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Comparative Analysis between Clinicopathologic Characteristics and Prognosis in Patients with Local and Infiltrative Gastric Cancer

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OBJECTIVE To investigate the differences between the clinicopathologic characteristics and prognostic factors in patients with localized and infiltrative gastric cancer (GC).
METHODS Patients with advanced GC, who were admitted to the Department of Surgical Oncology of the First Affiliated Hospital of China Medical University, Shenyang, during a period of January 1980-January 2000, were divided into the localized and infiltrative GC groups. A comparative analysis of the clinicopathologic data and prognosis in the patients enrolled in the study was carried out based on the different macroscopic types.
RESULTS There were significant differences in the sex ratio, tumor location, histologic type, depth of invasion, lymph node metastasis, lymphovascular cancer embolus (LVCE), growth pattern, and degree of radical surgery between the 2 groups. However, there were no significant differences in age, tumor size, and intravenous cancer embolus between the 2 groups. The prognosis of the infiltrative GC group was poor. There were significant differences in the prognosis of the patients between the 2 groups when tumor infiltration was within the muscular layer or subserosa, yet the differences disappeared once the tumor infiltration was beyond the serosal layer. The prognosis of the patients with localized GC was closely related to tumor location and lymph node metastasis. The prognostic factors of the patients in the infiltrative GC group included lymph node metastasis, depth of invasion, and tumor size.
CONCLUSION There are significant differences in the clinicopathologic characteristics and prognosis between the 2 groups. Based on the biological characteristics of the tumors, individualized therapeutic plans will help to improve the treatment outcome.

KEY WORDS: gastric tumor, pathology, clinic, prognosis.

Introduction

In 1980, a standard for the macroscopic typing of gastric cancer (GC) was put forward by the Department of Gastrointestinal Oncosurgery, the First Affiliated Hospital of China Medical University, Shenyang, China. In the standard, the Borrmann I and Borrmann II-type GC were classified as local gastric cancer (LGC), and the Borrmann III, Borrmann IV and Borrmann V-type GCs were classified as infiltrative

gastric cancer (IGC). The typing standard is well-defined, simple, and convenient to use. It has been widely accepted and applied in clinical practice. In our study, the complete database of GC set up in our department in 1980 was used to analyze and discuss the clinicopathologic characteristics and prognosis of LGC and IGC, in order to provide a reliable indicator for working out a clinical treatment plan and evaluating the prognosis.

Materials and Methods

Clinical data

During the period of January 1980-December 2000**,** a total of 1,060 advanced GC patients were treated in our department and the complete clinicopathologic data has been made available. Aside from the 17 patients who died within 1 month after surgery, 1,043 patients were enrolled in the study, among which 781 were male, and 262 were female. The male-female ratio was 2.95:1. The age of the patients enrolled in the study ranged from 28 to 90 years, with an average age of 57.8 years.

Grouping and follow up

Following surgery, the patients were divided into 2 groups based on various pathologic macroscopic types, i.e., the LGC and IGC groups. In the LGC group, the macroscopic types included the Borrmann I and Borrmann II type, while in the IGC group, the macroscopic types included the Borrmann III, Borrmann IV, and Borrmann V types. There were 309 cases in the LGC group (29.9%), among which the Borrmann I cases accounted for 2.6% (27), and the Borrmann II cases accounted for 27.3% (282). In the IGC group, there were 734 cases (70.1%), in which 646 were diagnosed as Borrmann III type (62.5%), 85 as Borrmann IV type (8.4%), and 3 as Borrmann V type (0.1%). The follow-up rate attained 95.8% of the total patients in the 2 groups, in which the rate in the LGC group was 96.4% (298/309), and that in the IGC group was 95.6% (702/734). The follow-up period ranged from 0 to 327 months.

Statistical analysis

Spss13.0 was used for statistical analysis of all data. The chi-square test was used for comparison of the constituent ratios in the data of each group and the *t* test for comparison of the continuous variables. The survival curve was drawn, and the K-M method was used to calculate the survival rate of the patients. LOG-RANK test was performed for comparison of the survival rates, and COX multi-factorial analysis was utilized for the factors that might affect the prognosis. A value of $P < 0.05$ was considered significant.

Results

Analysis of clinicopathologic data

The clinocpathologic data from 1,034 GC patients are shown in Table 1. The proportion of male patients was significantly higher in the LGC group than in the IGC group (3.98 *vs*. 2.65). In the histologic typing, the occurrence of differentiated cancer cells was highest in the LGC group (57%), while undifferentiated cancer cells were found in most of the IGC cases (62%). All foci found in patients in the 2 groups were mainly localized to the inferior part of stomach; however, tumor involving the whole stomach presented more in the IGC group than in the LGC group (7.9% *vs*. 2.9%). Both depth of infiltration and extent of lymphatic metastasis were more severe in the IGC group than in the LGC group. In regards to growth pattern, massive growth was found in most of the LGC cases (36.6%) and diffuse growth in most of the IGC cases (61.4%). The rate of radical excision was significantly higher in the LGC group than in the IGC group (98.4% *vs*. 93.4%). There were no significant differences in the age, tumor size and intravenous cancer embolus between the 2 groups ($P < 0.05$).

Survival analysis

The median survival time of the patients in the 2 groups was 48 months, and the mean survival time was 120 months. The median and mean survival times were 98 months and 152 months in LGC group, and 38 months and 103 months in IGC group, respectively. After the LOG0-RANK test, there were significant differences in comparison of the accumulative survival rate (ASR) between the 2 groups ($\chi^2 = 27.99$, $P < 0.05$). The survival curve in each group is shown in Fig.1. The analysis of the ASR of the patients with different depths of infiltration in the 2 groups showed that there were significant differences in the ASR between the 2 groups once the tumor infiltrated into the muscular and subserosal layers (T_2), $P < 0.05$ (Fig.2). The significant differences in the ASR between the 2 groups disappeared as the tumor infiltrated beyond the serosal layer (T_2 or above), $P = 0.53$ (Fig.3).

Relationship among macroscopic typing, lymphatic metastasis and postoperative 5-year survival rate

Lymphatic metastasis and 5-year survival rate of the LGC and IGC patients were analyzed based on the UICC lymphatic metastasis grading, JAGC lymphatic metastasis grading[1], and grading of lymphatic metastasis ratio and number of lymph nodes, respectively[2]. See Table 2 for results of the analysis.

Multifactorial analysis of prognosis

The factors that might affect the prognosis of the advanced GC patients were utilized in the COX's proportional hazards model analysis. It was found that the factors that influenced the prognosis of LGC patients included the site of the diseased region and lymphatic metastasis (Table 3). The factors which affected the prognosis of IGC patients were lymphatic metastasis, depth of infiltration, and tumor size (Table 4).

Table 1. Clinicopathologic data of LGC and IGC patients.

Characteristics	LGC (n = 309)	IGC (n = 734)	P
Sex ratio (male/female)	3.98	2.65	< 0.05
Age (years)	57.91 ± 9.68	57.814 ± 10.48	> 0.05
Tumor size (cm)	5.36 ± 2.4	5.9 ± 3.12	> 0.05
Diseased region (%)			< 0.05
Superior part of stomach mainly	55 (17.8)	93 (12.7)	
Middle part of stomach mainly	45 (14.6)	127 (17.3)	
Inferior part of stomach mainly	200 (64.7)	456 (62.1)	
Whole stomach	9 (2.9)	58 (7.9)	
Histotype (%)			< 0.05
Differentiated	176 (54.9)	279 (38.0)	
Undifferentiated	131 (44.2)	449 (61.2)	
Others	2 (0.9)	6 (0.8)	
Depth of infiltration (%)			< 0.05
pT2	216 (70.0)	399 (54.4)	
pT3	89 (28.8)	287 (39.1)	
pT4	4 (1.2)	48 (6.5)	
Lymphatic metastasis (%)			< 0.05
No	138 (44.5)	247 (33.5)	
Yes	171 (55.5)	478 (66.5)	
LVCE* (%)			< 0.05
Yes	32 (12.3)	128 (23.1)	
No	229 (87.7)	427 (76.9)	
Intravenous cancer embolus* (%)			> 0.05
Yes	2 (0.7)	5 (0.9)	
No	266 (99.3)	532 (99.1)	
Growth pattern (%)			< 0.05
Massive	113 (36.6)	84 (11.4)	
Alveolar	106 (34.3)	199 (27.1)	
Diffuse	90 (29.1)	451 (61.4)	
Degree of radical excision (%)			< 0.05
Yes	304 (98.4)	687 (93.6)	
No	5 (1.6)	47 (6.4)	

* Intravenous cancer embolus and LVCE were not detected in 246 of the patients after surgery.

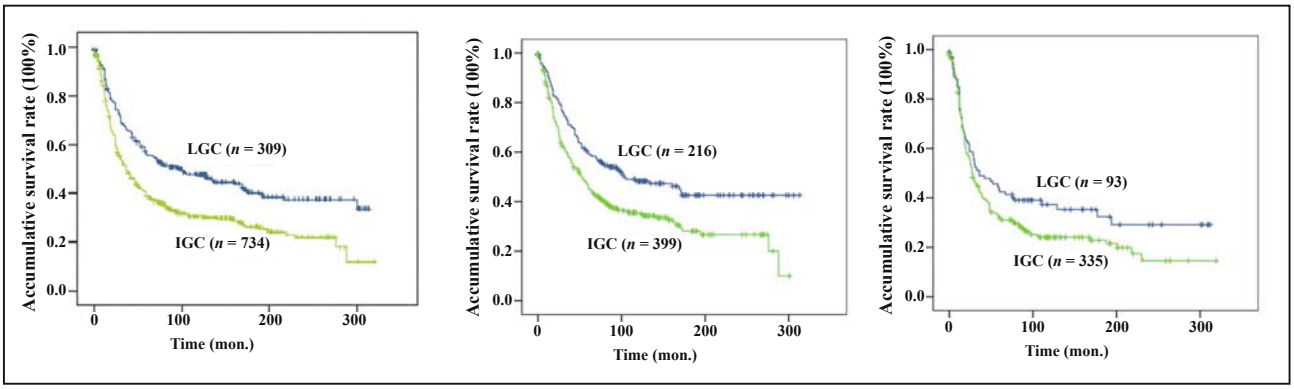

Fig.1. Comparison of the survival curve in the LGC and IGC groups.

Fig.2. Comparison of the survival curve in the T_2 LGC and IGC groups.

Fig.3. Comparison of the survival curve between the patients with LGC and IGC of T_2 and above.

Table 2. Lymphatic metastasis in LGC and IGC patients.

Types of grading	Localized (n = 309)		Infiltrative (n = 734)		P
	n	5-year survival rate (%)	n	5-year survival rate (%)	
JAGC					< 0.05
pN0	138	87.0	246	82.3	
pN1	83	77.9	232	69.9	
pN2	79	51.8	221	45.7	
pN3	9	15.0	35	10.6	
UICC					< 0.05
pN0	138	87.0	246	82.3	
pN1	143	72.5	327	62.5	
pN2	25	40.8	111	34.0	
pN3	3	18.9	50	9.6	
Lymphatic metastasis ratio					> 0.05
rN0	138	87.0	246	82.3	
rN1	80	69.9	224	71.2	
rN2	53	45.7	146	47.6	
rN3	39	10.6	118	12.6	

Table 3. Multifactorial analysis of prognosis in LGC patients.

Pathologic factors	Regression coefficients	Standard error	Relative risk	95% CI		P
				LL	UL	
Site of diseased region	0.314	0.092	1.369	1.141	1.642	< 0.001
Lymphatic metastasis	0.368	0.112	1.445	1.159	1.801	0.001

Table 4. Multifactorial analysis of the prognosis in IGC patients.

Pathologic factors	Regression coefficients	Standard error	Relative risk	95% CI		P
				LL	UL	
Lymphatic metastasis	0.235	0.051	1.265	1.145	1.399	< 0.001
Depth of infiltration	0.194	0.057	1.214	1.085	1.358	< 0.001
Tumor size	0.047	0.015	1.048	1.017	1.08	0.002

Relationship between macroscopic typing and the site of recurrence

The analysis of the relapse in 161 of the patients with a definite diagnosis of the recurrence was performed, which showed that hepatic relapse ranked first among sites of relapse of LGC (19 cases), and peritoneal relapse was first as the mode of relapse of IGC (59 cases). There were significant differences in the site of relapse between the cases in the 2 groups, $P < 0.05$ (Table 5).

Table 5. Comparison of the relapse rates between LGC and IGC patients.

Recurrence site	LGC (%)	IGC (%)
Peritoneal relapse	11 (22.0)	59 (53.2)
Hepatic relapse	19 (38.0)	11 (10.0)
Others	20 (40.0)	41 (36.8)

Discussion

Among the patients enrolled in the study, LGC patients accounted for 30% of the total cases, and IGC patients accounted for 70%, which was in agreement with the data reported in literature[3]. It was found that, after careful analysis of the clinicopathologic characteristics from the LGC and IGC patients, there were significant differences in the biological behaviors between the 2 groups, i.e., the degree of malignancy of LGC was low, with a tendency for tumor cell infiltration being limited to the gastric wall. In contrast, the degree of malignancy of IGC was high, with a tendency for extensively diffuse infiltration.

Lymphatic metastasis is one of the major factors that affect the prognosis of advanced GC patients. It was found, after thorough analysis of distant lymphatic

metastasis, the number of positive lymph nodes, and metastatic rate among patients in the 2 groups, that there were no significant differences in the comparison of the metastatic rates between the 2 groups; however, the number of metastasized nodes was large and the distance of the metastasis was further in the IGC group than in the LGC group. Concerning the invasion of lymphatic vessels, LVCE presented in 12.3% of the patients in the LGC group and in 23.1% of the patients in the IGC group. Although LVEC could only affect the prognosis of GC patients without lymphatic metastasis[4], it indicated that the invasion of IGC to the lymphatic system was more extensive.

Analysis of prognosis indicated that the 5-year survival rate was 60.4% in the LGC group and 42.2% in IGC group. The prognosis of IGC was poor ($P < 0.05$). There were significant differences in the prognosis between the 2 groups when the tumor infiltrated into the muscular layer and the subserosal layer (T2), but the differences disappeared when the infiltration of the tumor was beyond the serosal layer (T2 or above). The reason is probably because once the tumor breaks through the serosal layer, the probability of peritoneal metastasis can increase markedly, and thus the 5-year survival rate is significantly decreased. Variance in the biological behaviors of tumors can result in insignificant differences in the prognosis of patients, which is in conformity with the theory that the invasion of the seromembranous layer is an independent prognostic factor in GC patients[5].

It was found by multifactorial analysis that the factors influencing the prognosis of GC patients in the 2 groups are not identical. Based on the relative risk, the prognostic factors in LGC patients included the degree of lymphatic metastasis and site of diseased region, while those in IGC patients were the degree of lymphatic metastasis, depth of tumor infiltration, and tumor size. It is important to know that the depth of infiltration and tumor size, which are confirmed as the influencing factors in the prognosis of advanced GC patients, actually do not significantly affect the prognosis of LGC patients. This suggests that for LGC patients, favorable therapeutic outcome may still be achieved if active radical treatment is utilized, although the disease may reach the advanced stages, or the tumor may be large.

The rate of postoperative metastasis is high in GC cases, which is the main cause of death in patients after surgery. Macroscopic typing is one of the main factors affecting metastasis of GC[6,7]. Hepatic metastasis easily occurred in the gastric cancer patients of which the macroscopic types of the tumors were Borrmann I and II in the first surgeries, and the tumors were identified as the differentiated GCs[8]. In our study, the metastasis rate to the liver was 38% in LGC patients and only 10% in IGC patients. Peritoneal metastasis was most commonly seen in GC patients after surgery, accounting for approximately 40%-50% of the total cases[9]. Regarding the sites of metastasis in our study groups, peritoneal metastasis accounted for 53.2% in the IGC group, which was much higher than that of 22.2% in LGC patients. The main mechanism of peritoneal metastasis is the growth of cast-off cells after the tumor penetrates the serous membranes; nevertheless, dissemination of tumor cells to the peritoneum can also occur via the lymphatic route, which is in agreement with the characteristics of IGC deeply infiltrating and severely invading the lymphatic system.

Macroscopic typing of tumors is one of the few pieces of clinicopathologic data which can be obtained by oncology surgeons before surgery and facilitate the selection of the appropriate operative procedure and the formulation of an individualized treatment plan. The idea of "treatment based on the macroscopic typing" was first proposed by the Department of Oncosurgery, China Medical University, of which the priority is to adopt an individualized therapeutic regimen based on various biological behaviors of the tumor. Guidance regarding the correlation of macroscopic typing to clinical treatment includes 2 main considerations: one is the scope of tumor excision. According to Chen et al.[10], the excised margin of the LGC specimen should be 3-4 cm away from the edge of the cancer lesion, and in the IGC group it should be at least 5-6 cm. Total gastrectomy is the choice when treating patients with Borrmann IV type, a special cancer in IGC cases. The other consideration is the scope of the lymph node dissection. Concerning the TNM staging of LGC, most of the metastasized lymph nodes are limited to N2. Even though some metastasized nodes are found at N3, most of the nodes are at 11P, 12A, which is a favorable indication for D2, D3 lymph node dissection. Further, a better therapeutic outcome can be attained[11]. In IGC cases, an extended lymphadenectomy should be performed based on invasion of the serous membrane and tumor size, which is the major therapy in the combination of treatments[12].

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