

Research Paper

# Prognostic Factors and Recurrence Patterns in T4 Gastric Cancer Patients after Curative Resection

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## Abstract

**Background:** To investigate prognostic factors and recurrence patterns in T4 gastric cancer (GC) patients after curative resection.**Methods:** Between January 2004 and December 2014, 249 patients with T4 gastric cancer undergoing curative resection were recruited. Patient characteristics, survival, prognostic factors and recurrence patterns were analyzed.**Results:** Our results showed that the median survival time (MST) for T4 gastric cancer after curative resection was 55.47 months, with 59.47 months for T4a (tumor perforating serosa) and 25.90 months for T4b (tumor invasion of the adjacent structure). Multivariate analysis indicated that age (hazard ratio [HR], 1.86;  $P = 0.006$ ), location of tumor (HR, 1.25, 0.90 - 5.64;  $P < 0.001$ ) and intraoperative blood loss (HR, 1.85;  $P = 0.010$ ) were independent prognostic factors for overall survival (OS). After a median follow-up of 25.87 months, a total of 109 (43.8%) patients suffered from recurrence, and 90 patients had been observed specific recurrence sites, among which peritoneal metastasis was the most common recurrence pattern, 59.0% for T4a and 88.3% for T4b, respectively.**Conclusions:** For T4 gastric cancer patients after curative resection, older age, gastric cancer of the entire stomach and more intraoperative blood loss were associated with poor OS. The recurrence rate after curative resection for T4 was high, and the most common recurrence pattern was peritoneal metastasis.

Key words: T4 gastric cancer; curative resection; prognosis; recurrence; survival

## Introduction

Gastric cancer is the fifth most common malignant tumor in the world and the third most common cause of malignant tumor-related death [1]. Though the overall survival (OS) of gastric cancer patients has improved with the development of standardized D2 lymphadenectomy [2] and subsequent adjuvant chemotherapy in recent years [3, 4], the long-term survival rate is still unsatisfactory.

Moreover, the majority of gastric cancer patients in China were diagnosed as advanced gastric cancer (AGC) at an early visit. The overall 5-year OS for AGC patients is below 20%, and it is approximately 30% for those who undergo surgery. Even after curative resection, only 30–50% of patients are still alive after 5 years [5]. Among AGC T4 gastric cancer patients, which includes tumor perforating serosa (T4a) and

invasion of the adjacent structure (T4b), patients often suffered from recurrence and had dismal overall survival, even after R0 resection. Several studies have reported potential prognostic factors affecting the survival of T4 gastric cancer patients after curative resection, including lymph node metastasis, venous invasion, peritoneal washing cytology and tumor diameter [6-8]. However, the sample sizes of previous studies were small.

Recurrence is the most important factor affecting the survival of patients with GC. After curative resection for GC, recurrence patterns include local-regional recurrence, distant lymph node metastasis, hematogenous metastasis, and peritoneum implantation. According to soil and seed theory, T4 GC patients are prone to suffering peritoneal seeding. However, there are few studies exploring the recurrence patterns for T4 GC after curative resection.

In the present study, we aimed to clarify the prognostic factors and recurrence patterns for T4 GC after curative resection, which would help clinicians perform the appropriate treatment in order to improve survival.

## Methods and patients

Between January 2004 and December 2014, a total of 249 gastric cancer patients were treated with curative resection (R0 resection) and diagnosed as pathological T4 stage in Sun Yat-sen University Cancer Center. Standardized D2 lymphadenectomy or expanded resections for gastric cancer (including D2 + lymphadenectomy, or D2 lymphadenectomy plus the resection of other adjacent organs) were performed in these patients with curative resection. Tumors were staged according to the seventh edition of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system [9]. Patients were excluded if they received neoadjuvant treatment, were diagnosed as late-stage gastric cancer or underwent R1/2 (microscopically/macrospectically residual tumor) resection. According to NCCN Guidelines [10], our clinicians recommended that all the included patients received adjuvant chemotherapy. However, in clinical practice, whether or not they received adjuvant chemotherapy was determined by the will of the patients.

All patients were followed up every 3 months in the first 2 years, 6 months in the 3-5 years, and 12 months annually thereafter, the median follow-up time was 25.87 months (range, 0.3-137).

The following clinicopathological data were collected prospectively through a constructed database: gender, age, tumor size, weight loss, tumor location, type of gastrectomy, extent of

lymphadenectomy, intraoperative blood loss, postoperative complications, histological type, harvested lymph nodes, N stage, Lauren type, lymphatic invasion, venous invasion, perineural invasion and adjuvant chemotherapy. OS time was calculated from the time of surgery to death or the last follow-up date. Recurrence patterns were diagnosed based on imaging examination, gastroscopy with biopsy, and/or cytological examination of ascites, or intraoperative findings in patients who underwent reoperation.

## Statistical analysis

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc, Chicago, IL, USA). Categorical variables, presented as rate, were compared by the  $\chi^2$  (Chi-square) test. Continuous data, expressed as the mean  $\pm$  standard deviation (SD), were compared by Student's t-test. Survival outcomes were analyzed using the Kaplan-Meier method and compared using the log-rank test. Factors that were considered as significant in the univariate analysis ( $P < 0.05$ ) were included in the multivariate analysis by Cox regression. HR with 95% confidence intervals (CIs) were presented.  $P < 0.05$  was considered statistically significant.

## Results

### Patient characteristics

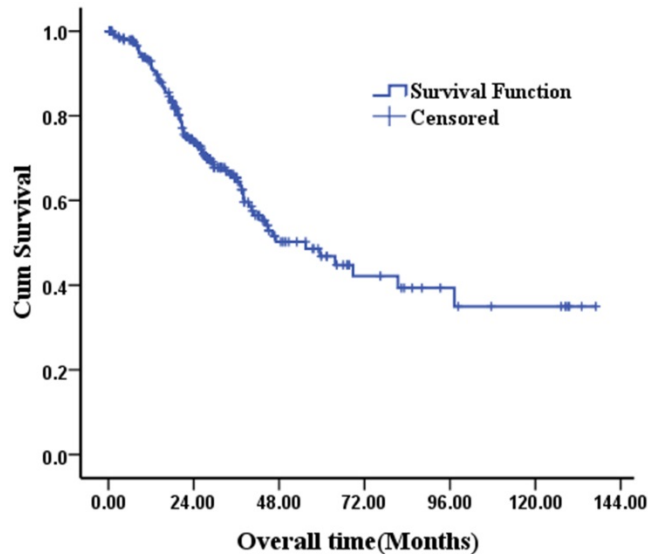
The clinicopathologic characteristics of 249 patients were summarized in Table 1. There were 221 T4a and 28 T4b GC patients receiving curative resection, comprising 165 males and 84 females, with a mean age of 56.10 years (range, 21-82 years). Some 221 patients underwent standard D2 lymphadenectomy, while 28 patients had expanded resection. The postoperative morbidity rate was 6.0%. A total of 184 patients (73.9%) received adjuvant chemotherapy after surgery. As shown in Table 2, the main organs invaded with T4b were the pancreas and spleen.

### Survival

The median follow-up duration was 25.87 months (range, 0.3-137.0 months). The OS rate of 249 patients was 92.5% at 1 year, 65.3% at 3 years and 46.8% at 5 years (Fig 1).

Our results showed that the MST for T4a gastric cancer was longer than that for T4b gastric cancer [59.47 (95% CI: 32.64-86.30) months versus 25.90 (95% CI: 12.32-39.48) months] (Fig. 2A). The MST difference was significant ( $P = 0.034$ ). In the univariate analysis, age ( $P = 0.007$ ) (Fig. 2B), weight loss ( $P = 0.013$ ), tumor location ( $P < 0.001$ ) (Fig. 2C), extent of lymphadenectomy ( $P = 0.034$ ), intraoperative blood loss ( $P < 0.001$ ) (Fig. 2D), postoperative complications

( $P = 0.038$ ) and N stage ( $P = 0.012$ ) were significant predictors of OS (Table 3). Multivariate analysis revealed that age ( $P = 0.006$ ), tumor location ( $P < 0.001$ ) and intraoperative blood loss ( $P = 0.010$ ) remained as independent prognostic factors for long-term survival (Table 3).



**Fig. 1.** Kaplan-Meier survival curves of 249 T4 gastric cancer patients after curative resection.

**Table 1.** Clinicopathologic characteristics for 249 patients with T4 gastric cancer after curative resection.

Variables	n (%)
Gender	
Male	165 (66.3)
Female	84 (33.7)
Age (y)	
≤60	156 (62.7)
>60	93 (37.3)
Tumor diameter (cm)	
≤6.5	176 (70.7)
>6.5	73 (29.3)
Weight loss (kg)	
≤5	197 (79.1)
>5	52 (20.9)
Location of tumor	
Upper 1/3	93 (37.3)
Middle 1/3	38 (15.3)
Lower 1/3	97 (39.0)
Entire	21 (8.4)
Type of gastrectomy	
Distal	103 (41.4)
Proximal	47 (18.9)
Total	99 (39.7)
Lymphadenectomy	
D2	221 (88.8)
Expanded D2	28 (11.2)
Intraoperative blood loss (ml)	
≤110	142 (57.0)
>110	107 (43.0)
Postoperative complications	
Absence	234 (94.0)
Presence	15 (6.0)
Histological type	
Moderate or well differentiated	26 (10.4)
Poorly differentiated	223 (89.6)

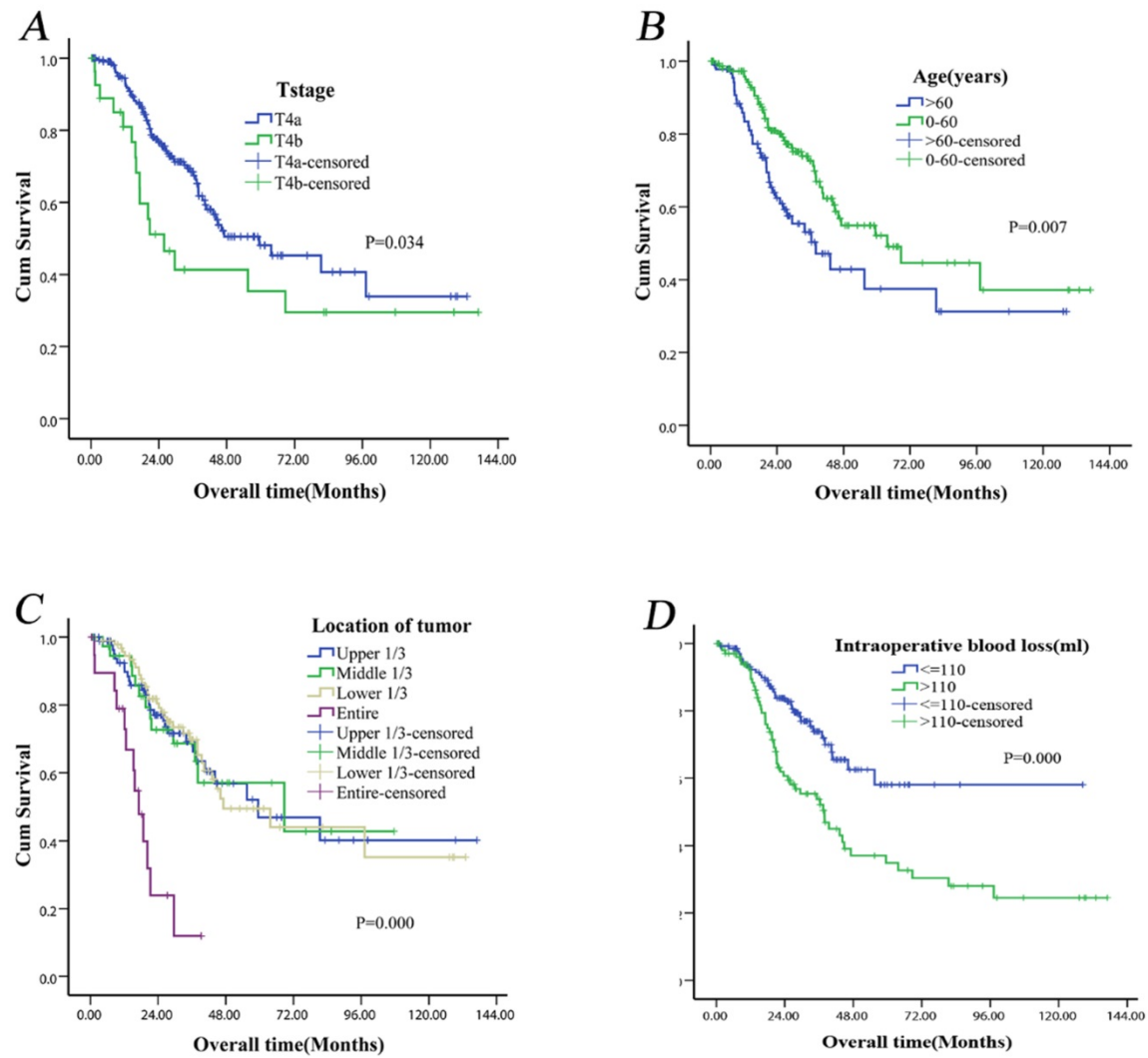
Number of harvested lymph nodes	
<15	21 (8.4)
≥15	228 (91.6)
N stage	
N0-N1	77 (30.9)
N2-N3	172 (69.1)
Lauren classification	
Intestinal	99 (39.8)
Diffuse	25 (10.0)
Mixed	38 (15.2)
Lymphatic invasion	
Absence	138 (55.4)
Presence	111 (44.6)
Venous invasion	
Absence	151 (60.6)
Presence	98 (39.4)
Perineural invasion	
Absence	113 (45.4)
Presence	136 (54.6)
Postoperative chemotherapy	
No	65 (26.1)
Yes	184 (73.9)

**Table 2.** Organs Invaded by T4b Gastric Cancer.

Invaded organs	n	%
Pancreas	15	53.6
Spleen	13	46.4
Liver	4	14.3
Transverse colon or mesocolon	3	10.7
Adrenal gland	2	7.2
Gallbladder	1	3.6
Diaphragm	1	3.6
No. of invaded organs		
One	20	71.4
Two	6	21.4
Four	2	7.2

### Pattern of recurrence and risk factors of recurrence

After a median follow up of 25.87 months, a total of 109 (43.8%) patients experienced recurrence. The recurrence rates for T4a and T4b patients were 92/221 (41.6%) and 17/28 (60.7%), respectively. Of these, the recurrence sites were obtained in a total of 90 patients, with a median of 15.90 (range: 1-71.1) months relapsing after curative surgery. The recurrence patterns were shown in Table 4. Among those 90 patients, peritoneal metastasis (62.2%) was the most frequent recurrence site, followed by hematogenous metastasis (26.7%), distant lymph node metastasis (24.4%) and locoregional metastasis (15.6%). The peritoneal metastasis was the most common recurrence pattern, accounting for 88.3% (10/12) recurrence in T4b, and 59.0% (46/78) in T4a. The multivariate analysis showed that the N stage and intraoperative blood loss were the independent risk factors for recurrence (Table 5).



**Fig. 2.** Kaplan-Meier survival curves of T4 gastric cancer patients after curative resection according to tumor invasion (T4a vs. T4b) ( $P = 0.034$ ) (A), age ( $P = 0.007$ ) (B), tumor location ( $P < 0.001$ ) (C), intraoperative blood loss ( $P < 0.001$ ) (D). All P-values were calculated using the log-rank test.

**Table 3.** Univariate analysis of risk factors and Multivariable Cox regression analysis of risk factors for patients with T4 gastric cancer.

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Gender		0.555		
Male	1			
Female	1.144 (0.732~1.787)			
Age (y)		0.007		0.006
≤60	1.769 (1.160~2.697)		1	
>60			1.859 (1.195~2.892)	
Tumor diameter (cm)		0.026		0.561
≤6.5	1		1	
>6.5	1.622 (1.055~2.494)		0.844 (0.477~1.494)	
Weight loss (kg)		0.013		0.067
≤5	1		1	
>5	1.785 (1.120~2.844)		1.593 (0.968~2.623)	
Location of tumor		0.000		0.000
Upper 1/3	1		1	
Middle 1/3	1.016 (0.526~1.963)		1.252 (0.626~2.503)	
Lower 1/3	0.966 (0.585~1.593)		0.899 (0.537~1.506)	
Entire	4.854 (2.463~9.567)		5.640 (2.463~12.915)	
Type of gastrectomy		0.204		
Proximal	1			
Distal	1.195 (0.682~2.094)			
Total	1.535 (0.954~2.468)			
Lymphadenectomy		0.034		0.819

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
D2	1		1	
Expanded D2	1.801 (1.037~3.125)		1.072 (0.588~1.955)	
Intraoperative blood loss (ml)		0.000		0.010
≤110	1		1	
>110	2.148 (1.392~3.316)		1.851 (1.162~2.950)	
Postoperative complications		0.038		0.223
Absence	1		1	
Presence	2.130 (1.027~4.420)		1.606 (0.750~3.439)	
Histological type		0.913		
Moderate or well differentiated	1			
Poorly differentiated	1.037 (0.536~2.007)			
Number of harvested lymph nodes		0.156		
≤15	1			
>15	0.663 (0.374~1.175)			
N stage		0.012		0.113
N0-N1	1		1	
N2-N3	1.874 (1.137~3.089)		1.520 (0.906~2.551)	
Lauren classification		0.849		
Intestinal	1			
Diffuse	0.896 (0.370~2.173)			
Mixed	0.790 (0.344~1.816)			
Lymphatic invasion		0.082		
Absence	1			
Presence	1.458 (0.951~2.235)			
Venous invasion		0.923		
Absence	1			
Presence	1.023 (0.644~1.625)			
Perineural invasion		0.549		
Absence	1			
Presence	0.871 (0.555~1.368)			
Postoperative chemotherapy		0.272		
No	1			
Yes	0.760 (0.465~1.242)			
T4 stage		0.034		
T4a	1			
T4b	1.801 (1.037~3.125)			

**Table 4.** Sites of recurrence in 90 patients.

Recurrence site	Total group (%)	T4a	T4b	P value
peritoneum implanting	56 (62.2)	46	10	0.105
Hematogenous	24 (26.7)	21	3	0.888
distant lymph node	22 (24.4)	20	2	0.501
Locoregional	14 (15.6)	14	0	0.110
No. of sites				
One	67 (74.4)			
Two	19 (21.1)			
Three	4 (4.5)			

## Discussion

Even with the development of standardized D2 lymphadenectomy [2] and subsequent adjuvant chemotherapy [4, 11] for gastric cancer, the survival outcomes are still unsatisfactory, causing a third of cancer-related deaths worldwide [1]. Patients often suffer from recurrence after curative resection in the first 5 years, especially T4 patients. Better understanding of the prognostic factors and recurrence patterns for T4 gastric cancer will help clinicians to perform more intensive treatment strategies for high-risk patients. In the present study, our results demonstrated that age, tumor location and intraoperative blood loss were the prognostications of

OS for T4 gastric cancer after curative resection. Moreover, peritoneal metastasis was the most common pattern of recurrence.

Several studies [6-8, 12, 13] had reported the prognostic factors for T4 gastric cancer. Fukuda et al [6] reported that number of metastatic lymph nodes, venous invasion and peritoneal washing cytology influenced the prognosis of T4 gastric cancer after potentially curative resection. Li et al [7] found that lymph node involvement was the only prognostic factor of OS. However, the sample sizes of previous studies were small, and they included patients with noncurative resection, such as R1/2 resection. While previous studies did not report the survival discrepancy regarding age, our results indicated that elderly patients (>60 years) had worse survival outcomes. The reasons for this might be considered as follows. First, disorder of immune function in elderly GC patients might relatively weaken antitumor capacity and lead to poor prognosis [14]. Second, compared to young patients, elderly patients cannot tolerate extensive lymphadenectomy and the toxicities of chemotherapy. Therefore, elderly patients get inadequate treatment, which affects survival.



**Table 5.** Relationship between the recurrence and clinicopathologic characteristics by univariate and multivariate analysis in T4 gastric cancer patients after curative resection.

Variables	Univariate analysis		$\chi^2$ test P value	Multivariate analysis	
	No recurrence	Recurrence		Hazard ratio (95% CI)	P value
No. of patients	(n=140)	(n=109)			
Gender			0.835		
Male	48	36			
Female	92	73			
Age (y)			0.385		
≤60	91	65			
>60	49	44			
Tumor diameter (cm)			0.090		
≤6.5	105	71			
>6.5	35	38			
Weight loss (kg)			0.050		
≤5	117	80			
>5	23	29			
Location of tumor			0.115		
Upper 1/3	58	35			
Middle 1/3	21	17			
Lower 1/3	54	43			
Entire	7	14			
Type of gastrectomy			0.291		
Proximal	58	45			
Distal	22	25			
Total	60	39			
Lymphadenectomy			0.055		
D2	129	92			
Expanded D2	11	17			
Intraoperative blood loss (ml)			0.004		0.041
≤110	91	51		1	
>110	49	58		1.778 (1.024~3.088)	
Postoperative complications			0.191		
Absence	134	100			
Presence	6	9			
Histological type			0.796		
Moderate or well differentiated	14	12			
Poorly differentiated	126	97			
Number of harvested lymph nodes			0.359		
≤15	14	15			
>15	126	94			
N stage			0.016		0.019
N0-N1	52	25		1	
N2-N3	88	84		1.992 (1.119~3.545)	
Lauren classification			0.308		
Intestinal	59	40			
Diffuse	16	9			
Mixed	28	10			
Lymphatic invasion			0.879		
Absence	77	61			
Presence	63	48			
Venous invasion			0.308		
Absence	81	70			
Presence	59	39			
Perineural invasion			0.029		0.139
Absence	55	58		1	
Presence	85	51		0.659 (0.379~1.145)	
Postoperative chemotherapy			0.315		
No	40	25			
Yes	100	84			
T4 stage			0.055		
T4a	128	92			
T4b	11	17			

The impact of intraoperative blood loss on long-term outcomes had been reported in various types of malignancy [15-18]. Dhar et al [19] reported that more than 500 ml blood loss during surgery was an independent predictor of survival in gastric cancer patients with transmural depth invasion following a curative resection. Liang et al [20] also found intraoperative blood loss was an independent prognostic factor for gastric cancer after curative resection. In line with previous studies, our results showed that more intraoperative blood loss (>110 ml) during surgery was an independent prognosis factor in T4 gastric cancer after curative resection. The exact mechanism of how blood loss affects the survival of patients remained unclear. It was considered that excessive intraoperative blood loss reduces the body's immunity, thus affecting the patients' ability to fight cancerous cells [19]. Therefore, our results implied that operating carefully to reduce intraoperative blood loss might improve the survival of T4 gastric cancer after curative resection.

In spite of improvements in surgical technique and adjuvant chemotherapy, advanced gastric cancer patients always suffered recurrence after curative resection. The majority of recurrences happened within 2 years postsurgery [21-25]. Previous studies had reported the recurrence patterns of gastric cancer [25-28], especially for patients with tumor invading serosa (T4 stage). However, the recurrence patterns of T4 gastric cancer with curative resection have not been reported. In the present study, 109 of 249 (43.8%) patients experienced relapse. Among them, 90 patients had specifically documented recurrence sites, and peritoneal metastasis was the most frequent recurrence pattern (n = 56), accounting for 62.2% of all relapsed patients. For T4b patients, the peritoneal metastasis ratio reached 88.3%. According to the seed and soil theory, when gastric cancer invades the serosa (T4), the cancer cells have a high possibility of falling into the peritoneal cavity where a suitable environment is provided for the cancer cells to grow. Kondo et al. reported that free cancerous cells could be found in 40% of stage II or III gastric cancers after peritoneal washings [29], suggesting that microscopic metastasis still remained after curative resection. Another study also reported that for advanced gastric cancer with serosal involvement, peritoneal metastasis usually occurred, with 15%-50% of patients having peritoneal metastasis at the time of surgery [30].

Peritoneal metastasis has been considered the terminal stage of gastric cancer, with a median overall survival of less than 6 months [31], accounting for almost 60% of all causes of GC death [32]. Therefore, understanding how to prevent and treat peritoneal

metastasis is clinically important. In 1988, Fujimoto et al reported that hyperthermic intraperitoneal chemotherapy (HIPEC) was effective for gastric cancer patients with peritoneal seeding. A large number of studies also reported similar results [33-37]. Moreover, several prospective randomized controlled trials [38-41] also reported that curative resection with HIPEC was a useful treatment to prevent occurrence of peritoneal metastasis in advanced gastric cancer. Theoretically, HIPEC after curative resection could help eliminate free cancer cells and micro metastases in the abdominal cavity for T4 gastric cancer, which might prolong survival of patients. Nevertheless, this remained to be confirmed through well-designed randomized controlled trials.

There were several limitations in the present study. First, the present study was a retrospective, single-center research project. Second, the time span of this study was long (10 years). Therefore, the results of this study should be interpreted cautiously. A large-scale, validation study is required to confirm the results.

## Conclusions

For T4 gastric cancer patients after curative resection, older age, entire gastric cancer and more intraoperative blood loss were associated with poor OS. The recurrence rate after curative resection for T4 was high, and the most common recurrence pattern was peritoneal metastasis.

## Competing Interests

The authors have declared that no competing interest exists.

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