

Clinicopathologic characteristics in patients with upper third gastric cancer following radical surgical treatment

A retrospective cohort study

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Abstract

The incidences of upper third gastric cancer (UTGC) have been increasing. However, the prognostic factors for UTGC following radical surgical treatment remains largely unknown. This study was to investigate prognostic factors for overall survival (OS), lymph node metastasis and recurrence of UTGC.

Clinicopathologic data of 126 UTGC patients who underwent radical surgical treatment were retrospectively analyzed. OS and univariate analysis were determined by Kaplan–Meier analysis and the significance of the difference between curves was calculated with the log-rank test. The Cox proportional hazards regression model was applied to perform multivariate analysis. Receiver operating characteristic (ROC) curve analysis was used to determine the prognostic accuracy.

The 1-, 3-, and 5-year OS for patients with UTGC were 81%, 47.6%, and 38.6% respectively. Univariate analysis showed that tumor size ($P = .019$), tumor invasion depth ($P < .001$), and lymph node metastasis ($P < .001$) were the risk factors for 5-year OS. Multivariate analysis identified tumor invasion depth ($P < .001$) and lymph node metastasis ($P < .001$) as independent prognostic factors for the 5-year OS in patients with UTGC. In addition, ROC curve analysis showed that tumor invasion depth ($P = .017$) or lymph node metastasis ($P = .001$) alone showed significantly effective prognosis for the 5-year OS in patients with UTGC. For UTGC patients with lymph node metastasis, tumor size ($P = .023$), lym embolism ($P = .003$), tumor invasion depth ($P = .002$), and invasion of tunica serosa ($P = .004$) were the risk factors for the 5-year OS. Multivariate analysis identified tumor size ($P = .048$), lym embolism ($P = .032$), tumor invasion depth ($P = .004$), and invasion of tunica serosa ($P = .031$) as independent prognostic factors for the 5-year OS. For UTGC patients with distant metastasis or tumor recurrence, univariate and multivariate analyses demonstrated that tumor invasion depth and lymph node metastasis were independent prognostic factors for the 5-year OS.

The results suggested that for UPGC patients undergoing the radical surgical treatment, tumor invasion depth and/or lymph node metastasis are the independent prognostic factors for the 5-year OS, lymph node metastasis, distant metastasis and tumor recurrence.

Abbreviations: CT = computed tomography, GC = gastric cancer, OS = overall survival, ROC = receiver operating characteristic, UICC = International Union Against Cancer, UTGC = upper third gastric cancer.

Keywords: lymph node metastasis, overall survival, prognosis, receiver operating characteristic, upper third gastric cancer

1. Introduction

Gastric cancer (GC) is the fourth most common cancer in the world^[1] and the second most common cancer in China.^[2] It is well-known that GC incidence varies with different geographic

regions. Qinghai Province in the North-Western China is one of the provinces with the highest gastric cancer incidence and mortality in China.^[3] Although the incidence of GC has recently plateaued, the frequency of the upper third GC (UTGC), also defined as gastric cancer in the upper third (cardiac area) of the stomach or gastric cancer in the upper-third stomach, has increased worldwide.^[4,5] Regional incidences of UTGC are variable.^[6–8] The West countries has relatively higher proportions of UTGC compared with Asian countries.^[11] Some studies have reported an increasing trend in the incidence of UTGC in Japan, China, and Korea.^[6,8–10] The incidences of UTGC in different parts of China are also variable. The northern parts has relatively higher rate of UTGC compared with the southern parts.^[8] Some studies in both Western and Eastern countries have reported a poorer prognosis with UTGC.^[11,12] Others, however, found that the prognosis of patients with UTGC was no poorer than that of patients with middle and lower GC in each equal TNM stage.^[13,14] These discrepancies prompted us to investigate the clinicopathological characteristics and prognosis of UTGC. In this study, we retrospectively examined the clinicopathological changes and the potential prognostic factors of UTGC patients

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who underwent radical surgical treatment from August 2008 to July 2013 in the Affiliated Hospital of Qinghai University, China.

2. Materials and methods

2.1. Patients

A total of 126 patients with UTGC who underwent the radical surgical treatment from August 2008 to July 2013 in the Affiliated Hospital of Qinghai University (Xining, China) were retrospectively analyzed. The pathologic diagnosis and classification of UTGC were based on the Guidelines of the Japanese Gastric Cancer Association.^[15] Lymph node metastasis was evaluated using the International Union Against Cancer (UICC) TNM classification system.^[16] Preoperative evaluation included endoscopic examination with biopsy and computed tomography (CT). Clinical lymph node metastasis was diagnosed by CT. Adjuvant chemotherapy was administered within 8 weeks of surgery to 20 patients with tumors that had invaded deeper than the subserosal layer, in addition to lymph node metastasis. This study was approved by the Review Board of the Affiliated Hospital of Qinghai University. Written informed consent was obtained from each participant.

2.2. Operative procedures

All patients underwent radical resection (complete removal of the tumor with microscopic examination of margins showing no tumor cells). Radical lymph node dissection was performed D1 in 18 patients and D2 in 108 cases. Total gastrectomy combined with splenectomy was performed in 4 cases, simple total gastrectomy in 10 cases, proximal gastric resection combined with splenectomy in 11 cases, proximal resection in 101 cases. All operations were conducted by the surgeons with over 10 years of experiences.

2.3. Follow-up

Postoperative follow-up was conducted by telephone and outpatient examinations every 3 months for the first year, every 6 months for the second year, and annually thereafter until at least 5 years after the operation or the date of the patient's death.

As of April 2, 2018, the percentage of follow-up was 95.2% (120/126).

2.4. Statistical analysis

Statistical analyses were performed with SPSS 22.0 (SPSS Inc., Chicago, IL). Receiver operating characteristic (ROC) curve analysis was used to determine the prognostic accuracy. Pearson χ^2 test and Fisher exact test were applied for categorical variables; continuous variables were analyzed by the student *t* test. Survival and univariate analysis were determined by Kaplan–Meier analysis, and the significance of the difference between curves was calculated with the log-rank test. The Cox proportional hazards regression model was applied to perform multivariate analysis. All statistical analyses were 2-sided, and *P* value < .05 was considered statistically significant.

3. Results

3.1. Clinicopathologic characteristics of patients with UTGC

Demographically, there were 113 (89.7%) males and 13 (10.3%) females in a total of 126 UTGC patients who

Table 1

Clinicopathologic characteristics of UTGC and univariate analysis of factors affecting 5-year OS of UTGC.

	Number of case (%)	5-year OS (%)	<i>P</i>
Sex			.907
Male	113 (89.7)	37.7	
Female	13 (10.3)	38.5	
Age, y			.058
≤44	5 (4.0)	80.0	
45–59	35 (27.8)	41.9	
≥60	86 (68.2)	33.4	
Tumor size, cm			.019
≤5	77 (61.1)	47.8	
>5	49 (38.9)	24.4	
Macroscopic types			.830
EGC	9 (7.1)	53.3	
Borrmann1	10 (7.9)	20.0	
Borrmann2	14 (11.1)	26.8	
Borrmann3	86 (68.3)	35.5	
Borrmann4	7 (5.6)	42.9	
Histological type			.826
Differentiated	111 (88.1)	38.4	
Undifferentiated	15 (11.9)	40.0	
Depth of invasion			<.001
T1	8 (6.3)	94.4	
T2	67 (53.2)	90.1	
T3	24 (19.0)	71.2	
T4	27 (21.5)	49.4	
Lymph node metastasis			<.001
N0	53 (42.1)	61.9	
N1	52 (41.2)	31.5	
N2	19 (15.1)	21.4	
N3	2 (1.6)	10.0	
Growth types			.501
Mass	32 (25.4)	43.1	
Nest	33 (26.2)	30.3	
Infiltration	61 (48.4)	34.8	
Lym embolism			.174
Absent	96 (76.2)	43.4	
Present	30 (23.8)	22.9	
Venous infiltration			.101
Absent	123 (97.6)	38.0	
Present	3 (2.4)	66.7	
Adjuvant chemotherapy			.064
Absent	106 (84.1)	31.4	
Present	20 (15.9)	50.0	

OS=overall survival, UTGC=upper third gastric cancer.

underwent radical operation (Table 1). There were 5 cases less than or equal to 44 years old, 35 in 45 to 59 years old, 86 equal to or more than 60 years old. Macroscopically, 7 cases had the tumor diameter of less than or equal to 5 cm and 49 cases of more than 5 cm. There were only 9 cases (7.1%) in early stage, 24 (19.0%) in progressive stage (Borrmann1+2), and 93 (73.9%) in invasive type (Borrmann3+4). Histologically, 111 tumors were differentiated and 15 were undifferentiated. T1 tumors were found in 8 patients (6.3%), T2 in 67 patients (53.2%), and T3 in 24 (19.0%) and T4 in 27 (21.5%). At least 15 lymph nodes were examined pathologically in all patients. Lymph node involvement was detected in 73 patients. According to the UICC TNM classification system, 52 patients were N1, 19 were N2, and 2 were N3.

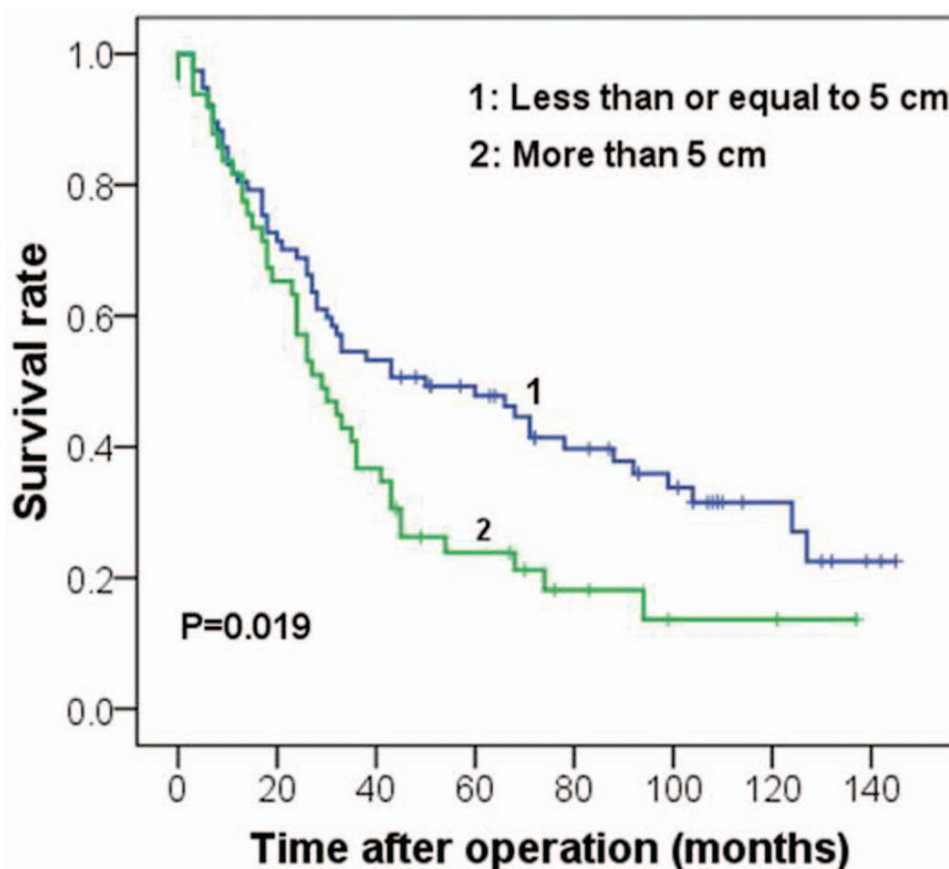


Figure 1. Survival curves for UTGC patients with different tumor size.

3.2. Univariate and multivariate analysis of factors affecting 5-year overall survival (OS) in patients with UTGC undergoing radical surgical treatment

The 1-, 3-, and 5-year OS for patients with UTGC were 81%, 47.6%, and 38.6% respectively. Univariate analysis was employed to estimate the clinical factors affecting the 5-year OS in patients with UTGC. As described in Table 1, no differences in 5-year OS were found in terms of sex, ages, macroscopic types, histological type, tumor growth types, lym embolism, venous infiltration, and adjuvant chemotherapy. However, tumor size ($P=.019$), tumor invasion depth ($P<.001$) and lymph node metastasis ($P<.001$) were risk factors for 5-year OS (Table 1 and Figs. 1–3). Five-year OS for tumor size of ≤ 5 and > 5 cm were 47.8% and 24.4% respectively. Five-year OS for T1, T2, T3, and T4 were 94.4%, 90.1%, 71.2%, and 49.4% respectively. 5-year OS for N0, N1, N2, and N3 were 61.9%, 31.5%, 21.4%, and 10.0% respectively. To further identify the independent prognostic factors for 5-year OS rates in patients with UTGC, all risk factors for 5-year OS identified by univariate analysis were underwent multivariate Cox regression analysis. As shown in Table 2, tumor invasion depth (relative risk, RR, 1.536; 95% confidence interval, CI, 1.403–1.682; $P<.001$) and lymph node metastasis (RR, 1.811; 95% CI, 1.592–2.059; $P<.001$) were identified as independent prognostic factors for the 5-year OS in patients with UTGC.

ROC curve analysis was performed to evaluate the prognostic accuracy of the tumor invasion depth and lymph node metastasis, 2 independent prognostic factors for the 5-year OS in patients with UTGC. As presented in Figure 4, tumor invasion depth (area

under curve [AUC], 0.637; 95% CI, 0.531–0.743; $P=.017$) or lymph node metastasis alone (AUC, 0.689; 95% CI, 0.589–0.788; $P=.001$) showed significantly effective prognosis for the 5-year OS in patients with UTGC.

3.3. Clinicopathologic comparison in UTGC patients with or without lymph node metastasis

As showed in Table 3, no differences in UTGC patients with or without lymph node metastasis were found in terms of sex, ages, macroscopic types, histological type, tumor growth types, lym embolism, and venous infiltration. However, univariate analysis of clinical factors affecting the 5-year OS in UTGC patients with lymph node metastasis revealed that tumor size ($P=.023$), lym embolism ($P=.003$), tumor invasion depth ($P=.002$), and invasion of tunica serosa ($P=.004$) were risk factors for the 5-year OS (Table 4). Five-year OS for tumor size of ≤ 5 and > 5 cm were 57.2% and 32.7% respectively. Five-year OS for the absence and presence of lym embolism were 56.4% and 23.9%, respectively. Five-year OS for T1, T2, T3 and T4 were 83.3%, 53.6%, 34.6%, and 25.9%, respectively. Five-year OS for the absence and presence of invasion of tunica serosa were 56.5% and 34.7%, respectively. Multivariate Cox regression analysis of all these risk factors showed that tumor size (RR, 1.587; 95% CI, 1.005–2.506; $P=.048$), lym embolism (RR, 1.687; 95% CI, 1.046–2.721; $P=.032$), tumor invasion depth (RR, 1.421; 95% CI, 1.118–1.806; $P=.004$) and invasion of tunica serosa (RR, 1.619; 95% CI, 1.044–2.509; $P=.031$) were identified as

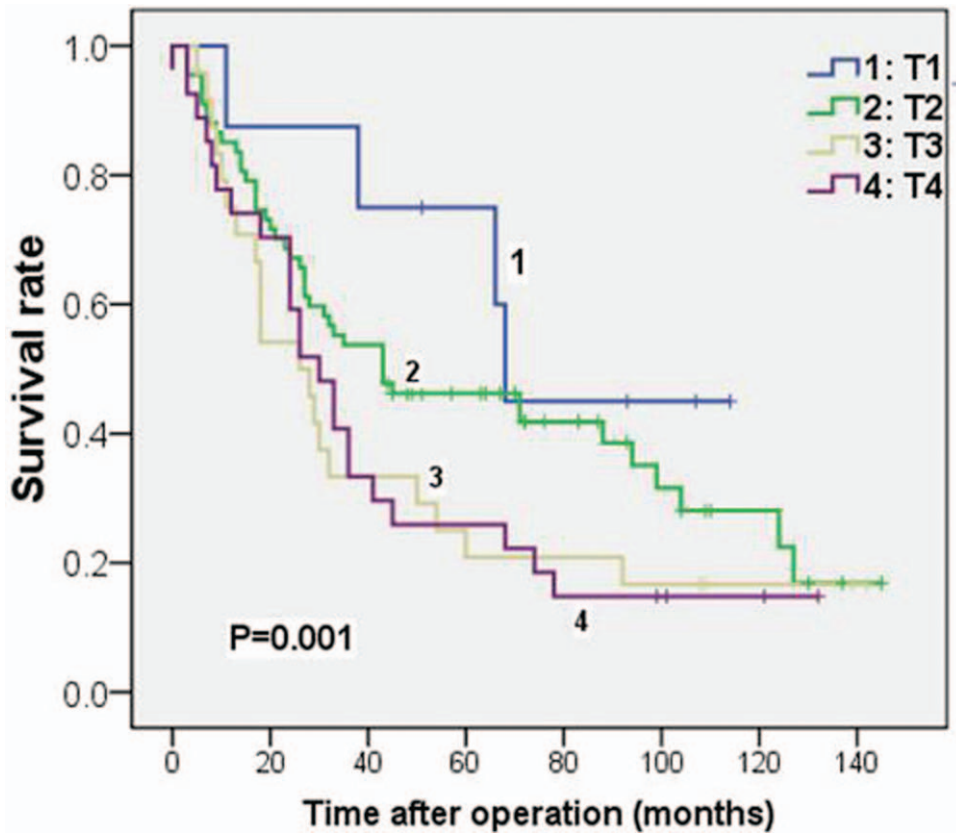


Figure 2. Survival curves for UTGC patients with different T stages.

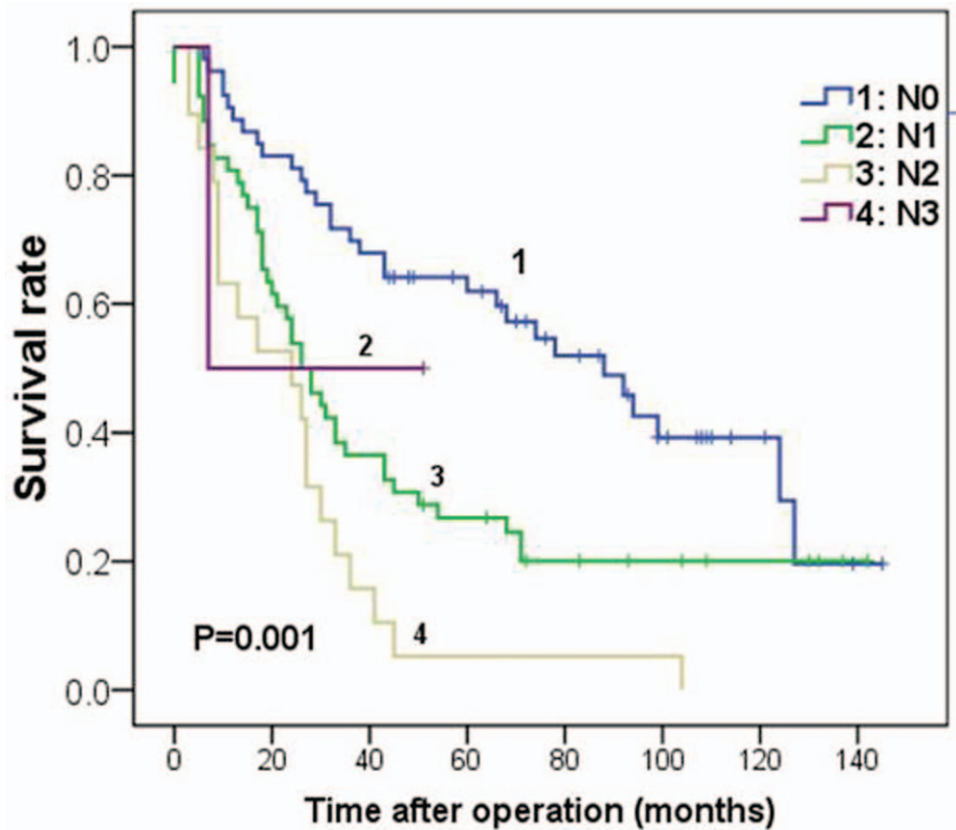


Figure 3. Survival curves for UTGC patients with different N stages.

Table 2
Multivariate analysis of factors affecting 5-year OS in patients with UTGC.

	RR	95% CI	P
Depth of invasion	1.536	1.403–1.682	<.001
Lymph node metastasis	1.811	1.592–2.059	<.001

OS=overall survival, UTGC=upper third gastric cancer.

independent prognostic factors for the 5-year OS in UTGC patients with lymph node metastasis (Table 5).

3.4. Clinicopathologic comparison in UTGC patients with or without distant metastasis

The results showed that no differences in UTGC patients with or without distant metastasis were found in terms of sex, ages, tumor size, macroscopic types, histological type, tumor growth

types, lym embolism, and venous infiltration (Table 6). However, univariate analysis of clinical factors affecting the 5-year OS in UTGC patients with distant metastasis revealed that tumor invasion depth ($P < .001$) and lymph node metastasis ($P < .001$) were risk factors for the 5-year OS (Table 7). Five-year OS for T1, T2, T3 and T4 were 89.5%, 68.3%, 25.6%, and 15.0%, respectively. 5-year OS for N0, N1, N2, and N3 were 90.8%, 69.5%, 46.7%, and 50.5%, respectively. Multivariate Cox regression analysis of these two risk factors showed that tumor invasion depth (RR, 1.536; 95% CI, 1.403–1.682; $P < .001$) and lymph node metastasis (RR, 1.811; 95% CI, 1.592–2.059; $P < .001$) were identified as independent prognostic factors for the 5-year OS in UTGC patients with distant metastasis (Table 8).

3.5. Clinicopathologic comparison in UTGC patients with or without tumor recurrence

As showed in Table 9, no differences in UTGC patients with or without tumor recurrence were found in terms of sex, ages, tumor

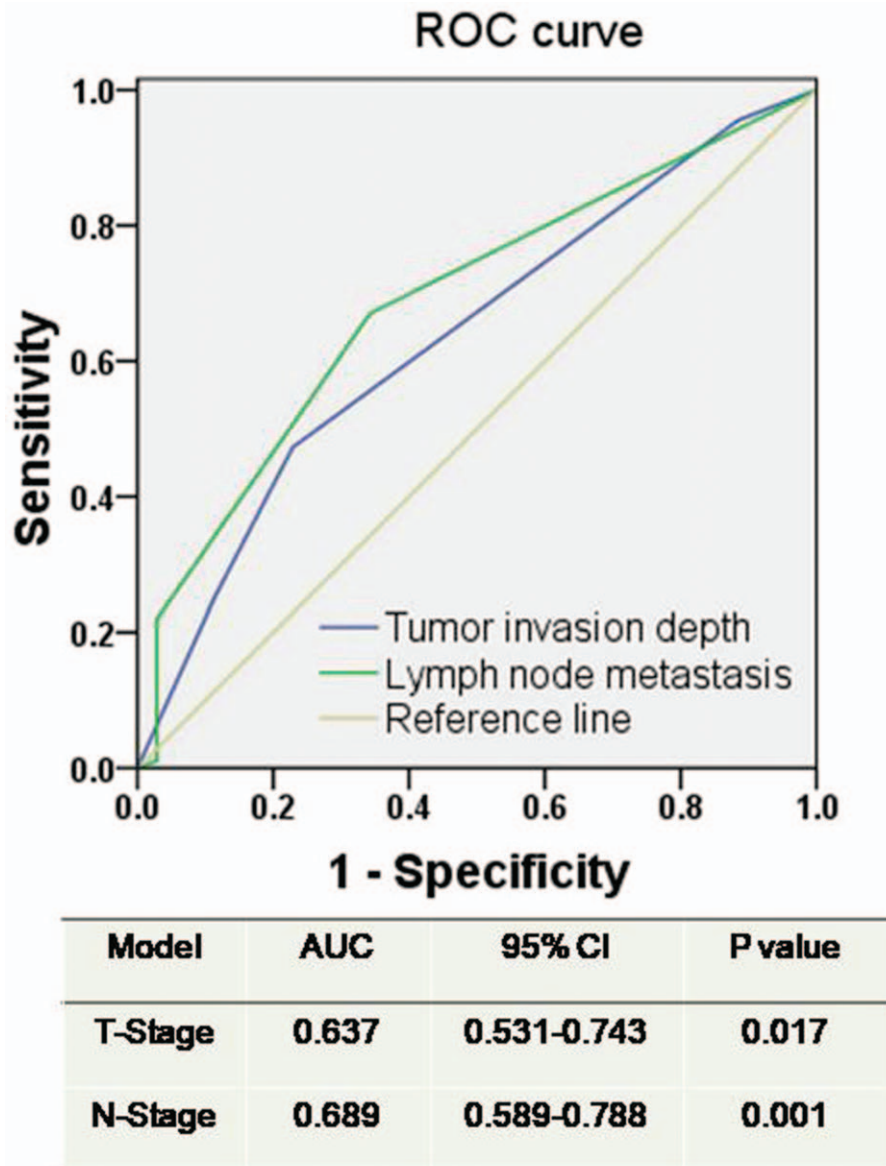


Figure 4. ROC curves for UTGC patients with different T and N stages.

Table 3

Demographic and pathological comparison in UTGC patients with or without lymph node metastasis.

	Cases without lymph node metastasis (%)	Cases with lymph node metastasis (%)	P
Sex			.774
Male	47 (88.7)	66 (90.4)	
Female	6 (11.3)	7 (9.6)	
Ages, y			.430
≤44	3 (5.7)	2 (2.7)	
45–59	12 (22.6)	23 (31.5)	
≥60	38 (71.7)	48 (65.8)	
Tumor size, cm			.007
≤5	36 (67.9)	31 (42.5)	
>5	17 (22.1)	42 (57.5)	
Macroscopic types			.011
EGC	7 (13.2)	1 (1.4)	
Borrmann 1	5 (9.4)	5 (6.8)	
Borrmann 2	8 (15.1)	6 (8.2)	
Borrmann 3	32 (60.4)	55 (75.3)	
Borrmann 4	1 (1.9)	6 (8.2)	
Depth of invasion			.029
T1 + T2	35 (66.0%)	33 (45.2)	
T3 + T4	18 (34.0%)	40 (54.8)	
Growth types			.151
Mass	10 (18.9)	15 (20.5)	
Nest	19 (35.8)	15 (20.5)	
Infiltration	24 (45.3)	43 (59.0)	
Lym embolism			<.001
Absent	49 (92.5)	47 (64.4)	
Present	4 (7.5)	26 (35.6)	
Histological type			<.001
Differentiated	19 (35.8)	6 (8.2)	
Undifferentiated	34 (64.2)	67 (91.8)	
Invasion of tunica serosa			.029
Absent	35 (66.0)	33 (45.2)	
Present	18 (34.0)	40 (54.8)	

UTGC=upper third gastric cancer.

size, macroscopic types, histological type, tumor growth types, lym embolism, and venous infiltration. However, univariate analysis of clinical factors affecting the 5-year OS in UTGC patients with tumor recurrence demonstrated that tumor

Table 4

Univariate analysis of factors affecting 5-year OS in UTGC patients with lymph node metastasis.

	Number of case (%)	5-year OS (%)	P
Tumor size, cm			.023
≤5	31 (42.5)	57.2	
>5	42 (57.5)	32.7	
Lym embolism			.003
Absent	47 (64.4)	56.4	
Present	26 (35.6)	23.9	
Depth of invasion			.002
T1	1 (1.4)	83.3	
T2	32 (43.8)	53.6	
T3	19 (26.0)	34.6	
T4	21 (28.8)	25.9	
Invasion of tunica serosa			.004
Absent	33 (45.2)	56.5	
Present	40 (54.8)	34.7	

OS=overall survival, UTGC=upper third gastric cancer.

Table 5

Multivariate analysis of factors affecting 5-year OS in UTGC patients with lymph node metastasis.

	RR	95% CI	P
Depth of invasion	1.421	1.118–1.806	.004
Tumor size, cm	1.587	1.005–2.506	.048
Lym embolism	1.687	1.046–2.721	.032
Invasion of tunica serosa	1.619	1.044–2.509	.031

CI=confidence interval, OS=overall survival, RR=relative risk, UTGC=upper third gastric cancer.

invasion depth ($P < .001$) and lymph node metastasis ($P = .002$) were risk factors for the 5-year OS (Table 10). Five-year OS for T1, T2, T3 and T4 were 75.0%, 68.1%, 65.9%, and 57.9%, respectively. Five-year OS for N0, N1, N2 and N3 were 84.4%, 57.7%, 23.6%, and 50.0%, respectively. Multivariate Cox

Table 6

Demographic and pathological comparison in UTGC patients with or without distant metastasis.

	Cases without distant metastasis (%)	Cases with distant metastasis (%)	P
Sex			NS
Male	56 (90.3)	57 (89.1)	
Female	6 (9.7)	7 (10.9)	
Ages, y			.355
≤44	4 (6.5)	1 (1.6)	
45–59	16 (25.8)	19 (29.7)	
≥60	42 (67.7)	44 (68.8)	
Tumor size, cm			.07
≤5	43 (69.4)	34 (53.1)	
>5	19 (30.6)	30 (46.9)	
Macroscopic types			.827
EGC	5 (8.1)	3 (4.7)	
Borrmann 1	5 (8.1)	5 (7.8)	
Borrmann 2	7 (11.3)	7 (10.9)	
Borrmann 3	41 (66.1)	45 (70.3)	
Borrmann 4	7 (11.3)	4 (6.3)	
Growth types			.932
Mass	13 (21.0)	12 (18.8)	
Nest	16 (25.8)	18 (28.1)	
Infiltration	33 (53.2)	34 (53.1)	
Lym embolism			.835
Absent	48 (77.4)	48 (75.0)	
Present	14 (22.6)	16 (25.0)	
Invasion of tunica serosa			<.001
Absent	43 (69.4)	8 (12.5)	
Present	19 (30.6)	56 (87.5)	
Depth of invasion			.013
T1	6 (9.7)	2 (3.1)	
T2	39 (62.9)	28 (43.8)	
T3	10 (16.1)	14 (21.9)	
T4	7 (11.3)	20 (31.3)	
Lymph node metastasis			.007
N0	33 (53.2)	20 (31.3)	
N1	25 (40.3)	27 (42.2)	
N2	3 (4.8)	16 (25.0)	
N3	1 (1.6)	1 (1.6)	
Histological type			NS
Differentiated	7 (11.3)	8 (12.5)	
Undifferentiated	55 (88.7)	56 (87.5)	

UTGC=upper third gastric cancer.

Table 7
Univariate analysis of factors affecting 5-year OS in UTGC patients with distant metastasis.

	Number of case (%)	5-year OS (%)	P
Depth of invasion			<.001
T1	2 (3.1)	89.5	
T2	28 (43.8)	68.3	
T3	14 (21.9)	25.6	
T4	20 (31.3)	15.0	
Lymph node metastasis			.026
N0	20 (31.3)	90.8	
N1	27 (42.2)	69.5	
N2	16 (25.0)	46.7	
N3	1 (1.6)	50.0	

OS=overall survival, UTGC=upper third gastric cancer.

regression analysis of these 2 risk factors showed that tumor invasion depth (RR, 1.308; 95% CI, 1.135–1.688; $P=.001$) and lymph node metastasis (RR, 1.282; 95% CI, 1.361–1.631; $P=.004$) were identified as independent prognostic factors for the 5-year OS in UTGC patients with tumor recurrence (Table 11).

4. Discussion

The present study has some limitations. First, this was a retrospective study with a small sample size at a single institution. Second, no comparison of UTGC with middle or lower GC was performed, which need further investigation in the future. Third, effect of operative approaches on outcome remains to be examined.

In this retrospective study, we analyzed the clinical and pathological findings of 126 UTGC patients undergoing the radical surgical treatment in Qinghai Province of the Northwest China during a period of 5 years. We found that the 1-, 3-, and 5-year OS for UTGC patients were 81.1%, 47.6%, and 38.6% respectively. Multivariate analysis revealed that tumor invasion depth and/or lymph node metastasis are the independent prognostic factors for the 5-year OS, lymph node metastasis, distant metastasis, and tumor recurrence of UTGC.

The epidemiology of gastric cancer remains largely unknown. *Helicobacter pylori* has been reported to chronically infect the stomach of more than 50% of the human population, representing the major cause of gastric cancer.^[17] UTGC is biologically aggressive and typically are diagnosed at advanced stages of the disease. As a result, they are difficult to treat, and patient prognosis is poor.^[18] The OS rate of UTGC varies in different population.^[19] Li et al^[20] found that the 1-, 3-, and 5-year OS of 367 UTGC patients were 76.0%, 28.9%, and 13.6%, which are much lower than that of 81.1%, 47.6%, and 38.6% accordingly in the present study. The reason might be explained by the facts that the percentages of stages of both (T3 + T4)/(T1 +

Table 8
Multivariate analysis of factors affecting 5-year OS in UTGC patients with distant metastasis.

	RR	95% CI	P
Depth of invasion	1.536	1.403–1.682	<.001
Lymph node metastasis	1.811	1.592–2.059	<.001

CI=confidence interval, OS=overall survival, RR=relative risk, UTGC=upper third gastric cancer.

Table 9
Demographic and pathological comparison in UTGC patients with or without local recurrence.

	Cases without local recurrence (%)	Cases with local recurrence (%)	P
Sex			NS
Male	81 (90.0)	32 (88.90)	
Female	9 (10.0)	4 (11.1)	
Ages, y			.844
≤44	4 (4.4)	1 (2.8)	
45–59	24 (26.7)	11 (30.6)	
≥60	62 (68.9)	24 (66.7)	
Tumor size, cm			.544
≤5	53 (58.9)	24 (66.7)	
>5	37 (41.1)	12 (33.3)	
Macroscopic types			.557
EGC	5 (5.6)	3 (8.3)	
Borrmann 1	8 (8.9)	2 (5.6)	
Borrmann 2	12 (13.3)	2 (5.6)	
Borrmann 3	59 (65.6)	27 (75.0)	
Borrmann 4	9 (10.0)	2 (5.6)	
Growth types			.576
Mass	19 (21.1)	6 (16.7)	
Nest	22 (24.4)	12 (33.3)	
Infiltration	49 (54.4)	18 (50.0)	
Lym embolism			.821
Absent	69 (76.7)	27 (75.0)	
Present	21 (23.3)	9 (25.0)	
Invasion of tunica serosa			.422
Absent	34 (37.8)	17 (47.2)	
Present	56 (62.2)	19 (52.8)	
Depth of invasion			.720
T1	6 (6.7)	2 (5.6)	
T2	50 (55.6)	17 (47.2)	
T3	17 (18.9)	7 (19.4)	
T4	17 (18.9)	10 (27.8)	
Lymph node metastasis			.012
N0	45 (50.0)	8 (22.2)	
N1	35 (38.9)	17 (47.2)	
N2	9 (10.0)	10 (27.8)	
N3	1 (1.1)	1 (2.8)	
Histological type			.362
Differentiated	9 (10.0)	6 (16.7)	
Undifferentiated	81 (90.0)	30 (83.3)	

OS=overall survival, UTGC=upper third gastric cancer.

Table 10
Univariate analysis of factors affecting 5-year OS in UTGC patients with local recurrence.

	Number of case (%)	5-year OS (%)	P
Depth of invasion			.001
T1	2 (5.6)	75.0	
T2	17 (47.2)	68.1	
T3	7 (19.4)	65.9	
T4	10 (27.8)	57.9	
Lymph node metastasis			.002
N0	20 (31.3)	84.4	
N1	27 (42.2)	57.7	
N2	16 (25.0)	23.6	
N3	1 (1.6)	50.0	

OS=overall survival, UTGCupper third gastric cancer.

Table 11**Multivariate analysis of factors affecting 5-year OS in UTGC patients with local recurrence.**

	RR	95% CI	P
Depth of invasion	1.308	1.135–1.688	.001
Lymph node metastasis	1.282	1.361–1.631	.004

CI = confidence interval, OS = overall survival, RR = relative risk, UTGC = upper third gastric cancer.

T2 + T3 + T4) and (N2 + N3)/(N0 + N1 + N2 + N3) in the previous study by Li et al^[20] are much higher than that of our finding (93.2% vs 40.5% for T stage and 47.9% vs 16.7% for N stage). These differences in survival rate, T stage and N stage suggested that the deeper of tumor invasion and the more lymph node metastasis, the less survival rate of UTGC. In addition, studies have been shown that the depth of gastric wall infiltration, lymph node metastasis and distant metastasis have been recognized as the important independent prognostic indicators,^[21] among which pT and pN are most significant.^[22] Some scholars^[23] think that lymph node metastasis is the most important prognostic factor. Kunisaki et al^[13] reported the prognostic factors for 191 early UTGC patients following the surgical treatment and found that esophageal invasion, macroscopic appearance, tumor diameter, histological type, depth of invasion, lymph node metastasis, lymphatic invasion, and venous invasion all significantly affected prognosis, whereas sex, age, and adjuvant chemotherapy did not as assessed by univariate analysis. In the multivariate analysis, depth of invasion, and lymph node metastasis both independently influenced prognosis.^[13] Inconsistently, the present study showed that only tumor size, tumor invasion depth and lymph node metastasis were the risk factors for 5-year OS as evaluated by univariate analysis. These inconsistencies might be attributed to the early UTGC in the previous study and relatively more advanced UTGC in our study. Consistently, our study also identified tumor invasion depth and lymph node metastasis as independent prognostic factors for the 5-year OS in patients with UTGC as assessed by multivariate analysis. ROC curve analysis also revealed that tumor invasion depth or lymph node metastasis alone showed significantly effective prognosis for the 5-year OS in patients with UTGC.

Lymph node metastasis is one of the most important factors that affect postoperative OS of UTGC.^[19,24] The lymph node metastasis rate in this study is 57.9%. It is well known that the prognosis of non lymph node metastases is better than that of those without metastasis.^[19] The surgical effect and prognosis of gastric cancer are closely related to the lymph node metastasis with 3 folds of the 5-year OS with or without lymph node metastasis.^[25] Consistently, the present study revealed that the 5-year OS with or without lymph node metastasis were 21.7% and 61.9% respectively. Multivariate analysis identified tumor size, lymph embolism, tumor invasion depth, and invasion of tunica serosa as independent prognostic factors for the 5-year OS in UTGC patients with lymph node metastasis. The present study also showed that 5-year OS in UTGC patients with lymph node metastasis for T1, T2, T3, and T4 were 83.3%, 53.6%, 34.6%, and 25.9% respectively, suggesting that with the increase in T stage, the 5-year OS decreases accordingly.

Local recurrence and distant metastasis are the other most important factors that affect postoperative OS of UTGC.^[26] In spite of the significant effect of enlarged lymph node dissection and joint viscera resection for gastric cancer, the overall effect is still unsatisfactory. More than half of the patients relapse after radical

gastrectomy, which is the main cause of death after radical gastrectomy. It has been reported that the recurrence rate of gastric cancer after radical resection is as high as 50.0% to 70.0%^[27]. Macdonald et al^[28] reported that in patients with lymph node metastases in the resected specimen, the relapse and death rates from recurrent cancer are at least 70% to 80%. Yoo et al^[29] evaluated the long-term results of a proximal gastrectomy of 63 UTGC patients to analyze the risk factors of local recurrence affecting survival in these patients. The authors found that during a median follow-up period of 37 months, 25 of the 63 patients (39.7%) developed a recurrence of cancer, with local recurrence in 15 patients (23.8%), the majority of these occurring at the remnant stomach or anastomosis. Univariate analysis of risk factors for local recurrence revealed an infiltrative or diffuse gross type, with a tumor sizes > 5 cm, a distal resection margin < or = 3 cm and serosal invasion. In the present study, multivariate Cox regression analysis showed that tumor invasion depth and lymph node metastasis were identified as independent prognostic factors for the 5-year OS in UTGC patients with local recurrence and distant metastasis.

5. Conclusion

The present study has suggested that for UPGC patients undergoing the radical surgical treatment, tumor invasion depth and/or lymph node metastasis are the independent prognostic factors for the 5-year OS, lymph node metastasis, distant metastasis, and tumor recurrence. The results are of clinically useful for the early diagnosis and treatment of UTGC.

Author contributions

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