example, due to the higher incidence of gastric cancer in Japan, systematic screening programs are common and result in the detection of gastric cancer in its early stages [3]. On the other hand, screening programs are not performed in the West due to a lower incidence of gastric cancer. Therefore, Western patients present with more advanced stages at initial diagnosis, whereas nearly half of patients in Japan present with early

stage disease. These differences in national screening programs between countries might contribute to differences in prognosis. Analysis of the Surveillance Epidemiology and End Results (SEER) Database suggests that in 34% of patients, tumors have metastasized to distant organs at initial examination [4]. This indicates that one third of patients are diagnosed with stage IV gastric cancer upon initial hospital examination, and underscores the importance of establishing a standard therapy for these patients.

Based on previous clinical evidence, the Gastric Cancer Guidelines in the East and West provide mostly the same recommendations for treating gastric cancer in Stages 0-III [5-7]. Many strategies, such as surgery (gastrectomy or bypass), chemotherapy, radiation therapy, gastric stent, or palliative care, have been conducted for stage IV gastric cancer. However, the optimal strategy for treating these patients remains unknown. Prospective randomized controlled trials (RCTs) are very difficult to conduct with stage IV patients due to the heterogeneous status of disease progression, performance status (PS), and age. Therefore, retrospective analysis is indispensable for studying this disease in the clinical setting. In this paper, we discuss current strategies for treating stage IV gastric cancer based on individual symptoms and prognosis.

PROGNOSIS OF STAGE IV PATIENTS

The prognosis of patients with stage IV gastric cancer is very poor [8]. Usually, aggressive treatment is not suitable for these patients given the difficulty of securing returns (survival benefit) that correspond with the level of risk (severe therapeutic complications). It is also unreasonable to conduct high-risk, aggressive treatment in patients with a very short life expectancy. In a few cases, even among those with peritoneal metastases, relatively good prognoses have been demonstrated over three years with aggressive treatment [9]. Thus, it is important to select patients who can expect a relatively good prognosis with aggressive treatment. In the 6th Edition of the Union for International Cancer Control (UICC) TNM classification, stage IV included distant metastasis-negative (M0) cases and distant metastasis-positive (M1) cases [10]. However, in some stage IV patients, patients with M0 showed a significantly better survival rate than those with M1, and patients with M0 were good candidates for aggressive treatment [11-13]. In the 7th Edition of the UICC TNM classification, only M1 cases were classified as stage IV. Therefore, after publication of the 7th Edition in 2010, extraction of subgroups that showed relatively good prognosis in stage IV became difficult.

Many molecular targets and histological biomarkers have been identified that predict survival among gastric cancer patients [14, 15]. Making use of these targets and biomarkers is experimental, often time-consuming, and expensive in clinical practice. Objective assessments, using universal clinical data, are more important from the perspective of routine clinical application. Classically, Borrmann type IV gastric cancer has been confirmed to have a poor prognosis in many studies [16]. In stage IV gastric cancer, Borrmann type IV has been identified as an independent prognostic factor [17]. Some authors have focused on the systemic inflammatory response in stage IV gastric cancer. The application of data from peripheral blood samples as prognostic factors is easy and useful for universal and objective evaluation. Pretreatment evaluation of peripheral blood parameters has been reported using C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and the inflammation-based Glasgow Prognostic Score (GPS: scoring system using CRP and albumin), in order to predict patient prognosis [18-22]. Baba et al. [19] reported that CRP is an independent prognostic factor for survival of stage IV gastric cancer patients, and can be used for short-term survival prediction with a cut-off value of 1.7 mg/dL. Tanaka et al. [20] reported that, when stage IV gastric cancer patients were divided into low and high NLR groups based on a cut-off value of 2.5, long-term survival was observed in the low NLR group. They concluded that NLR may be used as a predictive marker to decide on surgical therapy for these patients. When selecting patients for aggressive treatment, the most important factor is a PS sufficiently good to endure chemotherapy. In addition, patients with low CRP levels and low NLR readings may be good candidates.

PALLIATIVE GASTRECTOMY (REDUCTION SURGERY)

There are two purposes in palliative gastrectomy: one is symptom relief and another is survival benefit. In the patients with advanced gastric cancer, symptom relief is very important, because gastric cancer frequently causes severe symptoms or complications, such as an obstruction, perforation or uncontrollable bleeding. Surgical resection is considered to be a prompt, certain strategy for alleviating cancer-related symptoms. Occasionally, an emergency operation should be unavoidable to save the patient's life [21, 22]. This might not be inevitable strategy regardless of mortality or survival rate.

On the other hand, surgical resection has been considered a potent strategy for prolonging patient life, as well as the only chance for a radical cure. In terms of survival benefit of palliative gastrectomy, the National Comprehensive Cancer Network guidelines suggest that gastrectomy is not indicated in patients with metastatic disease without major symptoms [5]. However, the Japanese Gastric Cancer Association guidelines indicate that patients with a single non-curative factor may be treated with gastrectomy [6]. The guidelines of three European societies (European Society for Medical Oncology, the European Society of Surgical Oncology, and the European Society of Radiotherapy and Oncology) suggest that palliative gastrectomy is not generally recommended except for a very small number of patients who have shown a good response to systemic chemotherapy [7]. Therefore, indications for palliative gastrectomy are still controversial, owing to concerns about the safety and survival efficacy of the procedure.

Palliative gastrectomy has been previously shown to have high mortality and morbidity rates. Data from 40 years ago reported high mortality rates, which often reached 20% [25]. However, recent reports show that these procedures can be performed with a very low postoperative mortality rate of 4% [26]. This significant improvement is due to the development of imaging technology for correct diagnosis, preoperative nutritional support, anesthesia, and surgical equipment [27].

Therefore, issues relating to patient safety have been resolved for the most part. Nonetheless, the question of how effective gastrectomy is remains difficult to address.

From the points of view of the survival benefit in non-curative resection, Hartgrink et al. [28] reported on the survival benefit of palliative gastrectomy in patients younger than 70 years in whom the tumor load was restricted to one metastatic site using 285 patients with liver, peritoneal, or distant lymph node metastases, or remnant tumors. They concluded that palliative resection may be beneficial for patients below 70 years of age if the tumor load is restricted to one metastatic site. Our previous report [9] also suggested that the median survival time for patients with both liver metastases and peritoneal dissemination was 3.4 months, while peritoneal dissemination patients without liver metastases showed a relatively good prognosis, averaging 9.6 months. Notably, when S-1 became commercially available in 2000, S-1 treatment significantly improved the three-year survival rates of patients with peritoneal dissemination from 2.8% to 24.1%. Prolonged survival was seen in patients who had one non-curative factor (peritoneal dissemination) and received effective chemotherapy after resection. Kim et al. [29] retrospectively examined the survival difference between 466 patients with palliative resection and 164 patients without resection. The only statistically significant prognostic parameter was the presence of peritoneal dissemination (hazard ratio, HR 0.739, 95%CI 0.564–0.967, $p<0.05$). Many groups have also retrospectively assessed the efficacy of non-curative resection for stage IV gastric cancer, concluding that patients treated with gastrectomy had a better prognosis than those treated with bypass or best supportive care [9, 27-30]. However, these reports contained significant selection biases, such as undocumented operative decision-making processes based on the presence or absence of comorbidities and the level of metastatic disease burden.

To address this bias problem to the furthest point possible, many systematic reviews and meta-analyses have been conducted. Sun et al. [30] conducted a systematic review and meta-analysis of 14 previously published articles, representing 3,003 patients, and reported that palliative gastrectomy in patients with stage IV gastric cancer significantly improved overall survival (OS) (HR 0.62; 95%CI; 0.49-0.78, $p<0.0001$). A meta-analysis conducted by Lasithiotakis et al. [27] reported on 19 non-randomized studies, representing a total of 2,911 stage IV gastric cancer patients. One-year OS in patients who underwent gastrectomy was significantly prolonged, as compared to those who received non-resectional treatment (OR 2.6, 95%CI 1.7-4.3, $p<0.0001$). This analysis also suggested the improvement of quality of life (QOL) and symptom after palliative gastrectomy. In summary, the above studies concluded that stage IV patients with good PS and one metastasis factor, especially peritoneal dissemination, would be good candidates for both reduction surgery and systemic chemotherapy.

However, it is difficult to determine whether palliative gastrectomy is practical for survival benefits. Therefore, all studies have advocated for a properly-designed randomized trial to investigate this topic. To clarify this question, the reductive gastrectomy for advanced tumor in three Asian countries (REGATTA) trial began in February 2008 as an international collaboration between Japan, Korea, and Singapore [31]. The trial investigated the superior survival benefit of palliative gastrectomy followed by chemotherapy, as compared with chemotherapy alone, in patients (age 20-75 years, PS 0-1) with stage IV gastric cancer with a single non-curable factor. Study patients received chemotherapy regimens of oral S-1 + cisplatin within eight weeks following surgery, and repeated this treatment every five weeks until the disease progressed. Results from an interim analysis revealed that reductive gastrectomy prior to chemotherapy had no survival benefit for advanced gastric cancer [32]. Based on these findings, the REGATTA study was interrupted in September 2013. However, the subset analysis indicated the possibility that distal gastrectomy for distal cancer may have a survival benefit, and this has been left to further analysis.

Recently, surgical resection following chemotherapy has drawn some attention [33-36]. Due to the development of new anticancer agents, macroscopic complete resection has become possible for some patients who had unresectable or metastatic gastric cancer at the first clinical visit. This strategy is referred to as salvage gastrectomy or secondary gastrectomy. Preoperative chemotherapy has frequently been conducted in locally advanced gastric cancer, T3-4M0 (Stage IIB, IIIA-C) [36], and several studies have assessed its utility in stage IV gastric cancer at the experimental clinical research level. There are three advantages to preoperative chemotherapy: downsizing/downstaging the primary tumor to obtain curative surgical resection; establishing a chemotherapy responder for additional postoperative chemotherapy; and allowing patients to have enough physical strength and dietary intake to endure the side effects of chemotherapy. Ito et al. [33] retrospectively examined the survival benefit of adjuvant surgery following chemotherapy for patients with initially unresectable stage IV gastric cancer. The 3-year overall survival rate in the adjuvant surgery group was 65.6% versus 7.7% in the non-adjuvant surgery group ($p<0.0001$). Adjuvant surgery showed particularly good results in patients in whom peritoneal dissemination was the sole non-curative factor, the median survival of the adjuvant surgery group was 29.5 months versus 11.4 months in the non-adjuvant surgery group ($p=0.023$). This study concluded that peritoneal dissemination is a promising candidate as a non-curative clinical factor for adjuvant surgery. Another study also showed that survival benefit of adjuvant surgery was found only in patients with peritoneal washings positive alone [34].

The use of chemotherapy following surgical resection was invalidated by the REGATTA study. The opposite strategy, in which surgical resection is performed following chemotherapy, secondary gastrectomy, may be of interest in future studies to prolong the survival of stage IV gastric cancer patients.

CHEMOTHERAPY

Rapid advances in the development of chemotherapeutic agents for treating gastric cancer have significantly improved the prognosis of this disease. Many trials have been published, and many authors have reviewed and meta-analyzed these trials [37-39]. In this section, we reviewed representative phase III trials published over the past 10 years (Table I). Although

Table I. Important phase III trials for metastatic gastric cancer during the last 10 years

Trial	Year	Regimens	n	HR for OS, (p value), 95% Confidence Interval	Median overall survival (OS)
Van Cutsem et al. [39] (V325)	2006	Docetaxel+Cisplatin +5-Fluorouracil	221	1.29 (0.02) 1.0-1.6	9.2
		Cisplatin+5-Fluorouracil	224		8.6
Cunnigham et al. [40] (REAL2)	2008	Epirubicin+Cisplatin +Capecitabine	250	0.92 (0.39) 0.76-1.11	9.9
		Epirubicin+Oxaliplatin +5-Fluorouracil	245	0.96 (0.61) 0.79-1.15	9.3
		Epirubicin+Oxaliplatin +Capecitabine	244	0.80 (0.02) 0.66-0.97	11.2
		Epirubicin+Cisplatin +5-Fluorouracil	263		9.9
Koizumi et al. [44] (SPIRITS)	2008	S-1+Cisplatin	148	0.77 (0.04) 0.61-0.98	13.0
		S-1	150		11.0
Bang et al. [45] (ToGA)	2010	Cisplatin+5-Fluorouracil/ Capecitabine +Trastuzmab	294	0.74 (0.0046) 0·60-0·91	11.3
		Cisplatin+5-Fluorouracil/ Capecitabine	290		11.0
Kang et al. [49]	2012	Docetaxel/Irinotecan	133	0.657 (0.007)	5.3
		BSC	69	0.485-0.891	3.8
Fuchs et al. [50] (REGARD)	2014	Ramucirumab	236	0.776 (0.047)	5.2
		Placebo	115	0.603-0.998	3.8
Ford et al. [48] (COUGAR-02)	2014	Docetaxel	84	0.67 (0.01) 0.49-0.92	5.2
		BSC	84		3.6
Wilke et al. [51] (RAINBOW)	2014	Ramucirumab+Paclitaxel	330	0.807 (0.017)	9.6
		Placebo+Paclitaxel	335	0.678-0.962	7.4

many combinations of chemotherapeutic agents have been proposed, the majority of these regimens were 5-fluorouracil (5-FU)-based regimens, with the next most frequently used drugs being platinum compounds, docetaxel, and epirubicin.

The V325 trial [40] in 2006 compared regimens of docetaxel, cisplatin, and 5-FU (DCF) with regimens of cisplatin and fluorouracil (CF). The time-to-progression (TTP) was longer in patients treated with DCF versus CF (5.6 vs. 3.9 months, p=0.001). The median OS was also longer for DCF versus CF (9.2 vs. 8.6 months, p=0.02). The two-year survival rate was 18% with DCF and 9% with CF. However, grade three to four toxicities were more frequent with DCF than CF. This study concluded that the addition of docetaxel to CF could be recommended for use in patients with good PS.

The results of the randomized ECF for advanced and locally advanced esophagogastric cancer (REAL)-II trial [41] in 2008 assessed a change from cisplatin (requiring hydration) and/or 5-FU (continuous infusion) to capecitabine (no need for hydration) and/or oxaliplatin (oral administration) in triplet therapy with epirubicin, 5-FU, and cisplatin. This randomized trial of two-by-two comparisons demonstrated a superior median OS in patients treated with capecitabine rather than 5-FU, as well as in patients treated with oxaliplatin rather than cisplatin. The median OS time was longer with epirubicin, capecitabine, and oxaliplatin than with epirubicin, 5-FU, and cisplatin, averaging 11.2 versus 9.9 months. Meta-analysis of the REAL-II and MLI17032 trials [42] also showed superior OS in patients treated with capecitabine combinations, as compared with 5-FU combinations, in advanced oesophagogastric cancer (OS 322 vs. 285 days, HR 0.87, 95%CI 0.77-0.98, p=0.027).

Based on the favorable Japanese trial [43], S-1 (an oral antitumor agent) became a key drug for treating gastric cancer in Japan. The S-1 plus cisplatin versus S-1 in RCT in the treatment for stomach cancer (SPIRITS) trial [44] in 2008 showed that treatment with S-1 plus cisplatin prolonged OS, as compared to treatment with S-1 alone, averaging 13 versus 11 months (p=0.04). Progression-free survival was also significantly longer in patients treated with S-1 plus cisplatin than in those treated with S-1 alone, averaging six versus four months (p<0.0001). Treatment with S-1 plus cisplatin showed a high response rate of 54% (in a total of 87 patients treated with S-1 plus cisplatin, one patient had a complete response and 46 patients had partial responses).

With the development of molecular technology, targeted therapies have drawn attention due to their potentially greater anticancer activity and fewer side effects than traditional chemotherapeutic agents. Human epidermal growth factor receptor 2 (HER2) is a transmembrane receptor that belongs to the ErbB/HER family of receptor tyrosine kinases. Anti-HER2 therapies using trastuzumab have made rapid progress in the field of breast cancer treatment. The trastuzumab for gastric cancer (ToGA) trial [45] in 2010 examined the effectiveness of trastuzumab for treating gastric cancer. The 584 patients who had HER2-positive metastatic gastric or gastroesophageal junction cancer were randomly assigned to chemotherapy (consisting of cisplatin plus 5-FU or capecitabine) with or without trastuzumab. The addition of trastuzumab to cisplatin plus 5-FU in HER2-positive patients significantly improved OS from 11.1 to 13.8 months (p=0.0046), as compared with chemotherapy alone. In addition, progression-free survival increased from 5.5 to 6.7 months (HR 0.7, 95%CI; 0.59-

0.85, p=0.0002). A greater survival benefit was detected in an exploratory subgroup analysis of the HER2-enriched population, which had 3+ or 2+ immunohistochemistry and fluorescent in-situ hybridization (FISH)-positive status. The addition of trastuzumab increased survival from 11.8 to 16.0 months (HR 0.65, 95%CI 0.51-0.83, p=0.036). This combination chemotherapy became a useful strategy for patients with HER2-positive stage IV gastric cancer. However, the small proportion of HER2-positivity (22%) was a problem, with only a few patients benefitting from this treatment.

Despite the successful results of advanced colorectal cancer treatment using the anti-angiogenic antibody bevacizumab, the avastin in gastric cancer (AVAGAST) trial [46, 47] in 2011 showed that bevacizumab with platinum-based chemotherapy did not prolong patient survival. Nevertheless, adding bevacizumab to platinum-based chemotherapy was associated with significant increases in progression-free survival and overall response rate in first-line treatment of advanced gastric cancer. These results indicate that the mechanism of tumor growth differs by cancer, and that it is difficult to explain the mechanism of tumor growth through the angiogenesis theory.

To prolong the survival of stage IV gastric cancer patients, the establishment of second-line chemotherapy is very important. In the docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02) trial, Cook et al. [48] randomized 186 patients to receive either docetaxel plus best supportive care (BSC) or BSC alone. Docetaxel significantly improved OS compared to BSC alone (docetaxel vs. BSC = 5.2 vs. 3.6 months, p=0.01). Kang et al. [49] reported on monotherapy using docetaxel or irinotecan, and also suggested a small increase in OS, as compared with BSC.

Based on the theory that vascular endothelial growth factor receptor-2 (VEGFR-2) contributes to the pathogenesis and progression of gastric cancer, the efficacy of ramucirumab (a monoclonal antibody VEGFR-2 antagonist) was examined in patients with advanced gastric cancer in the ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD) trial in 2014 [50]. This international, randomized, placebo-controlled, phase 3 trial was conducted at 119 centers in 29 countries. Median OS improved from 3.8 months among patients in the placebo group to 5.2 months among those in the ramucirumab treatment group (p=0.047). They concluded that VEGFR-2 signaling is an important therapeutic target in advanced gastric cancer.

In succession, the ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW) trial [51] was conducted to elucidate the added effect of ramucirumab to routine paclitaxel regimens. A total of 665 patients were randomly assigned to treatment, with 330 receiving ramucirumab plus paclitaxel, and 335 receiving placebo plus paclitaxel. Overall survival was significantly increased in the ramucirumab plus paclitaxel group, as compared to the placebo plus paclitaxel group (9.6 vs. 7.4 months; p=0.017). Median progression-free survival with ramucirumab plus paclitaxel was significantly longer than placebo plus paclitaxel (4.4 vs. 2.9 months, HR 0.635, 95%CI 0.536-0.752, p<0.0001). These results indicate that the combination of ramucirumab and paclitaxel could be regarded as a new standard second-line treatment, within acceptable bounds of severity and frequency of side effects, for patients with advanced gastric cancer.

Development of further molecular technology will enable more rapid and detailed analyses of gene amplifications and genetic alterations in gastric cancer. During this decade, many targeted therapy regimens have been developed for the treatment of various cancers. The development of more potent cancer growth inhibitors is expected in the near future.

RADIOTHERAPY

Many studies have reported on the effectiveness of radiotherapy for stage IV gastric cancer patients. However, the majority of patients were defined as stage IV based on T4N1-3M0 or T1-3N3M0 status in the 6th edition of the UICC TMN classification. In other words, these studies included many locally advanced patients without remote organ metastasis (M1). Radiotherapy was conducted to downstage or downsize tumors, and to enable curative resections (or improvement of tumor resectability) [52]. With the 7th edition of UICC TMN classification, which states that stage IV is diagnosed by only one M factor, the significance of radiotherapy in the treatment of stage IV gastric cancer has decreased, because remote organ metastases are not a target for radiotherapy. Currently, most patients treated with radiotherapy have far advanced gastric cancer, with very short life expectancies. The main goal of radiotherapy is palliation, or a reduction of symptoms such as bleeding, stenosis, and pain. Specifically, radiotherapy has been frequently applied to control bleeding from gastric cancer when patients cannot undergo palliative gastrectomy due to their poor general condition. Bleeding from gastric cancer leads to anemia, malnutrition, and dehydration, and interrupts the continuity of chemotherapy [53]. Therefore, control of bleeding is important for QOL improvement [54]. Asakura et al. [55] reported that 22 of 30 patients (73%) responded to radiotherapy, with rebleeding occurring in 11 (50%) of the 22 patients who responded to radiotherapy. The median actuarial time to rebleeding was 3.3 months. This study concluded that radiotherapy with 30 Gy in 10 fractions is adequate for the treatment of bleeding in patients with poor prognosis. Other methods for hemostasis include endoscopic argon plasma coagulation (APC), which stopped bleeding in 67% of patients with gastroduodenal tumor bleeding [56]. However, APC has been shown to cause perforation in 5-15% of patients, and recurrence of bleeding is frequently observed.

Typically, patients who have indication for radiotherapy are those with very poor prognosis. However, as potent chemotherapeutic agents that significantly increase patient prognosis are developed, the role of hemostasis using radiation will become more important. Indeed, radiochemotherapy, a combination of radiotherapy and chemotherapy, may become a potent strategy for T4 patients with M1 in the future.

STENT OR BYPASS

Gastric outlet obstruction is a frequently observed symptom in advanced gastric cancer patients. It causes

vomiting, dehydration, and malnutrition, and a deterioration in QOL. Fast and secure improvement of oral intake and symptom relief are very important for short hospitalization due to limited life expectancy. There are three strategies for treating gastric outlet obstruction. One is palliative gastrectomy (as previously mentioned), which is conducted among patients who have relatively good prognoses and good PS. The other two strategies, endoscopic self-expandable metal stents (SEMS) and palliative gastrojejunostomy (GJ), apply to patients with more advanced gastric cancer, lower PS, and who are free of active gastric bleeding [57]. However, the indications for SEMS and GJ remain unclear. Nagaraja et al. [58] conducted a systematic review and meta-analysis of 3 RCTs and 17 non-RCTs that reported on patients who underwent SEMS or GJ for malignant gastroduodenal outflow obstruction. The results of the three RCTs demonstrated that SEMS resulted in fewer major (OR 0.62, 95% CI 0.021-18.37, p=0.02) and minor complication (OR 0.32,95% CI 0.049-2.089, p=0.16), and a shorter hospital stay (SEMS: 5.1 days and GJ: 12.1 days, p<0.01). The 17 non-RCTs had essentially the same results. This review concluded that SEMS placement provides better short-term outcomes. However, SEMS has some long-term disadvantages, such as stent reobstruction (18%) and stent migration (5%) [59]. Takeno et al. [60] reported that indications for GJ are good PS, no prior chemotherapy, and low CRP levels, because poor PS, prior chemotherapy, and high CRP levels were significant independent predictors of poor survival in patients with gastric outlet obstruction. Based on this, patients with poor PS prior chemotherapy, and high CRP levels should be considered potential candidates for SEMS.

CONCLUSION

The main goals of the treatment for stage IV patients are the effective cure for cancer or the best possible quality of life, which considerably prolong life of patients. The key point is the development of new chemotherapeutic agents. Specifically, molecular targeted therapy has shown successful results in cancer treatment. During this decade, many targeted therapies for gastric cancer have been developed, and it is expected that more potent cancer growth inhibitors will be developed in the near future. Anti-HER2 therapies and trastuzumab regimens have shown significant success in gastric cancer treatment, but anti-angiogenic antibodies and bevacizumab regimens did not prolong gastric cancer patient survival. This suggests that the development of new cancer treatment strategies will require the discovery of more candidates to target. The development of new DNA sequencing technologies, such as second generation sequencing techniques, may dramatically increase the speed and reduce the cost of DNA sequencing, enabling more rapid, detailed analysis of gene amplifications and genetic alterations in gastric cancer. This, in turn, will spur the development of more potent chemotherapeutic agents for treating gastric cancer. The survival efficacy of palliative gastrectomy, secondary gastrectomy, radiotherapy, stent, and bypass may dramatically improve when combined with new molecular targeted therapies. When this is realized, the significance of these strategies should be reassessed.

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REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 2010; 127: 2893–2917. doi: 10.1002/ijc.25516
2. Baba H, Kuwabara K, Ishiguro T, et al. Prognostic factors for stage IV gastric cancer. Int Surg 2013; 98: 181-187. doi: 10.9738/INTSURG-D-12-00027.1
3. Yamamoto M, Rashid OM, Wong J. Surgical management of gastric cancer: the East vs. West perspective. J Gastrointest Oncol 2015; 6: 79-88. doi: 10.3978/j.issn.2078-6891.2014.097
4. Howlader N, Noone AM, Krapcho M, et al. SEER cancer statistics review 1975–2008 (Internet). Bethesda: National Cancer Institute.
5. Ajani JA, Bentrem DJ, Besh S, et al. National Comprehensive Cancer Network. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines. J Natl Compr Canc Netw 2013; 11: 531-546.
6. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011; 14: 113-123. doi: 10.1007/s10120-011-0042-4
7. Waddell T, Verheij M, Allum W, et al; European Society for Medical Oncology (ESMO); European Society of Surgical Oncology (ESSO); European Society of Radiotherapy and Oncology (ESTRO). Gastric cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013; 24 Suppl 6: vi57-vi63. doi: 10.1093/annonc/mdt344
8. An JY, Ha TK, Noh JH, Sohn TS, Kim S. Proposal to subclassify stage IV gastric cancer into IVA, IVB, and IVM. Arch Surg 2009; 144: 38-45. doi: 10.1001/archsurg.2008.502
9. Izuishi K, Haba R, Kushida Y, et al. S-1 and the treatment of gastric cancer with peritoneal dissemination. Exp Ther Med 2011; 2: 985-990. doi: 10.3892/etm.2011.290
10. Zurleni T, Gjoni E, Ballabio A, et al. Sixth and seventh tumor-node-metastasis staging system compared in gastric cancer patients. World J Gastrointest Surg 2013; 5: 287-293. doi: 10.4240/wjgs.v5.i11.287
11. Kwon SJ. Evaluation of the 7th UICC TNM Staging System of Gastric Cancer. J Gastric Cancer. 2011; 11: 78-85. doi: 10.5230/jgc.2011.11.2.78
12. Park JM, Park SS, Mok YJ, Kim CS. pN3M0 gastric cancer: the category that allows the sub-classification of stage IV gastric cancer (IVa and IVb). Ann Surg Oncol 2007; 14: 2535-2542. doi: 10.1245/s10434-007-9445-1
13. Li C, Yan M, Chen J, et al. Prognostic influence of sub-stages according to pTNM categories in patients with stage IV gastric cancer. J Surg Oncol 2009; 99: 324-328. doi: 10.1002/jso.21242
14. Kubo N, Ohira M, Sakurai K, et al. SPan-1 is a useful prognostic marker for patients with stage IV gastric cancer who underwent palliative gastrectomy: a retrospective multivariate study. World J Surg 2013; 37: 1681-1687. doi: 10.1007/s00268-013-2016-7
15. Sekikawa A, Fukui H, Zhang X, et al. REG Iα is a biomarker for predicting response to chemotherapy with S-1 plus cisplatin in patients with unresectable stage IV gastric cancer. Br J Cancer 2013; 108: 395-401. doi: 10.1038/bjc.2012.572
16. An JY, Kang TH, Choi MG, et al. Borrmann type IV: an independent prognostic factor for survival in gastric cancer. J Gastrointest Surg 2008; 12: 1364-1369. doi: 10.1007/s11605-008-0516-9

17. Yang B, Wu G, Wang X, Zhang X. Discussion of modifying stage IV gastric cancer based on Borrmann classification. Tumour Biol 2013; 34: 1485-1491. doi: 10.1007/s13277-013-0673-7
18. Jin H, Zhang G, Liu X, et al. Blood neutrophil-lymphocyte ratio predicts survival for stages III-IV gastric cancer treated with neoadjuvant chemotherapy. World J Surg Oncol 2013; 11: 112. doi: 10.1186/1477-7819-11-112
19. Baba H, Kuwabara K, Ishiguro T, et al. C-reactive protein as a significant prognostic factor for stage IV gastric cancer patients. Anticancer Res 2013; 33: 5591-5595.
20. Tanaka H, Muguruma K, Toyokawa T, Kubo N, Ohira M, Hirakawa K. Differential impact of the neutrophil-lymphocyte ratio on the survival of patients with stage IV gastric cancer. Dig Surg 2014; 31: 327-333. doi: 10.1159/000369278
21. Kotan C, Sumer A, Baser M, Kızıltan R, Carparlar MA. An analysis of 13 patients with perforated gastric carcinoma: A surgeon's nightmare? World J Emerg Surg 2008; 3: 17. doi: 10.1186/1749-7922-3-17
22. Adachi Y, Mori M, Maehara Y, Matsumata T, Okudaira Y, Sugimachi K. Surgical results of perforated gastric carcinoma: an analysis of 155 Japanese patients. Am J Gastroenterol 1997; 92: 516-518.
23. Mimatsu K, Oida T, Fukino N, et al. Glasgow prognostic score is a useful predictive factor of outcome after palliative gastrectomy for stage IV gastric cancer. Anticancer Res 2014; 34: 3131-3136.
24. Crumley AB, McMillan DC, McKernan M, McDonald AC, Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer 2006; 94: 637-641. doi: 10.1038/sj.bjc.6602998
25. Hallissey MT, Allum WH, Roginski C, Fielding JW. Palliative surgery for gastric cancer. Cancer 1988; 62: 440-444. doi: 10.1002/1097-0142(19880715)62:2<440::AID-CNCR2820620232>3.0.CO;2-N
26. Dittmar Y, Rauchfuss F, Goetz M, et al. Non-curative gastric resection for patients with stage 4 gastric cancer--a single center experience and current review of literature. Langenbecks Arch Surg 2012; 397: 745-753. doi: 10.1007/s00423-012-0902-3
27. Lasithiotakis K, Antoniou SA, Antoniou GA, Kaklamanos I, Zoras O. Gastrectomy for stage IV gastric cancer. a systematic review and meta-analysis. Anticancer Res 2014; 34: 2079-2085.
28. Hartgrink HH, Putter H, Klein Kranenbarg E, et al. Value of palliative resection in gastric cancer. Br J Surg 2002; 89: 1438-1443. doi: 10.1046/j.1365-2168.2002.02220.x
29. Kim DY, Joo JK, Park YK, et al. Is palliative resection necessary for gastric carcinoma patients? Langenbecks Arch Surg 2008; 393: 31-35. doi: 10.1007/s00423-007-0206-1
30. Sun J, Song Y, Wang Z, et al. Clinical significance of palliative gastrectomy on the survival of patients with incurable advanced gastric cancer: a systematic review and meta-analysis. BMC Cancer 2013; 13: 577. doi: 10.1186/1471-2407-13-577
31. Fujitani K, Yang HK, Kurokawa Y, et al. Randomized controlled trial comparing gastrectomy plus chemotherapy with chemotherapy alone in advanced gastric cancer with a single non-curable factor: Japan Clinical Oncology Group Study JCOG 0705 and Korea Gastric Cancer Association Study KGCA01. Jpn J Clin Oncol 2008; 38: 504-506. doi: 10.1093/jjco/hyn058
32. Tsujinaka T. Lessons from REGATTA Trial: Japanease point of view. Abstract book of the 86th Japanese Gastric Cancer Congress 2014: 412.
33. Ito S, Oki E, Nakashima Y, et al. Clinical significance of adjuvant surgery following chemotherapy for patients with initially unresectable stage IV gastric cancer. Anticancer Res 2015; 35: 401-406.
34. Satoh S, Okabe H, Teramukai S, et al. Phase II trial of combined treatment consisting of preoperative S-1 plus cisplatin followed by gastrectomy and postoperative S-1 for stage IV gastric cancer. Gastric Cancer 2012; 15: 61-69. doi: 10.1007/s10120-011-0066-9
35. Kanda T, Yajima K, Kosugi S, shikawa T, Ajioka Y, Hatakeyama K. Gastrectomy as a secondary surgery for stage IV gastric cancer patients who underwent S-1-based chemotherapy: a multi-institute retrospective study. Gastric Cancer 2012; 15: 235-244. doi: 10.1007/s10120-011-0100-y
36. Schuhmacher C, Gretschel S, Lordick F, et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer randomized trial 40954. J Clin Oncol 2010; 28: 5210-5218. doi: 10.1200/JCO.2009.26.6114
37. Chen WW, Wang F, Xu RH. Platinum-based versus non-platinum-based chemotherapy as first line treatment of inoperable, advanced gastric adenocarcinoma: a meta-analysis. PLoS One 2013; 8: e68974. doi: 10.1371/journal.pone.0068974
38. Takashima A, Yamada Y, Nakajima TE, Kato K, Hamaguchi T, Shimada Y. Standard First-Line Chemotherapy for Metastatic Gastric Cancer in Japan Has Met the Global Standard: Evidence From Recent Phase III Trials. Gastrointest Cancer Res 2009; 3: 239-244.
39. Iacovelli R, Pietrantonio F, Farcomeni A, et al. Chemotherapy or targeted therapy as second-line treatment of advanced gastric cancer. A systematic review and meta-analysis of published studies. PLoS One. 2014 30; 9: e108940. doi: 10.1371/journal.pone.0108940
40. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006; 24: 4991-4997. doi: 10.1200/JCO.2006.06.8429
41. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008; 358: 36-46. doi: 10.1056/NEJMoa073149
42. Okines AF, Norman AR, McCloud P, Kang YK, Cunningham D. Meta-analysis of the REAL-2 and ML17032 trials: evaluating capecitabine-based combination chemotherapy and infused 5-fluorouracil-based combination chemotherapy for the treatment of advanced oesophago-gastric cancer. Ann Oncol 2009; 20: 1529-1534. doi: 10.1093/annonc/mdp047
43. Tsuburaya A, Sakamoto J, Morita S, et al. A randomized phase III trial of post-operative adjuvant oral fluoropyrimidine versus sequential paclitaxel/oral fluoropyrimidine; and UFT versus S1 for T3/T4 gastric carcinoma: the Stomach Cancer Adjuvant Multi-institutional Trial Group (Samit) Trial. Jpn J Clin Oncol 2005; 35: 672-675. doi: 10.1093/jjco/hyi179
44. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol 2008; 9: 215-221. doi: 10.1016/S1470-2045(08)70035-4
45. Bang YJ, Van Cutsem E, Feyereislova 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: 687-697. doi: 10.1016/S0140-6736(10)61121-X
46. Ohtsu A, Shah MA, Van Cutsem E, 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: 3968-3976. doi: 10.1200/JCO.2011.36.2236

47. Van Cutsem E, de Haas S, Kang YK, 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: 2119-2127. doi: 10.1200/JCO.2011.39.9824
48. Ford HE, Marshall A, Bridgewater JA, et al. Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial. Lancet Oncol 2014; 15: 78-86. doi: 10.1016/S1470-2045(13)70549-7
49. Kang JH, Lee SI, Lim do H, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. J Clin Oncol 2012; 30: 1513-1518. doi: 10.1200/JCO.2011.39.4585
50. Fuchs CS, Tomasek J, Yong CJ, 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: 31-39. doi: 10.1016/S0140-6736(13)61719-5
51. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224-1235. doi: 10.1016/S1470-2045(14)70420-6
52. Min C, Bangalore S, Jhawar S, et al. Chemoradiation therapy versus chemotherapy alone for gastric cancer after R0 surgical resection: a meta-analysis of randomized trials. Oncology 2014; 86: 79-85. doi: 10.1159/000354641
53. Hashimoto K, Mayahara H, Takashima A, et al. Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience. J Cancer Res Clin Oncol 2009; 135: 1117-1123. doi: 10.1007/s00432-009-0553-0
54. Pereira J, Phan T. Management of bleeding in patients with advanced cancer. Oncologist 2004; 9: 561-570. doi: 10.1634/theoncologist.9-5-561
55. Asakura H, Hashimoto T, Harada H, et al. Palliative radiotherapy for bleeding from advanced gastric cancer: is a schedule of 30 Gy in 10 fractions adequate? J Cancer Res Clin Oncol 2011; 137: 125-130. doi: 10.1007/s00432-010-0866-z
56. Loftus EV, Alexander GL, Ahlquist DA, Balm RK. Endoscopic treatment of major bleeding from advanced gastroduodenal malignant lesions. Mayo Clin Proc 1994; 69: 736-740.
57. Keränen I, Kylänpää L, Udd M, et al. Gastric outlet obstruction in gastric cancer: a comparison of three palliative methods. J Surg Oncol 2013; 108: 537-541. doi: 10.1002/jso.23442
58. Nagaraja V, Eslick GD, Cox MR. Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction-a systematic review and meta-analysis of randomized and non-randomized trials. J Gastrointest Oncol 2014; 5: 92-98. doi: 10.3978/j.issn.2078-6891.2014.016
59. Dormann A, Meisner S, Verin N, Wenk Lang A. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. Endoscopy 2004; 36: 543-550. doi: 10.1055/s-2004-814434
60. Takeno A, Takiguchi S, Fujita J, et al. Clinical outcome and indications for palliative gastrojejunostomy in unresectable advanced gastric cancer: multi-institutional retrospective analysis. Ann Surg Oncol 2013; 20: 3527-3533. doi: 10.1245/s10434-013-3033-3