·Original Article·

Prognosis of 980 patients with gastric cancer after surgical resection

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[Abstract] Background and Objective: Although surgery is the only possible means to cure gastric cancer, the prognosis is often discrepant. The American Joint Committee on Cancer / International Union against Cancer (AJCC/UICC) published the TNM classification of Malignant Tumors (seventh edition) for gastric cancer recently. This study aimed to use this new edition staging system to investigate the prognostic factors for gastric cancer. **Methods:** The clinicopathologic data of 980 patients with gastric cancer treated by surgical resection in our hospital between January 2000 and December 2006 were analyzed retrospectively. The overall survival rate was determined by using Kaplan-Meier method and log-rank test was used to determine significance. The prognosis was analyzed using univariate analysis and multivariate analysis with the Cox proportional hazards model. The 6th and 7th edition AJCC/UICC TNM staging systems were used to compare the survival outcomes for the cohort of patients. **Results:** The overall 1-, 3-, 5-year survival rates for the whole group were 82.5%, 58.7%, and 52.6%. The 5-year survival rates for patients with pTNM stage I, II, III, and IV disease classified by the 7th edition staging system were 93.2%, 72.4%, 39.1%, and 5.2%, respectively. In both univariate analysis and Cox multivariate analysis, age, tumor site, tumor size, histological type, resection type, radical resection, lymphatic/venous invasion, depth of invasion, nodal status, metastasis, retrieved lymph nodes, metastatic lymph node ratio, and adjuvant chemotherapy were prognostic factors with these patients. **Conclusion:** Compared with the 6th edition system, the new edition of TNM staging system for gastric cancer can accurately predict the survival after operation.

Key words: Gastric neoplasm, surgical resection, prognosis, multivariate analysis

Currently, the worldwide incidence of gastric cancer is descending, however, in China gastric cancer is still one of the most common malignant tumors, and the number of new cases per year is larger than that in other countries[1]. Although perioperative adjuvant chemotherapy or neoadjuvant chemotherapy for advanced gastric cancer attracts more and more attention and the genes and molecular targets are deeply studied, surgery is still the only possible means to cure gastric cancer, and postoperative clinical pathologic classification (TNM classification) can best predict prognosis of the patients. TNM staging system

was established based on the most fundamental and important factors which influence the prognosis of patients with malignant tumors. It is widely accepted and highly valued because of its brevity, reliability and clinical application, and is used to guide clinical treatment and prognosis prediction. Nevertheless, prognosis of patients in the same TNM stage is still discrepant. Apart from tumor heterogeneity and individual differences, are there any determinant clinicopathologic factors for the prognosis of gastric cancer patients beyond tumor depth, nodal status, and metastasis? Which of those factors are the key factors influencing the prognosis of gastric cancer patients? Whether those important factors could be included in the TNM staging system? Different opinions exist in this regard. Relevant prognostic factors include gender, age, tumor size, location of tumor, histological type, resection type, lymphatic/venous invasion, depth of invasion, number of metastatic lymph nodes, retrieved lymph nodes, metastatic lymph node ratio, radical resection, adjuvant chemotherapy,

and so on. It is widely known that the clinical classification of malignant tumors needs constant improvements. With increasing knowledge about biological behaviors of tumors, it is necessary to make constant adjustment and update to previous staging system. Therefore, the American Joint Committee on Cancer / International Union against Cancer (AJCC/UICC) revised and published the TNM Classification of Malignant Tumors (seventh edition) for gastric cancer in 2010[2] based on a lot of medical evidences of gastric cancer prognosis from worldwide clinical centers in the recent years. Compared with the sixth edition of the TNM classification published in 2002[3], this new TNM classification made revisions in the depth of invasion (T category), the number of metastatic lymphatic nodes (N category), and the redefinition of stage IV patients. It is expected to better predict the survival of gastric cancer patients after operation and to show the consistency between the classification and the prognosis, so that clinicians can use it as a clinical guideline in mastering clinical features of gastric cancer and in adopting individual treatment for patients at different stages to achieve better effects. Currently, there are only a few studies in the world about the clinical application and the prognosis prediction accuracy of the new classification system. Therefore, to further investigate the significance of the new classification system and the correlation of the new classification system to the clinicopathologic factors and the prognosis of gastric cancer patients, we analyzed postoperative pathologic and follow-up data of 980 patients with gastric cancer who underwent surgical resection between January 2000 and December 2006 in Sun Yat-sen University Cancer Center, re-staged the patients using the new staging system, and compared it with the sixth edition to investigate the prognostic factors for gastric cancer.

Subjects and Methods

Subjects

We used the case management system of Sun Yat-sen University Cancer Center to retrieve the clinical records of 1046 gastric cancer patients who underwent surgical resection between January 2000 and December 2006. Inclusion criteria: (1) cases with complete clinical records, postoperative pathologic and follow-up data; (2) cases with complete preoperative examination data, including blood routine examination, liver and kidney function examination, electrocardiogram (ECG), chest radiography, abdominal B mode ultrasonography or CT; (3) no other malignant gastric tumors such as gastric lymphoma, gastric cancer recurrence and remnant gastric cancer; (4) no other primary malignant tumors synchronous or metachronous such as colorectal cancer, breast cancer, and gastrointestinal

stromal tumor; (5) no patients dead of operative complications. A total of 980 cases were included.

Methods

Criteria of diagnosis

In AJCC/UICC TNM Classification of Malignant Tumors (seventh edition) [2] for gastric cancer, gastric cancers are divided into 8 substages (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV) according to the postoperative pathologic findings. Category T includes T1 (invasion of lamina propria, muscularis mucosae or submucosa), T2 (invasion of muscularis propria), T3 (penetration of subserosal connective tissue without invasion of visceral peritoneum or adjacent structures), T4a (invasion of serosa (visceral peritoneum)), T4b (invasion of adjacent structures including the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, retroperitoneum); category N includes N0 (no lymph node metastases), N1 (metastases in 1 to 2 lymph nodes), N2 (metastases in 3 to 6 lymph nodes), N3 (metastases in more than 6 lymph nodes); category M includes M0 (no distant metastasis), M1 (distant metastasis).

In AJCC/UICC TNM Classification of Malignant Tumors (sixth edition) [3] for gastric cancer, gastric cancers are divided into 6 substages (IA, IB, II, IIIA, IIIB, IV) according to their postoperative pathologic findings. Category T includes T1 (invasion of lamina propria or submucosa), T2 (invasion of muscularis propria or subserosa), T3(penetration of serosal (visceral peritoneum) without invasion of adjacent structures), T4 (invasion of adjacent structures including the spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine, retroperitoneum); category N includes N0 (no lymph node metastases), N1 (metastases in 1 to 6 lymph nodes), N2 (metastases in 7 to 15 lymph nodes), N3 (metastases in more than 15 lymph nodes); category M includes M0 (no distant metastasis), M1 (distant metastasis).

Reexamination and follow-up

The patients were reexamined every 3 months for the first 2 years after operation, every 6 months for the following 3 years, and once every year thereafter. The reexamination included electronic gastroduodenoscope, abdominal ultrasonography (CT if necessary), chest X-ray, detection of CEA, CA19-9, and CA724, etc. They were followed up by telephone, short messages, and outpatient visit, starting from the day they were discharged till May 20th, 2010. The end point of follow-up was disease-related death.

Statistical analysis

The data were processed using SPSS 18.0 software package. Statistical methods included the Kaplan-Meier

analysis for overall cumulative survival rate, the log-rank test for the significance of survival rates between groups, the Cox proportional hazards model for multivariate analysis. $P < 0.05$ was considered significant.

Results

General data

Of the 980 gastric cancer patients, 663 were men and 317 were women, with a ratio of 2.09:1. The median age was 58 (range, 17–85). According to the 7th edition of the AJCC/UICC TNM Classification of Malignant Tumors for gastric cancer, 71 (7.2%) patients were at stage IA, 55 (5.6%) at stage IB, 79 (8.1%) at stage IIA, 173 (17.7%) at stage IIB, 122 (12.4%) at stage IIIA, 186 (19.0%) at stage IIIB, 178 (18.2%) at stage IIIC, and 116 (11.8%) at stage IV. Whereas according to the sixth edition classification, 71 (7.2%) patients were at stage IA, 115 (11.7%) at stage IB, 222 (22.7%) at stage II, 249 (25.4%) at stage IIIA, 81 (8.3%) at stage IIIB, and 242 (24.7%) at stage IV.

Treatment

Of the 980 patients, 825 (84.2%) underwent D2 radical resection, and the other 155 (15.8%) underwent palliative resection. As to the resection type, 368 (37.5%) patients underwent proximal gastrectomy, 480 (49.0%) with distal gastrectomy, 132 (13.5%) with total gastrectomy, and 68 (6.9%) with multivisceral resection (the diaphragm in 19 patients, body and tail of pancreas in 23 patients, spleen in 25 patients, and traverse colon in 12 patients. Postoperative adjuvant chemotherapy or palliative chemotherapy was used in 531 (54.2%) patients, and the major protocols were 5-fluorouracil-based monotherapy or 5-fluorouracil combined with platinum, taxane, or epirubicin.

Survival situation

The median follow-up duration was 63 months, and 518 patients still survive. The overall 1-, 3-, 5-year survival rates were 82.5%, 58.7%, and 52.6%, respectively. The 5-year survival rates for patients with pTNM stage I, II, III, and IV disease classified by the 7th edition classification were 93.2%, 72.4%, 39.1%, and 5.2%, respectively (Figure 1).

Univariate analysis and multivariate analysis

Gender, age, location of tumor, tumor size, histological type, resection type, radical resection, lymphatic/venous invasion, tumor depth, nodal status, metastasis, retrieved lymph nodes, metastatic lymph node ratio, chemotherapy were included in the univariate analysis. The results showed that all the above factors except for gender significantly affected the prognosis (Table 1).
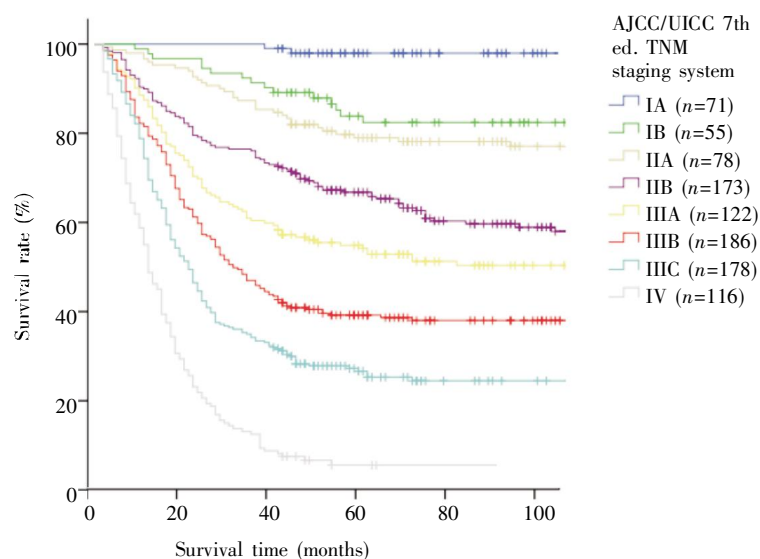

Figure 1 Survival curves of the 980 patients undergoing surgical resection for gastric cancer at different stages according to AJCC/UICC 7th TNM staging system

Table 1 Univariate survival analysis of clinicopathologic variables in 980 patients with gastric cancer

Variable	No. of patients (%)	5-year survival rate (%)	Log-rank χ^2 value	P
Sex			0.372	0.542
Female	317 (32.3)	51.2		
Male	663 (67.7)	53.1		
Age (years)			11.342	0.003
≤ 60	578 (59.0)	54.4		
> 61	402 (41.0)	48.2		
Tumor site			69.543	< 0.001
Proximal/middle	537 (54.8)	46.2		
Distal	388 (39.6)	67.1		
Two-thirds or more	55 (5.6)	19.0		
Tumor size (cm)			125.760	< 0.001
≤ 2.5	131 (13.4)	90.0		
3.0–5.0	463 (47.2)	58.2		
> 5.0	386 (39.4)	33.8		
Histological type			17.216	< 0.001
Well/moderately differentiated adenocarcinoma	352 (35.9)	61.1		
Poorly differentiated adenocarcinoma	468 (47.8)	50.3		
Signet-ring cell carcinoma / mucinous adenocarcinoma	160 (16.3)	42.1		
Resection type			45.203	< 0.001
Proximal partial gastrectomy	368 (37.5)	47.4		
Distal partial gastrectomy	480 (49.0)	63.7		
Total gastrectomy	132 (13.5)	32.2		
Radical resection			200.981	< 0.001
Yes	825 (84.2)	61.6		
No	155 (15.8)	7.2		
Lymphatic/venous invasion			118.506	< 0.001
Yes	118 (12.0)	16.3		
No	862 (88.0)	57.2		
7th ed. AJCC/UICC T stage			165.122	< 0.001
T1	87 (8.9)	96.0		
T2	93 (9.5)	78.3		
T3	176 (18.0)	61.1		
T4a	520 (53.0)	39.3		
T4b	104 (10.6)	18.0		
7th ed. AJCC/UICC N stage			154.479	< 0.001
N0	306 (31.2)	78.2		
N1	193 (19.7)	51.7		
N2	224 (22.9)	40.8		
N3	257 (26.2)	24.1		
7th ed. AJCC/UICC M stage			158.084	< 0.001
M0	864 (88.3)	59.2		
M1	116 (11.7)	5.2		
Retrieved lymph nodes			25.350	< 0.001
< 15	467 (47.7)	45.2		
≥ 15	513 (52.3)	60.7		
Metastatic lymph node ratio			248.181	< 0.001
0.00–0.25	543 (55.4)	72.5		
0.26–0.50	177 (18.1)	41.3		
0.51–0.75	138 (14.1)	23.3		
0.76–1.00	122 (12.4)	11.2		
Chemotherapy			70.788	< 0.001
Yes	531 (54.2)	68.2		
No	449 (45.8)	35.5		

Put those significant prognostic factors into Cox proportional hazards model, and the results showed that age, tumor size, histological type, radical resection, lymphatic/venous invasion, tumor depth, nodal status, metastasis, retrieved lymph nodes, metastatic lymph node ratio, and chemotherapy were still independent prognostic

Table 2 Multivariate prognostic analysis of 980 patients with gastric cancer

Variable	SE	Wald	P	HR
Age	0.074	4.786	0.029	1.176
Tumor size	0.084	26.085	0.000	1.533
Histological type	0.068	4.909	0.027	1.162
Operation type	0.194	4.062	0.044	1.477
Lymphatic/venous invasion	0.123	48.977	0.000	2.367
7th ed. AJCC/UICC T stage	0.063	46.869	0.000	1.537
7th ed. AJCC/UICC N stage	0.071	10.471	0.001	1.257
7th ed. AJCC/UICC M stage	0.206	6.533	0.011	1.691
Retrieved lymph nodes	0.111	23.211	0.000	0.585
Metastatic lymph node ratio	0.066	5.218	0.022	1.164
Chemotherapy	0.101	45.719	0.000	0.503

factors (Table 2).

Comparison of the sixth and seventh edition of the AJCC/UICC TNM Classification of Malignant Tumors for gastric cancer

Compared with the sixth edition of the TNM classification, the new TNM classification made revisions in the depth of invasion (T category), the number of metastatic lymphatic nodes (N category), and redefinition of stage IV patients. And it subdivided the 4 subsets of T category in the sixth edition into 5 subsets, emphasizing prognostic differences caused by the depth of invasion (T category); it made some revision with regard to the number of metastatic lymph nodes in N category to better predict prognosis; it only kept the M1 patients as stage IV patients, whereas degraded T4N+M0 and TanyN3M0 in the sixth edition into stage II and stage III. We found that both the 4 subsets of T category in the sixth edition and the 5 subsets in the seventh edition can well predict patients' prognosis ($P < 0.001$) (Figure 2). The postoperative survival rates of N2 and N3 patients in the sixth edition showed no significant difference ($P = 0.780$) (Figure 3A), whereas those of the subsets of N category in the seventh edition showed significant difference ($P < 0.001$) (Figure 3B). We compared the 5-year survival rates of stage IV patients (including T4N+M0 and TanyN3M0) in the sixth edition who were downstaged into stage III and remained in stage IV (TanyNanyM1) in the seventh edition, and found that there was significant difference between the two groups (27.2% vs. 5.2%, $P < 0.001$), which indicated that the redefinition of stage IV patients in the seventh edition was more appropriate (Figure 4).
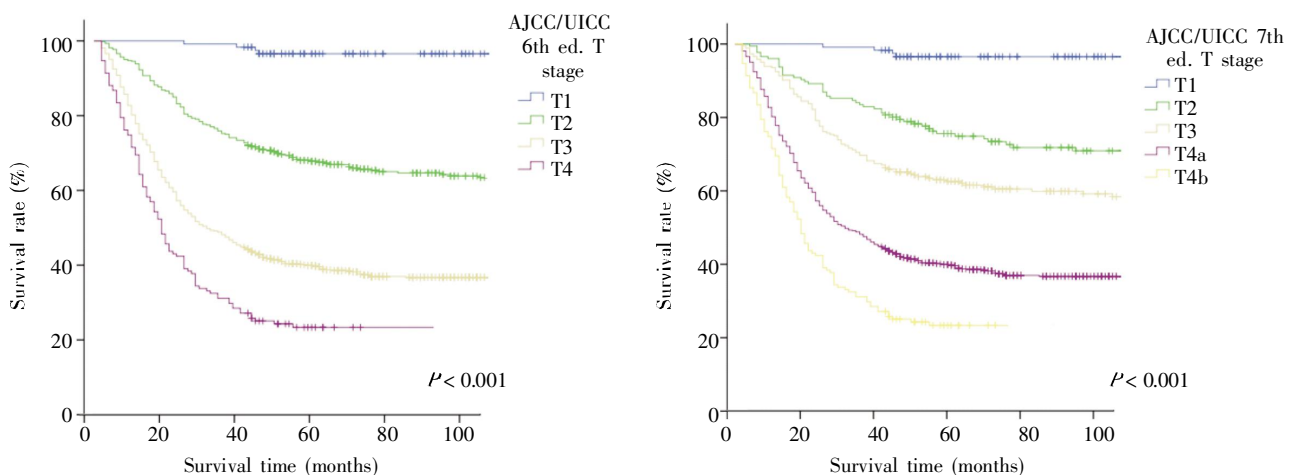

Figure 2 Comparison of survival curves according to T stage between the AJCC/UICC 6th (A) and 7th (B) edition system
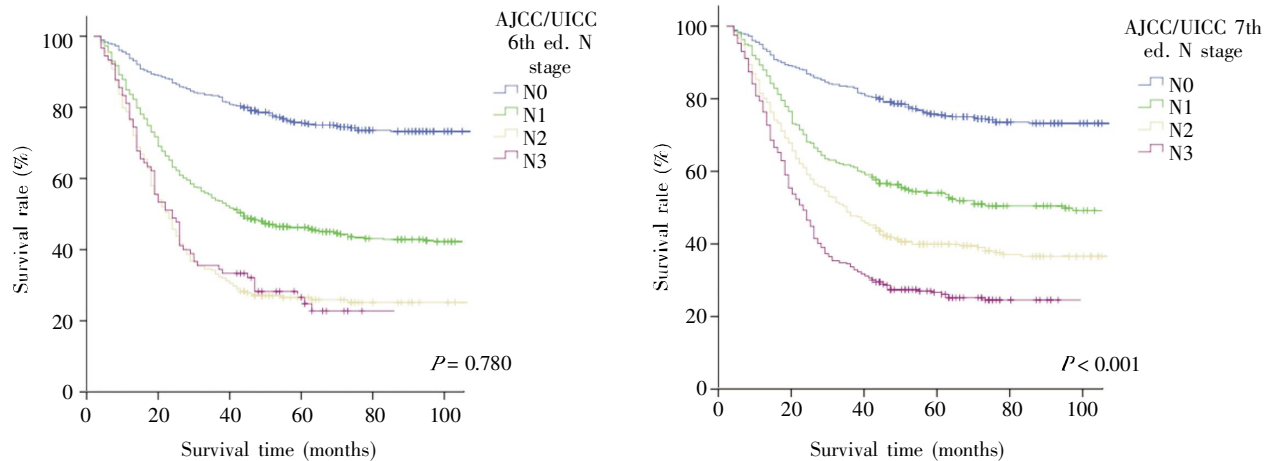
Figure 3 Comparison of survival curves according to N stage between the AJCC/UICC 6th (A) and 7th (B) edition system
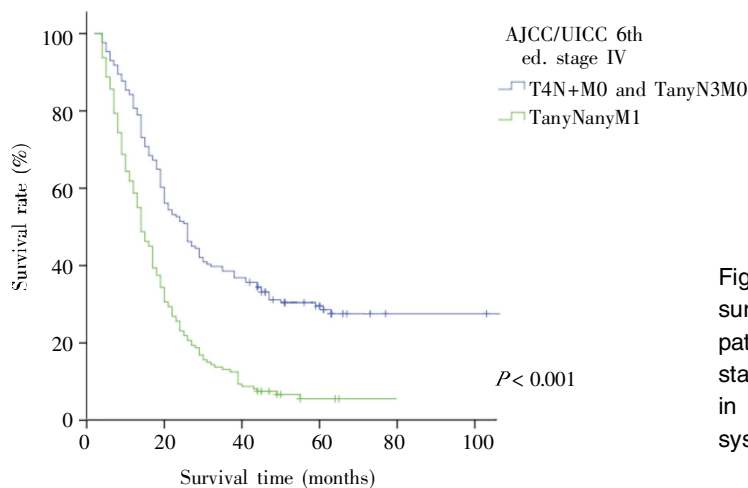

Figure 4 Comparison of survival curves between patients down-staged to stage III and those remaining in stage IV in the 7th edition system ($P < 0.001$)

Discussion

AJCC/UICC has revised and published the seventh edition of the TNM Classification of Malignant Tumors for gastric cancer recently. This new classification was made by computer processing based on a lot of objective data. With the depth of invasion (T) and metastatic scope of lymph nodes (N) as the main indicators and take distant metastasis (M) into consideration, it can reflect the overall progression of tumors and the biological behaviors of tumors to some degree. It abided by the most important standards of the classification system [4]: (1) homogeneity within subgroups (small difference in survival among patients within same stage); (2) discriminatory ability between different groups (greater differences in survival among patients in different stages); and (3) monotonicity of gradients shown in the association between stages and survival rates (patients with earlier stages have longer survival than those in later stages). The univariate analysis showed that 14 pathologic factors had significant correlation with postoperative survival rate of gastric cancer patients who underwent surgical resection; multivariate analysis showed that the T, N, M classification in the new AJCC/UICC classification system was one of the most important independent prognostic factors. In our study, the postoperative 5-year survival rates of stage I, II, III, and IV patients were 93.2%, 72.4%, 39.1%, and 5.2%, respectively, whereas the postoperative 5-year survival rates of subset

IA, IB, IIA, IIB, IIIA, IIIB, IIIC, and IV patients were 98.0%, 82.0%, 79.1%, 67.4%, 54.2%, 39.1%, 26.1%, and 5.2%, respectively, which reflected the good homogeneity, discriminatory ability, and monotonicity of the new classification system and the results were similar to those of other large scale studies [5-8]. Meanwhile, compared with the sixth edition, the new classification has an obvious advantage in the classification of N category and stage IV, which shows that it had better consistency between the classification and the prognosis. It also provides the clinicians with clinical references so that they can better master clinical features of gastric cancer and adopt individual treatment for patients with different stage tumors to achieve better effects.

Studies differ in the conclusions of correlation between prognosis and other clinicopathologic factors which were significant in our multivariate analysis. The prognostic value of age in gastric cancer patients remains controversial. Some researchers thought that it was not an independent prognostic factor [8-10], whereas others thought that younger patients has worse prognoses than elderly due to the worse biological behaviors of tumors and histological type [11]. However, Saito et al.[12] held that elderly patients had worse prognosis because they had limited lymph node dissection and lower tolerance of chemotherapy. Our results support Saito et al., finding that elderly patients had worse prognoses, and that age was an independent prognostic factor by multivariate analysis. An et al.[9] held that although gastric cardia cancer was associated with severer clinicopathologic features at diagnosis compared with other gastric cancers, there were no significant differences in prognosis with other gastric cancers. Zhang et al. [10] analyzed the prognoses of 2613 gastric cancer patients and found that the prognosis of proximal gastric cancer patients was significantly worse than that of distal gastric cancer patients, and it was correlated with tumor size, depth of invasion, and metastatic type of lymph nodes (mainly metastasis to the mediastinum). Our results showed that although proximal gastric cancer patients had a worse prognosis than distal gastric cancer patients in the univariate analysis, the location of tumor was not verified as an independent prognostic factor in the multivariate analysis. Liu et al. [13] thought that lymphatic/venous invasion is an independent prognostic factor even in early stage gastric cancer. However, the study of Bedikian et al.[14] showed that there was no significant correlation between gastric cancer prognosis and lymphatic/venous invasion. Our study showed lymphatic/venous invasion was an independent prognostic factor in multivariate analysis, consistent with Liu's conclusion. Deng et al. [15] found that the differentiation of gastric cancer did not influence prognosis and that although the histological type of gastric cancer was not included in the model in multivariate analysis, it did not mean that histologic al type was not a relevant prognostic factor, because it may be replaced by the T, N, M stage in the model. Our study showed differentiation of gastric cancer was correlated with prognosis. The patients with well and moderately differentiated adenocarcinoma had better prognosis than those with poorly differentiated adenocarcinoma, and much better prognosis than those with signet ring cell cancer and mucinous adenocarcinoma. Besides, Liu et al.[16] reported that tumor size was correlated with gastric cancer prognosis, stating that as to T3 tumors, the patients who had tumor more than 6 cm in diameter had worse prognosis. In our study, we found that when the cut-off value of tumor size was determined at 2.5 cm and 5 cm, tumor size was an independent prognostic factor in multivariate analysis. Patients who had tumor less than 2.5 cm has better prognosis than patients who had tumor 3.0–5.0 cm and more than 5.0 cm ($P < 0.05$).

The impact of clinical treatment on prognosis remains as a focus of gastric cancer study. Radical resection is undoubtedly the key prognostic factor. Therefore, in the multivariate analysis of our study, the radical resection, the retrieved lymphatic nodes, and the positive lymph node ratio were independent prognostic factors. Patients who underwent radical resection had better survival than patients who underwent palliative resection ($P < 0.05$). Patients who had more than 15 retrieved lymph nodes had better prognoses than patients who had less than 15 retrieved lymph nodes ($P < 0.05$). The metastatic lymph node ratio which had received close attention in the recent years was also included in multivariate analysis because it might minimize stage migration, and the result showed that the higher the ratio, the worse the prognosis ($P < 0.05$). Our results were consistent with most reports[17-20].

However, surgical treatment is after all a localized treatment. Recently, the surgery plus adjuvant chemotherapy or neoadjuvant chemotherapy for advanced gastric cancer has been mostly accepted although its treatment effect remains controversial[21-24]. Our study did not include the patients who underwent neoadjuvant chemotherapy, but the 5-year survival rate of 531 patients who underwent adjuvant chemotherapy or palliative chemotherapy was higher than those who underwent surgery alone, supporting the opinions of most researchers.

All in all, currently gastric cancer is considered as a systemic disease. Adopting adjuvant chemotherapy based on surgery, paying attention to and early interfering some prognostic risk factors (such as larger tumor, lymphatic/venous invasion, and high metastatic lymph node ratio), and adopting individual comprehensive treatment protocols may prolong the survival of gastric cancer patients.

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