Original Article

Long-Term Outcome of A Large Series of Gastric Cancer Patients in China

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ABSTRACT

Objective: The outcome of gastric cancer treatment in China is relatively poor compared with those in Japan and Korea. Relevant factors are not quite clear till now. The aim of this study is to present data on gastric cancer patients from a single high volume cancer center of China and to illuminate relevant factors regarding unsatisfactory outcome.

Methods: A total of 2312 consecutive pathologically proven gastric carcinoma patients were treated in Beijing Cancer Hospital from January 1995 to December 2005. Clinical information including demographic information, tumor characteristics, therapeutic experience and survival was retrieved from the Database specially designed for Gastric Cancer Collaborative Group, Beijing Cancer Hospital.

Results: There were 1633 males and 679 females with a median age of 58.8 years (range 19–89). Merely 181 patients were in the early stage (7.8%). Curative resection was performed in less than 72% of the patients. The number of lymph nodes harvested varied from 0 to 71 (average 9) while the median number of positive lymph node was 2 (0–37). Only in 650 patients the number of lymph nodes harvested was more than 14. At the end of follow-up, 874 patients were still alive while 1132 died. The 1, 2, 5, 10-year overall survival were 68.50%, 51.88%, 36.83%, and 30.49%, respectively. Multivariate analysis demonstrated that TNM stage, tumor location, tumor size, surgery, and vascular invasion were independent prognostic factors.

Conclusion: The outcome of gastric cancer in China is not as good as expected. Early detection and standardized curative resection should be prompted at present to improve the outcome.

Key words: Gastric cancer; Management; Outcome

INTRODUCTION

Gastric cancer is rampant in many countries in the world, especially in Japan, Costa Rica, Peru, Brazil, China, Korea, Chile, and former Soviet Union[1–2]. Gastric cancer is often diagnosed at its early stage in countries as Japan and Korea where cancer screening is quite prevalent[3–7]. The mainstay of armamentarium against gastric cancer proves to be surgery, while multi- modality therapy integrating chemotherapy and radio- therapy is becoming more and more popular in recent years[8-10].

Generally speaking, the outcomes of gastric cancer patients in Asian countries are better than those in Western countries. The 5 year survival rate is 40%–60% compared to 20%–30% in Western countries. There have been controversies between Japanese and Western scholars about the etiology, histopathology, prevention, and management of gastric cancer for a long time[11]. The age of onset is approximately ten years younger in Japan, and ethnicity is not observed to be an independent

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prognostic factor according to Japanese viewpoint[12–14]. Standard D2 dissection is advocated by Japanese scholars while the rate of D2 dissection in Western clinical trials is relatively low[15, 16].

However, the data were generally from Japan. Though several reports have been issued in domestic journals or conference proceedings, few regarding the outcome of gastric cancer in China were available in English literatures. This study tries to give insight into the result and problematic nature of gastric cancer in China. In this article, we will present the data of 2312 gastric cancer patients treated in a single Chinese cancer center from 1995 to 2005.

MATERIALS AND METHODS

Patients

A total of 2312 consecutive pathologically proven gastric carcinoma patients were treated in Beijing Cancer Hospital from January 1995 to December 2005. The data of these patients were retrieved from the Database specially designed by Beijing Cancer Hospital. The database includes demographic information, tumor characteristics such as tumor size, tumor grade, histology, tumor stage, therapeutic information including details of the surgical intervention. The survival data were obtained from the follow-up group of Beijing Cancer Hospital, as well as direct contact with the patients and or their relatives. Patients with incomplete information were excluded.

Clinical Management

Newly diagnosed gastric cancer patients underwent complete history & physical examination (H&P), complete blood account (CBC), biochemical assays, blood coagulation assay and electrocardiogram (ECG). Patients more than 65 years old or with concomitant pulmonary disease were subject to pulmonary function evaluation. Gastroscopy with biopsy was warranted. Barium meal in proximal gastric cancer was necessary, especially when lower esophagus invasion was suspected. Chest X ray, computed tomography (CT) scan were performed generally to rule out extra-abdominal metastasis and to evaluate the feasibility of surgical resection. A pelvic CT scan or ultrasound was also recommended for women. Endoscopic ultrasound (EUS) was recommended for patients with potential resectable cancer.

Curative resection of gastric cancer together with D2 lymph node dissection was attempted. Patients with early stage gastric cancer might undergo local gastrectomy, subtotal gastrectomy with D1 lymphadenectomy or less. The surgical margins were more than 4 cm proximally and 2 cm or more distally for curative resection. Prophylactic splenectomy and distal pancreactomy were not performed except for tumor involvement. Resection of involved adjacent organs such as liver, spleen, and colon might be prudently performed in view of curative attempt. Gastro-intestinal reconstruction with various procedures might be used in cases of total gastrectomy. When curative resection was impossible, mostly under circumstances as peritoneal metastasis, liver metastasis and major vessel invasion, the alternatives would be palliative resection, gastro-intestinal bypass or surgical exploration when massive bleeding or outlet obstruction was present. Palliative resection was defined as removal of gastric tumor with the evidence of residual tumor including peritoneal metastasis, liver metastasis, lung metastasis, and/or lymph node metastasis. Neoadjuvant chemotherapy with oxaliplatin- or paclitaxol-based regimens was carried out in some patients with advanced lesions.

Tumor location, histological type and vascular invasion were recorded as well as histological grade. Pathologic staging was reported according to the TNM staging system (UICC, 1997). Patients with pathological stage II or more advanced were generally subjected to postoperative chemotherapy, with 5-fluororacil-based regimens for six months, if economically feasible. The patients were followed-up every 3 months for two years and then every 6 months for the next three years, and then annually.

Statistical Analysis

Analyses were performed with SPSS 12.0 for Windows (SPSS Inc., Chicago, IL). $P<0.05$ (two sided) was considered statistically significant. The χ^2 test or Fisher's exact test was used to compare qualitative variables. Student's *t*-test was used for quantitative variables if they were assumed to follow a normal distribution. Quantitative nonnormal variables were compared by using the Mann-Whitney U-test or the Kruskal-Wallis test. The effect of each prognostic variable was studied in univariate analysis with Kaplan-Meier method. Variables with a P value <0.05 were considered candidates to enter a multivariate Cox regression model.

Table 1. *Cumulative survival and events in 2312 patients with gastric cancer*

Time(month)	12	24	36	48	60	120
Cumulative survival	0.6850	0.5188	0.4406	0.3971	0.3683	0.3049
Cumulative evants	649	924	1031	1080	1106	1131

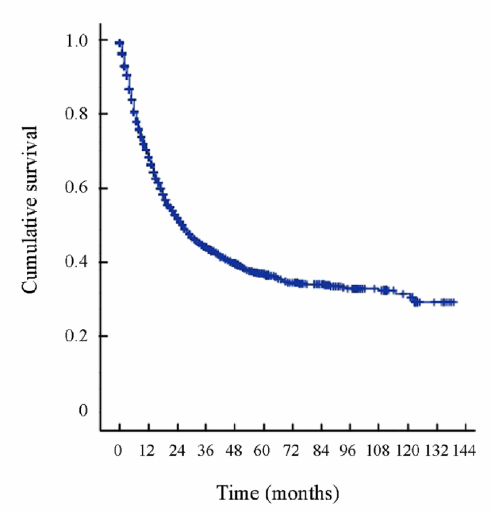

Figure 1. Survival curve of the 2312 gastric cancer patients.

RESULTS

Characteristics of the Patients

A total of 2312 consecutive gastric cancer patients, 1633 males and 679 females with a median age of 58.8 years (range 19–89), were treated in Beijing Cancer Hospital during this period. Nearly one third of the lesions located in the lower third of the stomach (32.5%), 24.7% (n=571) in the upper third, 20.6% (n=476) in the middle third, 11.2% (n=258) involving two parts of the stomach, and 9% (n=207) invading the whole stomach. Still there were 48 cases of which the locations were hard to define. As to Borrmann classification, there were 309 cases of type I, 237 type II, 1114 type III, and 535 type IV, respectively, leaving 117 cases undefined. More than 60% of the lesions were larger than 4 cm. 31.4% of the patients was identified as metastatic disease.

Clinical Management

Over 90% of the patients had symptoms related to gastric carcinoma. The most common symptoms were weight loss, anorexia, and supra-abdominal pain or mass. For gastric cancer patients with curative resection, the procedures included proximal gastrectomy, distal gastrectomy, and total gastrectomy with Roux-Y, loop, or interpositional reconstruction.

The number of lymph nodes harvested varied from 0 to 71 (average 9) while the median number of positive lymph node was 2 (0–37). In this series of patients, only in 650 patients the number of lymph nodes harvested was more than 14.

Surgical complications were defined as incision dehiscence, anastomotic leakage, subphrenic abscess, pneumonia, pulmonary failure, anastomotic narrowing, acute pancreatitis, alimentary hemorrhage, stress ulcer, thrombosis, and so on. Among the 1882 patients undergone surgical resection, 109 patients (5.8%) were documented to have postoperative complications. Perioperative mortality was defined as mortality within 30 days or in-hospital mortality, when still admitted beyond 30 days. The mortality rate was 4.2% (79/1882).

Survival Analysis

At the end of follow-up, 874 patients were still alive while 1132 died. Three hundred and six patients were lost of follow-up with a missing rate of 11.6%. The median time of follow-up was 13 (1–139) months. The 1, 2, 5, 10 year overall survival were 68.50%, 51.88%, 36.83%, and 30.49%, respectively (Table1, Figure 1).

Univariate analysis was performed and showed that tumor invasion depth, lymph node metastasis, distant metastasis, tumor location, TNM stage, pathology, gross type, surgery, vascular invasion, and neoadjuvant chemotherapy were prognostic factors (Table 2).

Because of insufficient information of some variables, we performed subgroup analysis for neoadjuvant chemotherapy (Figure 2), location, surgery, pathology and gross type. No statistical significant survival superiority was found in neo-adjuvant chemotherapy group compared with the control. Variables as TNM stage, pathology, gross type, tumor size, tumor location, surgery and vascular invasion were introduced into the Cox proportional hazards model and analyzed using the Backward: Wald method. The results demonstrated that TNM staging, tumor location, tumor size, surgery, and vascular invasion were independent prognostic factors (Table 3). The survival curves produced with Kaplan-meier method were illustrated in Figure 3, respectively.

Table 2. *Univariate prognostic analysis of 2312 gastric cancer patients*

	No.	Percent	Chi square	*P* value
Gender			2.44*	0.1183
Male	1633	70.6		
Female	679	29.4		
T (n=1890)			309.04	0.0000
Tis	6	0.3		
T1	175	9.3		
T2	742	39.3		
T3	811	42.8		
T4	156	8.3		
N (n=1645)			344.66	0.0000
N0	504	30.6		
N1	625	38.0		
N2	339	20.6		
N3	177	10.8		
M (n=2170)			679.07	0.0000
M0	1488	68.6		
M1	682	31.4		
Stage			862.39	0.0000
0	5	0.2		
I	391	16.9		
II	355	15.4		
III	496	21.5		
IV	945	40.8		
NS	120	5.2		
Surgery			1039.77	0.0000
Curative	1207	52.2		
Palliative	494	21.4		
No resection	181	7.8		
NS	430	18.6		
Pathology			91.32	0.0000
High differentiated	107	4.6		
Middle differentiated	775	33.5		
Low differentiated	1003	43.4		
Mucous	110	4.8		
Signet-ring cell	97	4.2		
Others	39	1.7		
NS	181	7.8		
Vascular invasion			548.93	0.0000
No	784	33.9		
Yes	832	36.0		
NS	696	30.1		
Neoadjuvant chemotherapy (n=2201)			279.69	0.0000
No	1717	78.0		
Yes	160	7.3		
NS	324	14.7		
Location of tumor in stomach			206.71	0.0000
U	571	24.7		
M	476	20.6		
L	752	32.5		
Involve two parts	258	11.2		
Total stomach	207	8.9		

(*to be continued*)

(*continued*)

NS	48	2.1		
Gross type			249.11	0.0000
Borrmann I	309	13.4		
Borrmann II	237	10.2		
Borrmann III	1114	48.2		
Borrmann IV	535	23.1		
NS	117	5.1		
Size of tumor			228.38	0.0000
<4 cm	689	29.8		
≥4 cm	1461	63.2		
NS	162	7.0		

*: t value; U: upper third; M: middle third; L: lower third; NS: not specified

Table 3. *Multivariate prognostic analysis of 2312 gastric cancer patients*

	HR (95.0% CI)	*P* value
Stage		0.000
I	0.001 (0.000–2.282)	0.880
II	0.631 (0.391–1.018)	0.059
III	1.425 (0.920–2.207)	0.113
IV	2.009 (1.335–3.022)	0.001
NS	2.064 (1.503–2.835)	0.000
Location of tumor in stomach		0.001
U	0.711 (0.466–1.087)	0.115
M	0.599 (0.390–0.920)	0.019
L	0.537 (0.353–0.818)	0.004
Total	0.726 (0.469–1.122)	0.149
Unknown	0.719 (0.463–1.117)	0.142
Size		0.005
<4 cm	1.010 (0.722–1.414)	0.953
≥4 cm	1.292 (0.945–1.768)	0.109
Surgery		0.000
Curative	0.204 (0.137–0.305)	0.000
Palliative	0.461 (0.339–0.628)	0.000
NS	1.138 (0.895–1.448)	0.292
Vascular invasion		0.000
None	0.664 (0.500–0.883)	0.005
Yes	1.078 (0.826–1.407)	0.581
Age	1.006 (1.001–1.011)	0.017

U: upper third; M: middle third; L: lower third; NS: not specified; HR: hazard ratio; 95%CI: 95% confidence interval

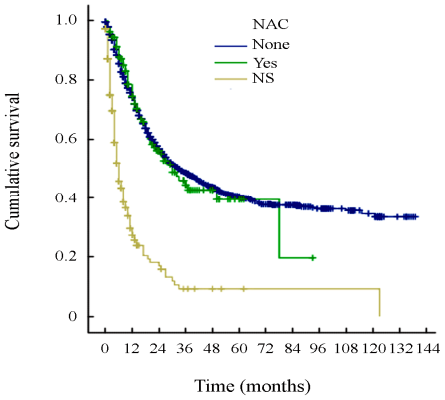

Figure 2. Survival curve of gastric cancer patients with/without neoadjuvant chemotherapy(NAC) (*P*>0.05).

DISCUSSION

The 5 Year Overall Survival Rate

The 5 year overall survival rate of gastric cancer was 36.83% in this series of 2312 patients, which was comparable to other domestic reports[17–20]. Chen et al in the General Hospital of PLA recently reported the surgical treatment result for 2335 gastric cancer patients treated between 1996 and 2005[18]. The 1-, 3-, and 5-year survival rate were 71.9%, 45.3%, and 40.1%, respectively. A relatively small number of cohort in Tianjin Cancer Hospital with 814 gastric cancer patients demonstrated that the 1-, 3-, and 5-year survival rate were 71.87%, 45.33%, and 40.05%[19]. Zhan et al reviewed the database of 2561 gastric cancer patients during the past 40 years and demonstrated an increase of survival rate from 18.0% to 37.5%. Even improvement of clinical outcome of gastric cancer patients has been made by Chinese peers, it was far below expectation and other Asian reports[21–23]. The best treatment result was made in Japan, about 70% at the peak, and generally 50%–60%[21]. Recently Hyung et al.[22] evaluated the changes in treatment outcomes of gastric cancer surgery over 45 years at Yonsei University, Korea. A total of 9282 patients with gastric cancer from 1955 to 1999 were reviewed and showed that the overall 5-yr survival rate significantly increased from 22% to 65%. Further analysis revealed that increased early diagnosis of early stage gastric cancer considerably

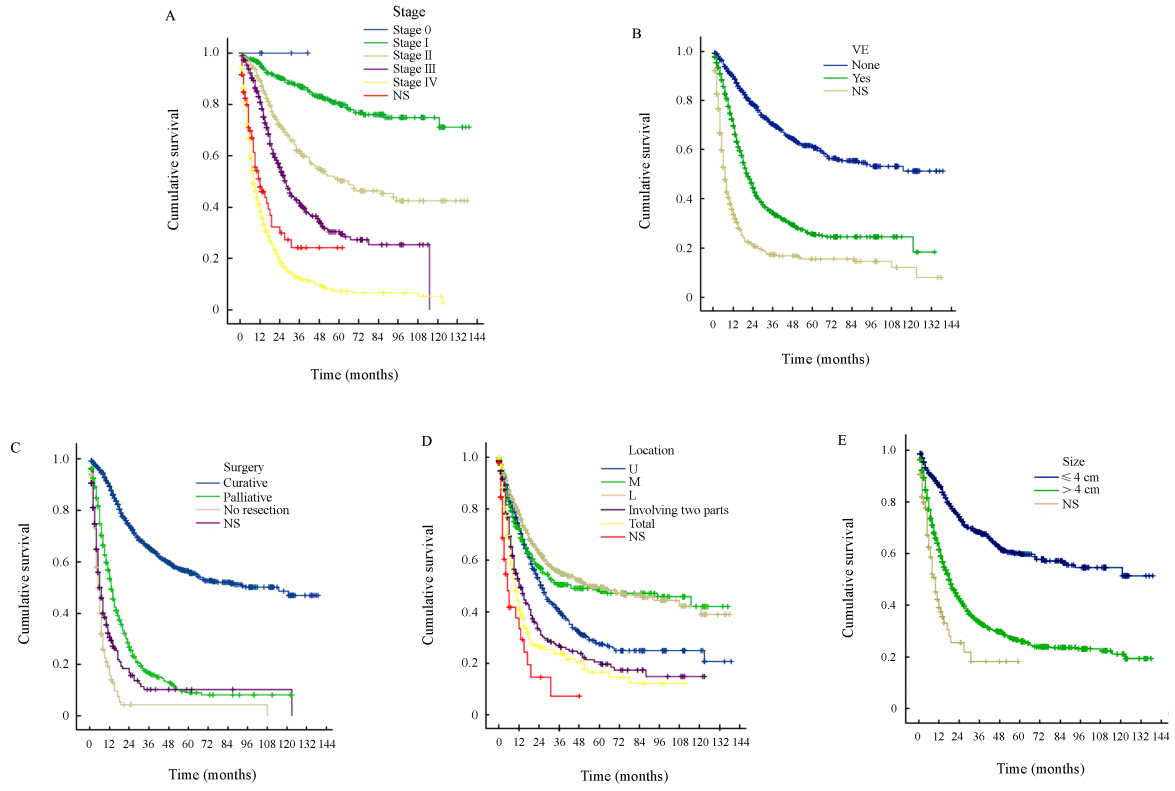

Figure 3. Survival curve of 2312 gastric cancer patients. (A) Overall survival by different stages (P<0.05); (B) Overall survival with/without vascular invasion (VE) (P<0.05); (C) Overall survival by surgery (P<0.05); (D) Overall survival by location of tumor (P<0.05); (E) Overall survival by tumor size (P<0.05).

contributed to the improved survival of gastric cancer patients. That was also one of the reasons accounting for the better outcome of Japanese gastric cancer patients[23].

The Rate for Early Gastric Cancer

Relative low rate of early gastric cancer are common in China, varying from 5%–15%[17–20]. In this series, merely 181 patients were in the early stage (7.8%), while more than 90% were local advanced or metastatic gastric cancer. Early gastric cancers has increased up to 32% in Korean reports, partly because of the prevalence of this malignancy, which called for population awareness and more common endoscopic or radiologic examinations[22]. One report from Japan also found favorable changes in the numbers of patients with early gastric cancer. In 2,152 gastric cancer cases from 1965 to 1995, the rate for early gastric cancer was 18% in the first 6 year, and 57% in the last 5 year. It was due to large scale screening program nationwide for gastric cancer. In the 15-year period 1970 to 1984, the Detection Center of Hokkaido Cancer Society discovered 2,508 gastric cancer cases among 2.01 million people with favorable outcome. The relative survival rate was 67.8% for 5-year, 64.0% for 10-year and 63.5% for 15-year[24].

These results demonstrated that early detection led to a relative good survival rate. In China, mass screening of gastric cancer may not be accessible because of non-cost-effectiveness, while opportunistic screening of high-risk individuals was adopted. The availability of endoscopic instruments and expertise for mass screening remains questionable, even in developed countries such as Japan. Unfortunately, there were no cost-effective methods for early detection of gastric cancer available to date. There is still a paucity of qualified data from Asia supporting screening for gastric cancer[7]. Maybe the best way is to increase the awareness of high risk population as well as mass screening for them.

Curative Resection Rate for Patients of Stage III and IV

Patients of stage III and IV consisted of approximately 65%, making curative resection rate

less than 60%, much lower than that of Korea and Japan, which was about 80% or higher[22-23]. Survival after curative resection was 56.43% in our group, still lower than 70.2% of Korean patients treated during 1989–1999, but higher than 12.4% from 1973 to 1982 and 30.4% from 1983 to 1988. Actually the curative resection did not include the extent of lymph node dissection.

Lymph Node Dissection

In the last decade, D2 dissections have gained popularity in some Western countries as well, yet no worldwide consensus regarding the extent of lymph node dissection. Nonrandomized gastric cancer studies from Germany, England, Norway, USA and some centers in Netherlands, have reported promising results with a postoperative mortality between 4% and 5% and morbidity between 22% and 30.6% with a better 5-year survival of 26.3% to 55% for D2 dissections. Most of the studies mentioned above were randomized controlled clinical trials well designed with good quality control. It was not the case in China. In the unpublished data in this series, D1+ or D2- or not standard Dx lymph node dissection was generally done in Chinese hospitals. For example, standard D2 dissection for distal gastric cancer should include lymph node 11p. Surgeons might adjust the extent of lymph node dissection according to what they found during the operation, which was quite common among Chinese gastrointestinal (GI) surgeons.

In addition to non-standardized surgery, pathologist was another factor for low lymph node harvest. Standardization of lymph node dissection was carried out nationwide in China in recent years, according to the Japanese Clinical Oncology Group (JCOG) guidelines. Therefore the question whether there was difference between D2 or D1 dissection could not be answered in this retrospective study. The impact of surgeon expertise on difficult surgical procedures and the observed associations between hospital volume and operative mortality are largely determined by surgery volume per surgeon. Most of the GI surgeons in our hospital performed gastric cancer surgery with high volume and low morbidity and mortality. The influence of surgery volume on long-term outcome of gastric cancer was not indicated in this study.

Proximal Gastric Cancer

Another difference between Korean reports and ours is the proportion of proximal tumor, which were 7%–13% and 23.7%, respectively. The proximal tumor has a much poorer prognosis than tumors of other locations. The 5 year overall survival of proximal tumor was not higher than 12.5% in Korean report, 28.97% in Zhan's report, and 27.49% in our series. One report from China showed that the resection rate increased from 69.6% to 94.8% for cancer of the gastric cardia between September 1952 and December 2000. But there was little change in the overall 5-year survival rate, increasing from 15.2% to 17.6%[25]. The prognosis of the proximal cancer has been reported to be poor for various reasons[26-28]. Increasing numbers of total gastrectomy and the complicated biologic features of proximal gastric cancers, especially esophagogastric junction cancers, require more sophisticated treatment strategies. As suggested by Siewert[29-31], to classify the proximal gastric cancers into three types according to location and to provide different operative options based on their classification may be a reliable treatment strategy for proximal cancers. The inconsistency of management of proximal gastric cancer has been existed for a long time. In China, proximal gastric cancer may be treated by either thoracic or abdominal surgeons via different approaches, including transhiatal or transthoracic, with different emphasis on lymph node dissection.

The Prognosis of Gastric Cancer Has Not Been Remarkably Improved

The present study confirmed that the prognosis of gastric cancer has not been remarkably improved even after many efforts throughout dozen of years. As to Korea and Japan, the improvement in survival was resulted mainly from host factors, the increase of early stage patients, which led to the increase of curative resection rate. However, the survival improvement in stages II and III might be due to recent advances in surgical treatment, including systematic lymph node dissection and postoperative adjuvant chemotherapy. Furthermore, the relatively worse outcome in Chinese gastric cancer patients in our series might be influenced by the relatively short time of follow up. The median follow up time was only 13 months. And the missing rate exceeded 10%. In China, even in specialized cancer hospitals, follow-up remained difficult as patients might come from all over the country, either rural or civil areas. People migration was quite common in China, especially in recent years with rapid economic development. Gastric cancer patients might refer to hospitals of various scales in China. Curative resection was generally attempted at diagnosis if resectable, otherwise they would be transferred to chemo- radiation or supportive care. The extent of

lymph node dissection was generally larger than D1 but not the standard D2 dissection recommended by JCOG. No standard adjuvant chemotherapy regimen has been established till now[17] and patients may have different opinions and compliance towards chemotherapy, for example, refusal or acceptance without informed consent as required by their relatives.

In all, the outcome of gastric cancer in China was not as good as expected. Early detection and standardized curative resection should be prompted at present.

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