RESEARCH COMMUNICATION

Multivariate Survival and Outcome Analysis of 154 Patients with Gastric Cancer at a Single Chinese Institution

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Abstract

This study was conducted to analyze and elucidate key prognostic factors for gastric cancer (GC), and to understand the current status of GC diagnosis and treatment in Hubei Province, China. Major clinical and pathological information on 154 GC patients was retrospectively collected, including gender, age, tumor site, surgical approach, histological type, TNM stage and chemotherapy cycles. Overall survival (OS) was analyzed in relation to these factors. The median OS was 12.0 months (0.5-69.0 months), and 1-, 2-, 3- and 5-year survival rates were 53.0%, 23.0%, 8.0% and 1.0%, respectively. The median OS by TNM stage was 21.0 months for stages I+II and 11.5 months in stages III+IV (P=0.043), and 1-, 2-, 3- and 5-year survival rates were 72.0% vs 50.0%, 40.0% vs 19.0%, 16.0% vs 6.0% and 0% vs 1.0 %, respectively. The median OS by chemotherapy cycles was 18.0 months in chemotherapy ≥6 cycles group and 11.0 months in chemotherapy <6 cycles group (P=0.009), and 1-, 2-, 3- and 5-year survival rates were 68.0% vs 49.0%, 41.0% vs 18.0%, 12.0% vs 7.0% and 0% vs 1.0%, respectively. Multivariate analysis identified tumor site, surgical approach and chemotherapy cycles as independent predictors for improved survival. Implementation of standardized radical surgery and reasonable adjuvant therapy could improve survival and prognosis of GC patients.

Keywords: Gastric cancer - clinico-pathological factors - multivariate analysis - China

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Introduction

According to GLOBOCAN 2008, gastric cancer (GC) is the fourth most common malignant tumors worldwide, with a total of 989,600 new GC cases and 738,000 deaths to have occurred in 2008, accounting for 8% of the total cases and 10% of total deaths. Over 70% of new cases and deaths occur in developing countries, particularly in China, where GC ranks the third cancer killer, with an estimated mortality of 27.41/100,000, according to the statistics from China's Ministry of Health. Multi-disciplinary comprehensive treatment is the only treatment strategy to improve survival and quality of life. A sound decision-making strategy depends on comprehensive analysis of pathological features, clinical stages, surgical principles and technical standardization, adjuvant therapy and other important factors. This study is to understand the current status of GC diagnosis and treatment in Hubei Province of central China, based on the analysis of clinico-pathological data of 154 GC patients with complete information on treatment and survival.

Materials and Methods

Complete clinico-pathological information on 154 GC patients who received curative resection at the Department of Oncology, Zhongnan Hospital of Wuhan University and Hubei Provincial Cancer Hospital, between January 2004 and December 2010 were collected. All patients were followed up from the date of surgery, and the last follow-up was on April, 30, 2011. All these 154 cases of GC had complete survival information. From inpatient medical files and outpatient follow-up records, complete clinical and pathological information on 154 GC patients was obtained, including gender, age, tumor site, surgical approach, histological type, TNM classification (7th edition of the AJCC cancer staging manual), chemotherapy cycles and other treatments. The primary end point was disease-specific overall survival (OS), defined as the time interval from the date of surgery to the date of GC-related death. The secondary end points were independent factors related to OS.

Statistical analysis

A comprehensive database containing all the clinico-pathological information was established. Statistical analyses were performed with SPSS statistical software, version 17.0 (SPSS, Chicago, IL, USA). OS were estimated by the Kaplan–Meier method, and Log-rank test was used to test the differences in OS of subgroups. The Cox proportional hazards model was used for the multivariate analysis of independent factors of OS.

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Table 1. Major Clinico-Pathologic Characteristics of the 154 GC Patients

Variables		N (%)
Gender	Male	99 (64.3)
	Female	55 (35.7)
Age (yr)	<65	104 (67.5)
	≥65	50 (32.5)
Tumor Site	Upper third	35 (22.7)
	Middle third	37 (24.0)
	Lower third	70 (45.5)
	Total stomach	12 (7.8)
Surgical Approach	PG	37 (24.0)
	DG	73 (47.4)
	TG	44 (28.6)
No of Lymph	<7	99 (64.3)
Nodes Dissected	≥7	55 (35.7)
Lymph Nodes Status	N0	28 (18.2)
	N1	31 (20.1)
	N2	43 (27.9)
	N3	52 (33.8)
Serosa Invasion	No	12 (7.8)
	Yes	142 (92.2)
Histological Typing	sAC	104 (67.5)
	MAC	24 (15.6)
	UDC	26 (16.9)
TNM Stage	I	5 (3.3)
	II	20 (13.0)
	III	114 (74.0)
	IV	15 (9.7)
Chemotherapy Cycles	≥6	34 (22.1)
	<6	120 (77.9)

AC, adenocarcinoma; MAC, mucinous adenocarcinoma; UDC, undifferentiated carcinoma; PG, proximal gastrectomy; DG, distal gastrectomy; TG, total gastrectomy

Significance was defined as $P < 0.05$.

Results

Patient characteristics

Among all 154 GC patients were 99 males and 55 females, with a male to female ratio of 1.8:1, and ages ranging from 20 to 85 years (median 58 years). Based on the World Health Organization (WHO) criterion, 104 (67.5%) patients were classified as the non-elderly group (<65 years) and 50 (32.5%) patients the elderly group (≥65 years). Major clinic-pathological features were listed in Table 1.

Overall Survival

The median OS of 154 GC patients was 12.0 months (0.5-69.0 months), and 1-, 2-, 3- and 5-year survival rates were 53.0%, 23.0%, 8.0% and 1.0%, respectively. The median OS by TNM stage was 21.0 months in stage I+II and 11.5 months in stage III+IV (P=0.043, Figure 1), and 1-, 2-, 3- and 5-year survival rates were 72.0% vs 50.0%, 40.0% vs 19.0%, 16.0% vs 6.0% and 0% vs 1.0 %, respectively. The median OS by surgical approach was 12.5 months in proximal gastrectomy, 15.0 months in distal gastrectomy and 10.0 months in total gastrectomy (P=0.013, Figure 2), and 1-, 2-, and 3-year survival rates were 54.0% vs 62.0% vs 39.0%, 27.0% vs 27.0% vs 11.0%, 5.0% vs 12.0% vs 2.0%, respectively. The median OS by chemotherapy cycles was 18.0 months in chemotherapy ≥6 cycles group and 11.0 months in chemotherapy <6 cycles group (P=0.009, Figure 3), and 1-, 2-, 3- and 5-year survival rates were 68.0% vs 49.0%, 41.0% vs 18.0%, 12.0% vs 7.0% and 0% vs 1.0%, respectively.

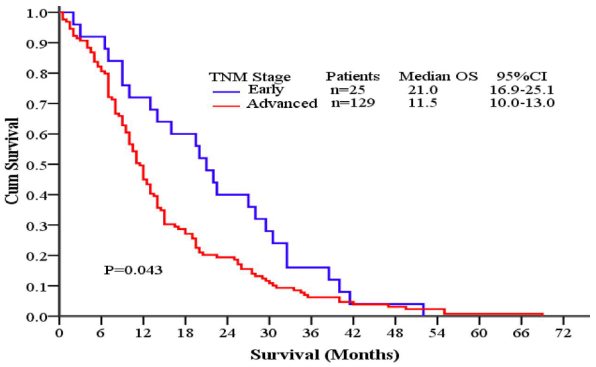

Figure 1. Survival Differences of GC Patients Between Early Stage (I+II) and Advanced Stage (III+IV)

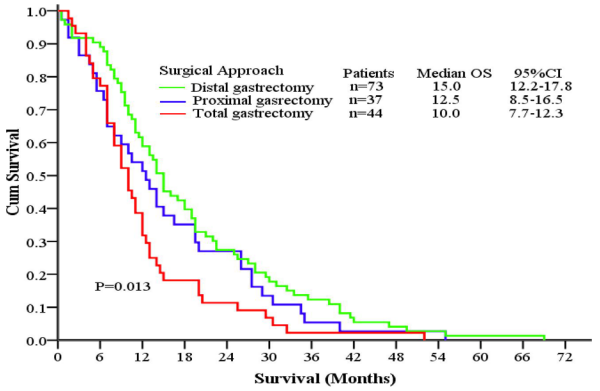

Figure 2. Cumulative Survival Relative to Gastrectomy

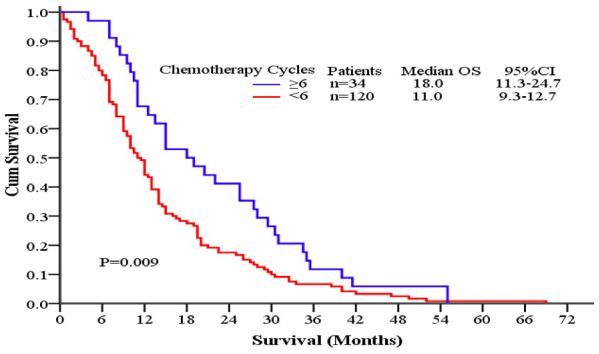

Figure 4. The Cumulative Survival of GC Patients with Different Chemotherapy Cycles

Univariate analysis on OS related factors

Univariate analysis identified five factors that had statistically significant associations with OS following a curative resection: tumor site (P=0.010), surgical approach (P=0.013), lymph nodes status (P=0.013), TNM stage (P=0.043) and chemotherapy cycles (P=0.009). Other factors were not statistically significant, such as gender, age, serosa invasion and histological typing (P>0.05) (Table 2).

Multivariate analysis on OS related factors

Five variables were entered into multivariate logistic regression to identified independent factors associated

Table 2. Univariate Analysis on the Relationship Between OS and Clinical Factors in 154 Cases

Variables	N (%)	Median OS (Range)	P*
Gender			
Male	99 (64.3)	12.0 (9.8-14.2)	0.368
Female	55 (35.7)	13.0 (11.0-15.0)	
Age			
<65	104 (67.5)	12.0 (10.2-13.8)	0.481
≥65	50 (32.5)	12.5 (10.0-16.0)	
Tumor Site			
Upper third	35 (22.7)	10.5 (5.3-15.7)	0.01
Middle third	37 (24.0)	10.0 (8.0-12.0)	
Lower third	70 (45.5)	15.0 (11.6-18.4)	
Total stomach	12 (7.8)	9.0 (7.3-10.7)	
Surgical Approach			
PG	37 (24.0)	12.5 (8.5-16.5)	0.013
DG	73 (47.4)	15.0 (12.2-17.8)	
TG	44 (28.6)	10.0 (7.7-12.3)	
No of Lymph Node Dissected			
<7	99 (64.3)	11.0 (8.9-13.1)	0.889
≥7	55 (35.7)	13.0 (11.3-14.7)	
Lymph Nodes Status			
N0	28 (18.2)	13.5 (1.8-25.2)	0.013
N1	31 (20.1)	20.0 (15.1-24.9)	
N2	43 (27.9)	11.0 (9.1-12.9)	
N3	52 (33.8)	10.0 (8.0-12.0)	
Serosa Invasion			
No	12 (7.8)	22.5 (12.3-32.7)	0.07
Yes	142 (92.2)	12.0 (10.4-13.6)	
Histological Typing			
AC	104 (67.5)	10.5 (10.3-14.7)	0.244
MAC	24 (15.6)	10.0 (8.4-11.6)	
UDC	26 (16.9)	15.0 (10.0-16.0)	
TNM Stage**			
Early	25 (16.2)	21.0 (16. -25.1)	0.043
Advanced	129 (83.8)	11.5 (10.0-13.0)	
Chemotherapy Cycles			
≥6	34 (22.1)	18.0 (11.3-24.7)	0.009
<6	120 (77.9)	11.0 (9.3-12.7)	

*Log-rank test (two-tailed); **early stage include I+II stage; advanced stage include III+IV stage

Table 3. Multivariate Cox Regression Analysis of Clinico-pathological Factors and OS

Variables	Regression Coefficient	P *	Hazard ratio (95%CI)
Tumor Site	0.381	0.003	1.464 (1.135-1.890)
Surgical Approach	-0.313	0.004	0.732 (0.593-0.903)
Chemotherapy Cycles	-0.702	0.001	0.496 (0.333-0.737)
Lymph Nodes Status	0.183	0.058	1.201 (0.994-1.452)
TNM Stage	0.409	0.148	1.505 (0.865-2.619)

*Log-rank test (two-tailed)

with OS. It was found that tumor site (P=0.003), surgical approach (P=0.004) and chemotherapy cycles (P=0.001) were independent factors associated with OS, but lymph nodes status and TNM stage were not statistically significant (P>0.05) (Table 3).

Discussion

Based on 2007 cancer registration across China, GC was the number one cancer in terms of incidence rate and mortality rate in rural areas, and the number three cancer in urban areas. Therefore, GC remains the top priority in China's anti-cancer campaign. Multi-disciplinary comprehensive treatment is the only treatment strategy to improve survival and quality of life. A sound decision-making strategy depends on comprehensive analysis of pathological features, clinical stages, surgical principles and technical standardization, adjuvant therapy and other important factors. Therefore, this study is focused on analyzing these major factors.

On pathological features, the study found that histological typing was not an independent prognostic factor of GC. This is not in conformity with many previous studies, which concluded that histological typing is an important factor to assess progression and prognosis of GC. On the other hand, there are some studies also indicating that histological typing is not associated with OS of GC. Maybe the typing methods could account for such contradictory conclusions. It has been well documented that Lauren histological classification is a simple and practical typing method to have significant correlation with long-term survival of GC. In a recent analysis of 308 GC patients from China, Deng et al also indicated that Lauren classification had a significant correlation with both loco-regional recurrence and distant metastasis after curative surgery. The diffuse type Lauren classification was associated with poor tumor differentiation, higher tumor cell proliferation and stronger tumor infiltration, which all increase the risk of loco-regional dissemination. In our study, however, we did not adopt the Lauren classification. This could be the reason why we did not found correlation of histological types with OS. As numerous studies have confirmed that Lauren classification is closely associated with malignant behaviors of GC, we need to adopt this classification in our future work.

On clinic stage, this study found that 25 (16.2%) patients were early stage (I+II) and 129 (83.8%) patients were advanced stage (III+IV). Our finding is in keeping with a recent large scale study of 1,503 GC patients in China, which revealed that 19.6% were early stage and 80.4% advanced stage, according to 7th edition of the AJCC cancer staging criteria. Our finding is different from the report of Li et al, who based on 6th edition of the AJCC cancer staging criteria, revealed that 39.6% were early stage and 60.4% advanced stage. All these results across China confirm the same fact that great majority GC patients are at least locally advanced disease at the time of first treatment. Although surgery is currently the most effective localized treatment, for most such patients however, surgical treatment only could not provide cure. Other comprehensive treatment options in an addition to surgery should be actively recommended.

On surgical principles and technical standardization, the study showed that surgical approach was the independent factor correlated with prognosis of GC. Among the 154 GC patients undergone curative resection, the median OS was 12.5 vs 15.0 vs 10.0 months in proximal gastrectomy, distal gastrectomy and total gastrectomy, respectively (P=0.013). This study found that the prognosis of OS was worst for total stomach tumor, intermediate for middle third and upper third stomach tumor, relatively better for

lower third GC. Our result is different from the previous Chinese report that the prognosis of upper third stomach tumor was worst. Several reasons could account for such difference. Firstly, the proportion of middle third GC patients received total gastrectomy was less in this study. This could make the curative resection was not curative in reality. Secondly, tumor of middle third stomach is more prone to spread both upward and downward and through the relatively richer vascular and lymphatic networks. Thirdly, total gastrectomy could have a more serious negative effect on the quality of life of GC patients, particularly in patients with inadequate nutrition support. In a standardized surgical operation on GC, lymph nodes dissection is a key procedure. According to the most recent 7th edition of the AJCC cancer staging criteria, N stage could be defined only when the number of lymph nodes tested is up to seven or more. In our study, there were 55 (35.7%) patients whose lymph nodes tested were less than seven. It implies that at least one to third GC curative surgery was either technically inadequate, or lymph nodes detection was not properly conducted. Future work should pay more attention to this problem.

On adjuvant therapy, although there have been controversies and skepticisms, some large scale and well-conducted clinical studies have produced high-level evidence that adjuvant chemotherapy and/or radiotherapy can improve prognosis of GC patients. MAGIC trial confirmed that preoperative chemotherapy could down-stage tumor, improve progression-free survival and five-year survival. The ACTS-GC and INT-0116 trials also concluded that adjuvant chemotherapy or chemoradiotherapy after curative resection could increase 3-year survival by 10%. Our previous phase III randomized clinical trial on patients with peritoneal cacinomatosis from gastric cancer demonstrated that postoperative chemotherapy was an independent factor of improving survival of GC patients. In addition, our study on postoperative recurrence in GC also revealed that time to tumor recurrence after surgery was 10.0 months in GC patients in ≥6 chemotherapy cycles group, and 5.0 months in <6 cycles group, respectively, suggesting that adjuvant chemotherapy could delay postoperative recurrence. This study testified again that adjuvant chemotherapy is indeed an independent factor correlated with OS of GC (the median OS was 18.0 vs 11.0 months in chemotherapy ≥6 cycles and <6 cycles group, respectively, P=0.009). Unfortunately, only 34 (22.1%) patients completed ≥6 cycles chemotherapy. Had all these patients completed ≥6 cycles chemotherapy, the OS could have been better. Taking together, we conclude that there should be no doubt any more on the benefit of adjuvant chemotherapy/radiotherapy; and the prognosis of majority of GC patients in this study could have been improved if they had received neoadjuvant chemotherapy before surgery and sound adjuvant treatment after surgery.

In summary, the study concludes that tumor site, surgical approach and chemotherapy cycles were independent factors associated with OS of GC. Multi-disciplinary comprehensive treatment is the foremost strategy to improve survival and quality of life.

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