Gastric carcinoma in China: Current status and future perspectives (Review)

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Abstract. Gastric cancer is one of the most frequently occurring cancers in China, with an estimated 380,000 new cases each year, accounting for more than 40% of the worldwide annual cancer incidence. There is geographical clustering of the distribution of gastric cancer in China, with most of the high-risk areas being rural. D2 resection is the standard lymphadenectomy for curative resection in China, but more extensive lymphadenectomy is conducted for selected patients. Perioperative chemotherapy, postoperative chemotherapy or chemoradiotherapy can be combined with surgery. It remains uncertain which option is best, but if surgery is insufficient, adjuvant chemoradiotherapy is recommended. In the palliative setting, although there is no standard first-line chemotherapy, regimens based on taxane, oxaliplatin or capecitabine, or the epirubicin, cisplatin, 5-fluorouracil regimen and its modifications are the most common options selected by Chinese oncologists. Several studies to evaluate target therapy are ongoing, but it is too early to draw any conclusions. However, the development of target therapy is likely to become a milestone in the treatment of gastric cancer.

Contents

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1. Epidemiology of gastric carcinoma in China

Gastric carcinoma is one of the most common cancers in China, and its incidence ranks third among all malignant tumors; after lung and liver cancer in men and after breast and lung cancer in women (1). There is an obvious geographical distribution for gastric cancer in China, with the highest mortality rates occurring mostly in the North [Liaodong Peninsula, Shandong Peninsula, Yangtze River Delta and mid-western provinces along Taihang Mountain and 'Hexi Zoulang' (Hexi Corridor)] (1). Another feature is that most of these high-risk areas are located in rural areas, especially in Gansu, Henan, Hebei, Shanxi and Shaanxi Provinces in the mid-western part of China (1). Although the mortality rate for gastric cancer in China showed an increasing trend overall during the 1970s and 1990s, the rate decreased in the urban but increased in the rural population. The mortality rates for gastric cancer in China are the highest worldwide, both for men and women, when adjusted for the world population (2). From the 1970s to the 1990s, the mortality rate showed a decreasing trend in the 30- to 59-year age group, but increased among people older than 60 years, showing that aging of the population is an important cause of the increase in gastric cancer mortality (2). From 1990 to 1992, the crude mortality rate for gastric cancer in China was 25.2 per population of 100,000 (32.8 per 100,000 for men and 17.0 per 100,000 for women), comprising 23.2% of the total number of cancer-related deaths in this period. According to a study by Sun *et al*, the mortality rate for gastric cancer in China in 2005 was 26.3 per 100,000, and nearly 340,000 people succumbed to the disease in 2005 (2).

2. Methods of staging gastric cancer

Two classification methods for staging gastric cancer are used in China: the Japanese Classification (3) and the American Joint Committee on Cancer/Union Internationale Contre le Cancer Classification (4). Although the surgical pathology method is the most accurate staging system, clinical staging, which has been greatly improved by advancements in imaging techniques such as high-resolution computed tomography and endoscopic ultrasonography, is used before operation and for patients with inoperable disease (5).

3. Surgery for gastric cancer

Surgical therapy is the primary treatment for gastric cancer. However, the type of resection and the role of extensive lymphadenectomy are still the subjects of international debate. For distal gastric cancers, subtotal gastrectomy has been shown to have an equivalent oncologic result to total gastrectomy, with significantly fewer complications (6). It is widely accepted by Chinese oncologic surgeons that subtotal gastrectomy is superior to total gastrectomy. For proximal gastric cancer, there is controversy over whether proximal gastrectomy or total gastrectomy is the best option, although both types of resection are accepted for proximal tumors.

The extent of lymph node dissection remains controversial in Western and Asian countries. Two well-known clinical trials were conducted to compare the overall survival and complications between D1 and D2 resection (7,8). Both the Dutch Gastric Cancer Group (DGCG) trial (7) and the Medical Research Council (MRC) trial (8) failed to demonstrate survival benefits of D2 over D1 lymphadenectomy, while showing increased morbidity and mortality associated with D2 resection. In Europe and the USA, D2 and more aggressive lymphadenectomies are not advocated, while D0 lymphadenectomy is thought to be insufficient; therefore, D1 lymphadenectomy is preferred (9,10). Previously, a phase II clinical trial of D2 resection by the Italian Gastric Cancer Study Group showed a morbidity rate of 20.9% and a postoperative mortality rate of 3.0%, which are similar to the rates for D1 dissections in both the DGCG (7) and MRC (8) trials, suggesting that D2 lymphadenectomy results in fewer complications in European as well as in Asian countries (11).

In China, D2 resection is the standard lymphadenectomy for curative resection. Although some Japanese data (12,13) have indicated that more extensive lymphadenectomy may provide better results, this approach has not been widely accepted.

A retrospective study analyzed the surgical treatment of 1,287 patients with gastric carcinoma from the Chinese Medical University, Shenyang, China, and of 1,151 patients from Tokyo University, Tokyo, Japan (14). The results showed that the curative resection rate, the overall 5-year survival rate and the number of patients with early stage disease in the curative population of Tokyo University were 85.9% (914/1064), 77.2% (706/914) and 57.2% (523/914), respectively. These rates were significantly higher than those of the Chinese Medical University at 67.5% (756/1120, P=0.000), 57.1% (432/756, P<0.0001) and 17.3% (131/756, P=0.000), respectively. The number of patients with highly advanced disease in the curative resection population was 52.1% (394/756) at the Chinese Medical University and 16.6% (152/914) at Tokyo University, and the difference was significant (P=0.000). The data from the two universities indicated that the more invasive the cancer, the poorer the prognosis; the 5-year survival rates for D2 and D3 dissections were higher than that of D1. Moreover, the survival rate sequence according to the type of surgical procedure was distal subtotal gastrectomy, total gastrectomy, proximal subtotal gastrectomy, combined with organ resection. It was suggested that the primary reason for the lower curative resection rate and lower overall survival rate was the lower diagnostic rate for early stage gastric cancer in China. Thus, improvement in the diagnosis of early stage disease is urgently required.

A prospective randomized phase III clinical trial that compared the survival and complications of D3 and D1 resection in Taiwan was reported in 2006 (15). The results indicated a superior 5-year overall survival rate for D3 resection (59.5 vs. 53.6%, P=0.041) with no surgical-related mortality in either group. These data support the view that D3 resection may result in survival benefit if the complications can be controlled. A pertinent question is whether D3 resection is superior to that of D2. To date, there is no phase III randomized trial to show that more extensive lymphadenectomy is superior to D2 lymphadenectomy. A randomized trial conducted in Japan, which compared D2 extensive lymphadenectomy with D2 lymphadenectomy, found that the postoperative mortality was low in the two groups, 0.8% in each group. The survival data are, however, currently not available (16).

As the data supporting extensive lymphadenectomy are limited or have minimal power and most randomized trials are negative, it is not possible to conclude that D3 resection is superior to D1 resection, nor that D3 resection is superior to D2 resection. Thus, in China, extensive resection is conducted only in clinical trials, or for a few selected patients.

Whether extensive lymphadenectomy can improve the survival of patients who present with N3 lymph node metastasis, and whether the complications and mortality can be controlled, remains controversial. Although D3 and D4 resections are not accepted by most oncologists, some small scale or retrospective studies have tried to address the problem. In a retrospective study of 527 patients with stage IV gastric cancer conducted in Ruijin Hospital, Jiaotong University, Shanghai, China, 231 patients had unresectable disease and only underwent gastric gastrojejunostomy, exploration or trophism jejunostomy, while 296 patients underwent resection surgery including 92 curative resections (D2, 58 patients and D3, 34 patients; 35 of the 92 patients received extended resection of involved organic areas) (17). The overall 1-, 3- and 5-year survival rates were 32.2, 10.6 and 4.5%, respectively, for resection surgery; 58.4, 20.8 and 9.7%, respectively, for curative resection; 45.8, 11.2 and 4.6%, respectively, for palliative resection; and 11.0, 3.1 and 0%, respectively, for inoperable disease. There were significant differences among the groups (P<0.05). The 1-, 3- and 5-year survival rates for patients with stage IV disease without remote metastasis were 68.1, 37.5 and 18.6%, respectively, after curative resection; and 57.5, 10.0 and 3.8%, respectively, after palliative resection (P<0.05). The mean survival of patients undergoing palliative resection was longer than that of patients with inoperable disease (13 vs. 6.7 months, P<0.05). It appears that D2 or more extensive lymphadenectomy may cure some stage IV patients who have T4 or N3 disease without remote metastasis. However, these data were retrospective and non-randomized, and did not have sufficient power to support more extensive lymphadenectomy.

4. Perioperative chemotherapy and new adjuvant therapy

Most patients with gastric cancer present with advanced disease, half of whom have no chance for curable resection. For patients who receive curable resection, the local recurrence and remote metastasis rates are very high. For example,

the local recurrence rate is >50% for patients with local lymph node metastasis after curative surgery. Therefore, studies of perioperative and new adjuvant chemotherapy that attempt to improve resection rates and reduce the risk of recurrence remain the focus for gastric cancer.

Theoretically, new adjuvant chemotherapy may result in tumor shrinkage, downstaging of the disease and increased rates of radical resection. The elimination of micrometastasis may decrease the risk of remote metastasis. There has been no large-scale randomized phase III study to show the efficacy of new adjuvant chemotherapy before the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial (18). The results of the MAGIC trial (16) found that perioperative chemotherapy improves the resection rate and disease-free survival, and the 5-year overall survival rate increased from 23 to 36%. Perioperative chemotherapy has therefore been written into the National Comprehensive Cancer Network guideline.

In China, neoadjuvant chemotherapy is also a focus for oncologists. Many studies focusing on the neoadjuvant setting have been reported recently. Fang *et al* reported that the oxaliplatin-leucovorin 5-fluorouracil (LV5FU2) regimen is effective and well-tolerated as a neoadjuvant therapy in patients with advanced gastric cancer (19). In the Yang and Wang study, the combination of docetaxel, cisplatin, 5-FU and LV increased the radical resection rate and was well tolerated (20). Today, neoadjuvant or perioperative chemotherapy has been accepted by more oncologists, and is especially recommended for patients with marginal resectable disease, with lymph node metastasis or locally advanced disease.

Furthermore, data have shown that preoperative radiotherapy may improve local control and survival. Zhang *et al* reported a randomized trial that resulted in a significant improvement in survival (30 vs. 20%; P=0.0094) and the resection rate (89.5 vs. 79%; P<0.01) with preoperative radiation compared with surgery alone (21). More studies in this setting are ongoing.

5. Adjuvant chemotherapy or chemoradiotherapy after surgery

Whether adjuvant chemotherapy is necessary after R0 resection has been debated for more than a decade. A small-scale randomized study found that adjuvant chemotherapy based on the semustine (ME-CCNU) and 5-FU regimen resulted in longer overall survival compared with surgery alone (22), although this result was not confirmed by a large-scale phase III trial (23).

In 1993, Hermans *et al* published a meta-analysis based on 11 trials reported between 1980 and 1991, in which adjuvant chemotherapy was compared with surgery alone and showed a non-significant trend towards improved survival [odds ratio, 0.88; 95% confidence interval (CI), 0.78-1.08] in favor of the chemotherapy group (24). In 1999, Earle and Maroun published a meta-analysis of 13 randomized clinical trials of adjuvant therapy conducted between 1980 and 1996; the regimens included 5-FU plus anthracene nucleus and 5-FU and/or nitrosourea (25). The hazard ratio was 0.80 (95% CI, 0.66-0.97), the mortality rate decreased by 4%, and patients with positive lymph nodes obtained more benefit than those with negative lymph nodes. These data indicate that adjuvant chemotherapy can result in small but statistically significant survival benefits for patients with gastric cancer undergoing R0 resection. In 2002, Janunger *et al* reported a meta-analysis that comprised 23 randomized controlled trials published from 1969 to 1996, and showed that the hazard ratio was 0.84 in favor of adjuvant chemotherapy (26). Further analysis showed that the data from Asia were statistically significant in favor of adjuvant chemotherapy, while the data from Europe and the USA showed no significant difference. Another meta-analysis based on 20 trials performed between 1983 and 1999 consisting of 3,500 patients was reported by members of the Gruppo Italiano per lo Studio dei Carcinomi dell' Apparato Digerente in Italy (27). The study showed a hazard ratio for death in the treated group of 0.82 (95% CI, 0.75-0.89), corresponding to an overall absolute risk reduction of approximately 4% in 5-year survival. A prospective phase III randomized trial was conducted in Japan to compare the effect of adjuvant chemotherapy with surgery alone. The results showed that the 3-year survival was 80.5% for the chemotherapy group and 70.1% for surgery alone (28). These data provide support for adjuvant chemotherapy after R0 resection of gastric cancer.

A key study, SWOG9008/INT0116, was reported in 2001, which included 556 patients with gastric cancer with lesions penetrating to the gastric wall and/or with regional node positivity but without remote metastases (29). The median follow-up duration was 5 years, and the median duration and the 3-year relapse-free survival rates were 30 months and 48%, respectively, for the adjuvant chemoradiotherapy group, and 19.9 months and 31%, respectively, for the surgery alone group (P<0.001). This trial provided evidence of adjuvant chemoradiotherapy, thereby improving the survival of patients with gastric cancer. However, many oncologists questioned whether the survival benefit may have resulted from the insufficiency of the surgery since only 10% of the patients in the trial received D2 resection and 54% of the patients received less than D1 resection. A Korean study achieved a positive result similar to the INT0116 trial, and it showed that adjuvant chemoradiotherapy decreased local recurrence and improved survival only for patients with T3-4N0M0 and T1-4N+ disease, but not for patients with T1-2N0M0 disease (30).

In China, adjuvant chemotherapy was considered to be the standard treatment for patients with gastric cancer who have positive lymph nodes or deeper than muscularis propria involvement. Currently, according to these adjuvant chemoradiotherapy data, more oncologists suggest that patients receive adjuvant chemoradiotherapy after surgery, if there are no major risk factors or insufficient surgery such as R1, R2 or R0 resection with D0 or D1 lymphadenectomy. Patients who cannot tolerate radiotherapy will receive chemotherapy alone. A valid question is which choice is best for patients with gastric cancer who accept surgery, i.e., perioperative chemotherapy, postoperative chemotherapy or chemoradiotherapy. There is still no consensus and more studies are needed to investigate this issue.

6. Palliative and salvage chemotherapy for metastatic patients

In the palliative chemotherapy setting of gastric cancer, there is still no standard regimen for either first- or second-

line chemotherapy. Before the newer drugs such as taxane and the third generations of platinum and capecitabine were introduced, the modified epirubicin, cisplatin, 5-fluorouracil (ECF; short-term infusion of 5-FU) and 5-FU plus cisplatin (FP) regimens were the most frequently used treatments in China. The treatment choices were widely enriched when more clinical trials using the new drugs were reported. The results of the ML17032 trial indicated that when replacing 5-FU with capecitabine in the FP regimen, the response rate was significantly improved (41 vs. 29%), and the overall survival was at least equal (with a trend towards improvement, 10.5 vs. 9.3 months) (31). The V325 trial showed that the addition of docetaxel to the CF regimen significantly increased time to progression (5.6 vs. 3.7 months), overall survival (9.2 vs. 8.6 months) and 2-year survival (18 vs. 9%) (32). The well-known Real-2 trial showed that oxaliplatin and capecitebine are not inferior to cisplatin and 5-FU in a 3-drug regimen (33). Currently, regimens based on taxane, oxaliplatin or capecitabine, or the ECF regimen and its modifications are the most prevalent for the palliative treatment of patients with metastatic gastric cancer.

Several domestic trials are ongoing using taxane, oxaliplatin or irinotecan (CPT-11) to treat patients with metastasis, most of which are phase II trials with small numbers of patients. Jin *et al* reported the results of a phase II trial using 5-FU plus CF and oxaliplatin in this setting at the American Society of Clinical Oncology meeting in 2002 (34). They showed that the regimen had a promising future. We also conducted a phase II trial to evaluate the efficacy and tolerability of the EOF5 regimen (epirubicin, oxaliplatin and 5-day continuous infusion of 5-FU) in patients with unresectable advanced or metastatic gastric cancer. Our trial demonstrated that the response rate and overall survival from the EOF5 regimen were 40% and 12.5 months, respectively (35). All of these trials have presented further evidence towards improving the management of metastatic gastric cancer.

7. Target therapy for patients with metastatic gastric cancer

For treatment of colorectal cancer (CRC), the target therapies of cetuximab and bevacizumab have greatly increased the efficacy of chemotherapy and have improved the time to progression and overall survival (36,37). At present, target therapy-based chemotherapy has become the standard treatment for metastatic CRC. However, the available data for target therapy, alone or in combination with chemotherapy, for gastric cancer are less than those for CRC. Most published data are from phase II studies, and no results from phase III multicenter randomized trials in this setting have been published. Shah *et al* reported a phase II trial of CPT-11 combined with cisplatin and bevacizumab to treat patients with metastatic gastric cancer in 2005 (38). After a median follow-up of 47 patients for 12.2 months, the time to progression and overall survival were 8.3 and 12.3 months, respectively, and the overall response rate in evaluable patients (n=34) was 65% with no significant increase in adverse events. In the Italian FOLCETUX trial (39), FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) plus cetuximab were used to treat patients with advanced gastric or esophageal gastric junction cancer. Of the 38 patients enrolled, 34 were evaluable, and the overall response rate and median time to progression were 44.1% and 8 months, respectively. After a median follow-up of 11 months, >55% of patients were still alive, and the estimated overall survival was 16 months. These data suggest that target therapy with a monoclonal antibody improves the efficacy of chemotherapy and provide a survival benefit to patients with gastric cancer, as in the case of colorectal cancer. Regarding the small molecular tyrosine kinase inhibitor, several small-scale studies have been reported. In a study of gefitinib for patients with metastatic gastric cancer who had failed second-line chemotherapy, only 1% of patients achieved partial response, and 16% achieved stable disease (40). Elotinib was also tested in a study of 70 patients with gastric or gastroesophageal junction adenocarcinoma. The overall response rate was found to be 12% for patients with gastroesophageal junction adenocarcinoma and 0 for those with gastric adenocarcinoma (41). Although these data indicate that the efficacy of a small molecular tyrosine kinase inhibitor in gastric cancer remains unproven, these data increase the treatment strategy for gastric cancer, together with a monoclonal antibody.

Target therapy is also very current in China, and many target studies are ongoing. Antiangiogenesis is a useful strategy for anticancer treatment, and it has been shown that the antiangiogenesis effect can inhibit the growth of tumors, increase the efficacy of chemotherapy and prolong the overall survival in several types of somatic tumors. Endostar is a new recombinant human endostatin which is designed and manufactured in China, and its antiangiogenesis effect has been shown in preclinical studies (42-44). A phase III randomized clinical trial conducted in China compared vinorelbine (NVB) plus Endostar vs. NVB alone patients with metastatic non-small cell lung cancer (45), and the results indicated that the addition of Endostar improved the efficacy of chemotherapy and significantly increased the time to progression and overall survival. Based on these results, we designed a phase II study of ECF combined with Endostar to treat patients with metastatic gastric cancer to improve the efficacy of usual chemotherapy (the ClinicalTrials.gov registration no. is NCT00595972).

Cetuximab, the monoclonal antibody targeting epidermal growth factor receptor (EGFR), has been widely used in CRC and some other somatic tumors. In patients with gastric cancer, the expression of EGFR is >40% (46). Based on the data from CRC, we designed a phase II trial using cetuximab plus FOLFIRI as a second-line treatment for metastatic gastric cancer, and the preliminary results revealed that this combination results in a higher response rate than the historical control (data not shown).

8. Future treatment for metastatic gastric cancer

Providing individual therapy for each gastric cancer patient is an ongoing objective. Thanks to the contribution of oncologists worldwide, thousands of clinical or preclinical studies have been conducted. Currently, we know that the k-ras mutation predicts whether patients derive benefit from cetuximab target therapy (47,48). Mutations of c-kit or platelet-derived growth factor receptors are predictors of the effect of imatinib in the treatment of gastrointestinal stromal tumors (49), and the

mutation of UGT-1A1 indicates the severity of adverse effects from irinotecan (50). These data suggest that the efficacy of chemotherapy and target therapy could be calculated in the near future. To be even more optimistic, each treatment will have its own predictors that may result in achieving individual treatment.

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