

Analysis of survival and prognosis of 298 gastric adenocarcinoma patients with no distant metastasis

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Abstract. This study investigated the survival and prognosis of 298 gastric adenocarcinoma patients with no distant metastasis. For analysis and comparison of the prognosis of patients, a retrospective analysis was performed in 298 patients with perfect clinical data and follow-up data who received the D2 resections for gastric cancer in Shandong Provincial Hospital Affiliated to Shandong University between January, 2005 and January, 2012, and were diagnosed as gastric adenocarcinoma with no distant metastasis in postoperative pathological examination. Among the gastric adenocarcinoma patients without distant metastasis, we found that differences of sex, age, differentiation and position of tumor had no statistical significance ($P>0.05$), while comparisons of the tumor diameter, regional lymphatic metastasis, vascular invasion and pathological TNM stages (pTNM; T for tumor, N for lymph node and M for metastasis) showed statistical significance ($P<0.05$). One-way analysis of variance (ANOVA) indicated the correlation between the prognosis of gastric adenocarcinoma patients and tumor diameter, regional lymphatic metastasis, vascular invasion and pTNM stages of patients ($P<0.05$). Multivariate analysis of Cox regression models was performed for discovering the factors associated with the prognosis of patients, and the results suggested that position of tumor ($P=0.016$), regional lymphatic metastasis ($P=0.042$), vascular invasion ($P=0.021$) and pTNM stage ($P=0.009$) were the independent risk factors affecting the prognosis of gastric adenocarcinoma patients. During 60-month follow-up, the median survival duration of gastric adenocarcinoma patients with no distant metastasis was 38 months, while the 5-year accumulate survival rate was 49.3%. The results indicated that in gastric adenocarcinoma patients without distant metastasis, tumor diameter,

regional lymphatic metastasis, vascular invasion and pTNM stage are major indicators affecting the prognosis of patients.

Introduction

Gastric cancer has become the 3rd leading cause for cancer death in the world (1), and ranks 1st in all malignant tumors in China. Most of the gastric cancer patients have been diagnosed as the adenocarcinoma type. Currently, pathogenesis of gastric cancer remains unknown due to the heterogeneity in histological and pathological features of gastric cancer, and the diagnostic rate in an early stage is relatively low; nowadays, resection has been used as the preferred option for treatment of gastric adenocarcinoma without distant metastasis (1,2). According to the literature, it is reported that tumor diameter, regional lymphatic metastasis, vascular invasion, pTNM stage and surgical method are major factors affecting the prognosis of gastric cancer patients (3-5). To investigate the clinicopathologic factors associated with the long-term survival of gastric cancer patients after surgery, and to assess the prognosis and guide the treatment, we evaluated the prognosis and the related factors of 298 gastric adenocarcinoma patients without distant metastasis who underwent D2 resection for gastric cancer in Shandong Provincial Hospital.

Patients and methods

General materials. Between January, 2005 and January, 2012, a total of 321 patients were admitted to the Gastrointestinal Surgery Department of Shandong Provincial Hospital Affiliated to Shandong University for D2 resection for gastric cancer, in which there were 23 patients with distant metastasis who were diagnosed as non-adenocarcinoma in postoperative pathological examination. The remaining 298 patients were confirmed as the gastric adenocarcinoma within stage I to III (M0), and those patients with their perfect clinicopathologic material and follow-up material were enrolled as the subjects in this study. In the participants, there were 201 males and 97 females with a sex ratio of 2.1:1.0; the age ranged from 23 to 83 years with an average of 61 years. All participants were confirmed as non-distant metastasis patients through examinations of ultrasonic B, computed tomography [CT; or magnetic resonance imaging (MRI)] and surgical exploration. This study was approved by the Ethics Committee of Shandong Provincial

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Hospital Affiliated to Shandong University. Signed written informed consents were obtained from the patients.

Material collection and follow-up. After surgery, follow-up was carried out as out-patient review in combination with call visit or mail. In addition, we collected the material of patients, including sex, age, income, tissue differentiation, tumor diameter, regional lymphatic metastasis, vascular invasion and pTNM stages. With month as unit and death as outcome event, statistics on survival time of patients were collected, while the material of patients was deleted for missing cases or other causes of death. The follow-up ended in January, 2017.

Statistical analysis. SPSS 22.0 (IBM, Armonk, NY, USA) was used for data analysis. Chi-square test was performed for enumeration data, postoperative survival rate was calculated using Kaplan-Meier survival curve and significance testing was carried out using log-rank method through one-way analysis of variance (ANOVA). Variables with statistical significance ($P < 0.1$) in one-way ANOVA were incorporated into the Cox regression model for multivariate analysis.

Results

Survival of patients. Of the 298 patients who received D2 resection for gastric cancer, there were 2 patients who died in perioperative period and 13 patients were lost to follow-up or died of other causes, and the follow-up rate was 94.96%. The follow-up was for 60 months. The median survival time was 38 months, while the 5-year accumulate survival rate was 49.3% (Fig. 1).

One-way ANOVA of prognostic factors on gastric cancer. Comparisons of tumor position, regional lymphatic metastasis, vascular invasion, pTNM stage and 5-year survival rate showed that the differences had statistical significance ($P < 0.05$), suggesting that those are the factors affecting the prognosis of M0 gastric adenocarcinoma. However, sex, age, tissue differentiation and position of tumor posed no significant effects on the 5-year survival rate of patients ($P > 0.05$), and the prognosis of M0 gastric adenocarcinoma (Table I).

Multivariate analysis of Cox regression model. Factors that were identified with effect on prognosis of gastric adenocarcinoma patients with no distant metastasis in one-way ANOVA ($P < 0.1$) received further multivariate analysis of Cox regression model, and the results showed that tumor position, regional lymphatic metastasis, vascular invasion and pTNM stages are the independent risk factors affecting the gastric adenocarcinoma without distant metastasis ($P < 0.05$). One-way ANOVA revealed the correlation between the tumor diameter and the prognosis of patients with M0 gastric adenocarcinoma, but this correlation showed no statistical significance in analysis of the final multivariate models (Table II).

Discussion

Gastric cancer is one of the major causes in cancer-related death in China, while the adenocarcinoma occupies over 95% in malignant tumors in the stomach. Thus, how to increase the

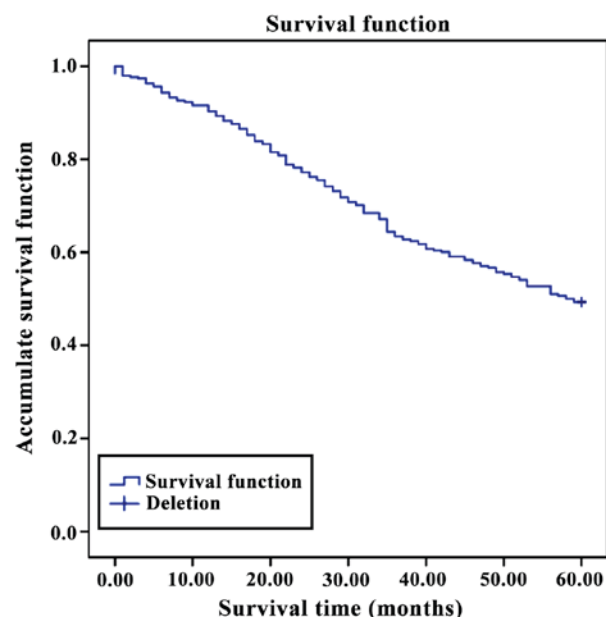


Figure 1. Survival curve of 298 patients without distant metastasis.

Table I. Clinicopathological material and 5-year survival rate of 298 patients with no distant metastasis.

Clinicopathological material	n	5-year survival rate	χ^2 value	P-value
Age (years)			3.95	0.138
≤40	26	30.8		
>40 and ≤60	107	50.5		
>60	165	51.5		
Sex			0.906	0.341
Male	201	51.2		
Female	97	45.4		
Differentiation			2.58	0.108
Non- or low-differentiation	166	45.2		
Mid- or high-differentiation	132	54.5		
Tumor position			5.44	0.066
Upper	54	38.9		
Median	69	43.5		
Lower	175	54.9		
Tumor diameter (cm)			4.84	0.028
≤5	119	57.1		
>5	179	44.147		
Regional lymphatic metastasis			17.39	<0.01
None	73	64.4		
Perigastric metastasis	108	54.6		
Metastasis outside stomach	118	35.0		
Vascular invasion			4.34	0.037
Yes	68	38.2		
No	230	52.6		
pTNM stages			33.65	<0.01
Stage I	46	78.2		
Stage II	108	58.3		
Stage III	144	33.3		

Table II. Multivariate analysis of the factors affecting the prognosis of 298 patients with distant metastasis.

Variate	Estimated value	Standard error	Wald value	P-value	Odds ratio	95% confidential interval
Tumor position	1.21	0.56	6.24	0.016	3.91	1.96-5.26
Regional lymphatic metastasis (n)	1.65	0.38	5.21	0.042	3.12	2.21-8.36
Vascular metastasis	1.29	0.24	11.45	0.021	3.52	2.36-7.56
pTNM stages	1.09	0.15	18.37	0.009	4.25	1.19-8.95

postoperative survival rate in gastric adenocarcinoma patients has become one of the primary targets in clinical research. Various factors affect the prognosis of gastric adenocarcinoma, in which pTNM stage is one of the most important factors (6). Precise pathological staging is conducive to assessment of prognosis and guidance of treatment. Currently, among the patients with gastric adenocarcinoma in an early stage, 5-year survival rate reaches over 90%, and improvement in survival and prognosis of patients with gastric adenocarcinoma in stage I, II or III (M0) can tremendously increase the overall survival rate of gastric cancer patients (7). In this study, we investigated the correlation between the pathological parameters (including sex, age, tumor position, differentiation of tumor, tumor diameter, regional lymphatic metastasis and vascular invasion) and the survival time of gastric cancer patients through retrospective analysis of 298 patients with gastric adenocarcinoma in stage I, II or III (M0) who received the D2 resection for gastric cancer.

The analysis of clinicopathological features of M0 gastric adenocarcinoma patients showed that the sex ratio of patients was 2.1:1.0, but the comparison of 5-year survival rate in patients revealed no statistically significant difference, suggesting that the difference in sex does not affect the prognosis of patients. As for the age of onset, young patients (age ≤ 40 years) occupied 8.7%, which coincide with the description in previous studies (8). Among young patients undergoing D2 resection for gastric cancer, the 5-year survival rate was only 30.7%, $< 50.5\%$ in middle-aged patients (41 to 60 years) and 51.5% in elder patients (age > 60 years). Comparison of prognosis among patients in different age showed no statistically significant difference ($P=0.138$). In this study, patients with gastric adenocarcinoma in non- or low-differentiation slightly outweighed those in moderate- or high-differentiation; among the young and middle-aged patients, most of them were with gastric adenocarcinoma in low- or non-differentiation, and were in stage III or above at the time of diagnosis due to the high malignancy and rapid progression. However, young patients are usually without other severe organic diseases and are tolerant to surgery. Thus, despite of the higher 5-year survival rate among the gastric adenocarcinoma patients in moderate- or high-differentiation, one-way ANOVA showed no statistically significant difference ($P>0.05$).

In this study, the proportion of patients with tumors in upper parts of stomach was relatively low, and their 5-year survival rate (38.9%) was inferior to those with tumor in middle or lower parts of stomach. While in the patients with tumor in lower part of stomach, the 5-year survival rate was 54.9%, significantly higher than that in the patients with

tumor in upper part of the stomach. Petrelli *et al* (9) reported tumors in upper 1/3 region of stomach can increase the risk of tumor-related death, suggesting that the position of tumor is a key prognostic factor (9). In this study, the results of one-way ANOVA showed $P=0.066$, slightly > 0.05 , but multivariate analysis suggested that the position of tumor is an independent risk factor. Also, analysis of results showed that patients with tumors in the upper region of stomach are more susceptible to regional lymphatic metastasis, which conforms to the results of previous studies in other countries (9,10). Studies have shown that regional lymphatic metastasis is one of the key risk factors leading to the postoperative recurrence and death of patients with gastric adenocarcinoma (11), which could serve as not only the prognostic indicator for development and outcome of patients, but also important evidence for stipulating the adjuvant therapy and follow-up procedure after surgery. Clinically, during the extraction and examination of lymph nodes, it is quite difficult to evaluate the quantity of lymph nodes if there is fusion of metastatic lymph nodes (12). In this study, all participants underwent standard D2 resection, and after lymph node dissection, > 20 lymph nodes would be obtained for biopsy, thereby confirming the regional lymphatic metastasis based on the statistics, which could also maximally reduce the bias in stages caused by uneven quantity of lymph nodes (13). Nitti *et al* (14) carried out a study involving 277 patients with lymphatic metastasis, and the results showed that the quantity of metastatic lymph nodes in gastric cancer patients is an effective prognostic factor, which is consistent with the results of our study. With 5 cm as a critical point, we divided the patients in gastric adenocarcinoma of stage T1-3 into the large-diameter group (> 5 cm) and small-diameter group (≤ 5 cm) and the 5-year survival rates of these two groups were 44.2 and 57.1%. One-way ANOVA of these results showed $P<0.05$, suggesting that the difference had statistical significance, but analysis in Cox regression models suggested no statistically significant differences in comparisons of tumor diameter and survival of patients. Hence, the diameter of tumor is not an independent risk factor affecting the prognosis of patients with gastric adenocarcinoma. Kunisaki *et al* (15) reported that the tumor diameter can be used as an independent risk factor affecting the prognosis of gastric adenocarcinoma patients depending on the infiltration of the tumors, while in gastric adenocarcinoma, the range of tumor infiltration to the adjacent organs is considered as the major factor influencing the prognosis of patients (15).

pTNM stage serves as the crucial reference for choice of clinical treatment strategy and assessment of prognosis for gastric adenocarcinoma (16). In late 2016, the American Joint Committee on Cancer (AJCC) released the TNM staging

system for gastric cancer (8th edition), with which physicians can stipulate more rational therapeutic procedure and assess the efficacy of the procedure in a scientific way, and the new edition of TNM staging system is conducive to increase precision of assessment of prognosis (17). Tokunaga *et al* (18,19), and the multivariate analysis in this study indicated that pTNM stage is one of the most important indicators influencing the postoperative prognosis of gastric adenocarcinoma patients after D2 resection. In the 298 participants, there were 68 cases with positive signs of vascular invasion, significantly lower than 230 cases with negative signs. Among those with positive signs, the 5-year survival rate was significantly lower, and the multivariate analysis suggested that vascular invasion is an independent risk factor of survival and prognosis of gastric adenocarcinoma (20). Besides, a significant correlation was identified with the vascular invasion and the poor prognosis of gastric adenocarcinoma (11,21).

In conclusion, the one-way ANOVA and multivariate analysis of Cox regression models suggested that pTNM stage, tumor position, regional lymphatic metastasis and vascular invasion are the independent risk factors affecting the prognosis of gastric adenocarcinoma patients with non-distant metastasis. Thus, comprehensive assessment of patient's condition and prophylactic and therapeutic measures should be taken to increase the survival rate of gastric adenocarcinoma patients.

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