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Risk factors for Recurrence in T1-2N0 Gastric Cancer in the United States and China

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Abstract

Introduction—Recurrence patterns after curative intent gastrectomy for T1-2N0 gastric adenocarcinoma are poorly defined. We sought to assess timing, patterns, and risk factors for recurrence in patients treated at two high-volume gastric cancer centers in the United States and China.

Methods—Between 1995 and 2011, 1,058 patients underwent curative intent gastrectomy. Recurrences were classified as locoregional, distant, or peritoneal. Univariate and multivariate analyses were performed to identify risk factors for recurrence.

Results—Overall, 7% (76) of our 1,058 patients from the United States (n=414) and China (n=644) recurred. Liver (43%) was the most common site of recurrence in both countries (US: 24%, China: 52%), followed by peritoneum (16%), lymph nodes (10%), and anastomosis (8%). Median time to recurrence was 23 months (US: 30 months, China: 23 months), which decreased with increasing T-stage (T1a: 27 months, T1b: 24 months, T2: 22 months). Tumor size (P=0.001), depth of invasion (P=0.010), histological type (P=0.022) and lymphovascular invasion (P=0.001) were independently associated with recurrence.

Conclusion—Patients infrequently recur following curative intent gastrectomy for T1-2N0 gastric adenocarcinoma. Almost all recurrences occur between six months and three years post-operatively, most frequently in distant anatomic locations, selective followup during this time period is recommended.

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Conflicts of interest: None

Keywords

gastric cancer; recurrence pattern; prognosis; gastric carcinoma; Eastern and Western; China and the US; post-operative follow up

Introduction

Gastric cancer is one of the leading causes of global cancer deaths annually¹, with an estimated 951,000 new diagnoses and 723,000 deaths due to gastric cancer in 2012. Though gastric cancer occurs primarily in Asia, Eastern Europe, and South America^{2,3}, the incidence in the United States (US) is increasing, with an estimated 21,600 new diagnoses in 2013⁴.

The proportion of early gastric cancer (T1 – 2) has increased in recent years^{5–8}, possibly due to a combination of increased screening and improved diagnostic techniques. Early gastric cancer (T1-2N0) rarely recurs following curative resection, and the current NCCN Gastric Cancer Guidelines do not recommend adjuvant treatment for this subgroup of gastric cancer patients⁹. The timing and patterns of recurrence following surgical resection for T1-2N0 gastric cancer remain unclear and post-operative screening is not standardized. We analyzed the post-operative course of early stage, node-negative (T1-2N0) gastric cancer patients from the US and China to assess patterns and timing of recurrence, risk factors of recurrence, and to compare recurrences between the two countries.

Methods

Following institutional board review approval, we queried the prospectively maintained gastric cancer databases at Memorial Sloan Kettering Cancer Center (MSKCC) and The First Affiliated Hospital of Dalian Medical University for T1-2N0 gastric adenocarcinoma patients who underwent R0 curative intent gastrectomy between 1995 and 2011. Patients were excluded if they had distant metastasis at the time of resection, received neoadjuvant or adjuvant chemoradiotherapy, or underwent endoscopic mucosal resection. In total we compared patient, surgical, and pathological variables from 414 US patients and 644 Chinese patients. Prior to initiation of this study, gastric surgeons confirmed that surgical techniques were similar and both centers.

Post-Operative follow-up

Post-operative follow-up strategies differed between centers. For patients at MSKCC, follow-up evaluation of MSKCC patients consisted of the patient's history, physical examination, laboratory tests, endoscopy and computerized tomography (CT). Various components of these assessments were repeated every 3 to 8 months until the third postoperative year, then every year thereafter for at least 5 years. Magnetic resonance imaging, CT of the brain or chest, and positron emission tomography were performed only when indicated by a change in clinical status.

In China, standard follow-up consists of the patient's history, physical examination, laboratory tests, tumor markers (carcinoembryonic antigen, alpha-fetoprotein, carbohydrate antigen 12-5 and carbohydrate antigen 19–9), chest radiography, endoscopy, CT, and bone

scintigraphy. These assessments were repeated every 6 months until the third postoperative year, then every year thereafter for at least 5 years. Magnetic resonance imaging, CT of the brain or chest, and positron emission tomography were performed only when indicated by a change in clinical status.

Recurrence location

Recurrence location was classified as locoregional (anastomotic, regional lymph nodes, and the resection bed), distant (other organs including left supraclavicular lymph nodes and para-aortic lymph nodes), or peritoneal (positive cytology of ascitic fluid or peritoneal nodules on cross-sectional imaging). Distant recurrence was defined according to the specific organ involved. Left supracerivical lymph nodes and para-aortic lymph nodes were considered distant recurrence.

Statistical analysis

Differences between groups were compared using chi square and t-tests and necessary. Cumulative survival curves were drawn using Kaplan–Meier methods; differences between the curves were analyzed by the log–rank test. Multivariate analysis was based on the Cox regression model. Statistical procedures were performed using SPSS version 22.0 (IBM, Armonk, NY, USA), $p < 0.05$ was considered statistically significant.

Results

Patient Demographics

Between 1995 and 2011, 1,058 patients (414 US patients and 644 Chinese patients) with T1-2N0 tumors underwent curative intent gastrectomy and 76 patients (7%) had a recurrence. Recurrence rates were similar between sites: 6% (25 / 414) in the US cohort and 8% (51 / 644) in the China cohort. Table 1 shows clinico-pathologic results for both cencers. In the United States recurrence was associated with increasing depth of invasion ($P=0.023$) and lymphovascular invasion ($P=0.047$), which in China recurrence was associated with tumor size ($P<0.001$), depth of invasion ($P<0.001$), Lauren's classification ($P=0.029$), lymphovascular invasion ($P<0.001$), lymph node retrieval ($P=0.020$) and histological type ($P=0.003$) (Table 2).

Tumor Recurrence Patterns

Of the 1,058 T1-2N0 patients in our combined cohort, 76 patients (7%) experienced recurrence at 93 specific sites of initial recurrence (Table 3). Distant locations were the most frequent site of recurrence (67%, 62 / 76 recurrences), followed by locoregional recurrence (17%, 16 / 76 recurrences) and peritoneal recurrence (16%, 15 / 76 recurrences). The liver was the most common individual site of recurrence (43% of all recurrences, followed by the peritoneum (16%), regional lymph nodes (10%), and anastomosis (8%). Of all patients who recurred, the vast majority (86%, 65 / 76) had a single site of recurrence, while the remaining 11 (14% of all recurrences) had multiple sites of recurrence.

Risk Factors for Recurrence

On both univariate and multivariate analysis tumor size > 4cm ($p = 0.001$), depth of invasion ($p = 0.01$), poorly differentiated histology ($p = 0.022$), and lymphovascular invasion ($p = 0.001$) were all independently associated with recurrence for the combined cohort (Table 4).

Survival and timing of recurrence

Overall, the 5-year recurrence-free survival rate for our cohort was 90%. The median time to recurrence was 23 months (range 6–134 months). Five-year recurrence free survival rates decreased with increasing T-stage (T1a: 98%; T1b: 91%; T2: 81%; $p < 0.001$ across groups), as did median time to recurrence (T1a: 27 months, T1b: 24 months, T2: 22 months). No T1a patients recurred before 12 months, the majority of these patients (86%) recurred after 18 months. The earliest recurrence in our cohort was at 6 months in a T2 patient, and the majority of recurrences (86%, 64 / 76) occurred by 36 months (Figure 1).

Discussion

Few studies have analyzed the recurrence of T1-2N0 stage gastric cancer patients after curative intent resection. Characterizing patterns of recurrence is important to frame guidelines for post-operative surveillance^{6,8,10,11}, and currently such guidelines do not exist for T1-2N0 patients. No patients in our cohort received neoadjuvant therapy, allowing us to compare data between the US and China without the contribution of US patients who were downstaged by neoadjuvant therapy, which is more common in the US than in China.

As in prior studies comparing Eastern and Western gastric cancer^{5,12}, our US cohort had a higher percentage of proximal tumors (43% vs 9%) while distal tumors were more common in the Chinese cohort (72% vs 32%). However, our two cohorts had similar proportions of intestinal (66% US and 69% China) and diffuse (26% US and 29% China) tumors, and similar distributions of histologic cancers in both cohorts and a similar distribution of well, moderate and poorly differentiated histology as well, making these groups more similar than different and a good cohort for combined analysis. In our US cohort we found recurrence rates of 2% (3/151) for T1a tumors, 7% (14/196) for T1b tumors, and 12% (8/67) for T2 tumors, quite similar to the rates in our Chinese cohort [T1a: 2% (4/209); T1b: 6% (12/187); T2: 14% (35/248)] and previous Eastern reports^{6,8,10,13–17}, which report recurrence rates ranging from 0.1%¹⁰ to 11.7%¹³ for T1a-1bN0 patients, and 2.5%¹⁰ – 20.6%¹⁴ in T2N0 patients.

Recurrences were classified as either locoregional, distant, or peritoneal, and as with previous reports, distant recurrences, though rare, were the predominant recurrence in our cohort of node-negative early gastric cancer^{7,8,15–17}. Patients with lymph node metastasis, perhaps the most important predictor for recurrence in gastric cancer^{15,18–21}, were purposely excluded from this study. We focused exclusively on T1-2N0 patients to identify other factors that predict recurrence, which is a generally believed to be unlikely in lymph node negative tumors. Tumor size ($P < 0.001$), depth of invasion ($P < 0.001$), histological type ($P = 0.001$) and presence of lymphovascular invasion ($P < 0.001$) were significant risk factors for recurrence, and on multivariate analysis tumor size ($P = 0.001$), depth of invasion

($P=0.010$), histological type [moderately and poorly differentiated subtypes ($P=0.022$)] and presence of lymphovascular invasion ($P=0.001$) were the independent risk factors for recurrence of T1-2N0 stage gastric cancer patients.

Recurrence in gastric cancer most commonly occurs within two years after curative intent resection^{16,19,20,22,23}. D'Angelica previously reported that 79% of all gastric cancer patients who recur do so within two years and 94% recurred within four years of resection.¹⁶ Among early gastric cancer patients who recur, Wu et al reported that 80% will recur within two years and 96% will recur within five years²³, while Lai et al reported that 61% of early gastric cancer patients who recur do so by two years and 91.1% of patients who recur do so by 5 years.²⁴

Recurrence rates among node negative early gastric cancer patients have not been previously reported, and as a result there are no recommendations for the intensity and duration of follow-up in these patients. Overall we found a low recurrence rate, and in keeping with previous reports, we found that the majority of recurrences occurred within the first five years (1 year: 28% of all recurrences; 2 years: 68%; 3 years: 84%; 4 years: 87%; 5 years: 91%; 10 years: 99%) (Figure 1). We did not find any recurrences prior to 15 months in our T1aN0 patients, suggesting limited utility of routine cross-sectional imaging or endoscopy prior to 12 months. For T1bN0 and T2N0 patients, first recurrences were at 8 months and 6 months respectively, suggesting that the 6 month mark may be a reasonable time to consider cross-sectional imaging in these patients, since recurrences in the liver, lung and peritoneum were the most common.

Interestingly, in our US cohort, recurrences occurred most commonly in the liver, lung, then lymph nodes, whereas in our Chinese cohort recurrences were most common in the liver, followed by the peritoneum, and lymph nodes, with lung being less common. The reason for these differences is not understood, especially since there were similar percentages of diffuse tumors in both groups, 25% in the US and 29% in China, as well as similar percentages of poorly differentiated histology, 47% in the US and 51% in China.

We expected to see more differences between the Chinese and US cohorts than we did. In prior studies, including South Korean gastric cancer patients, we found marked differences in the subtypes of gastric cancer between the two nations.⁵ Gastric cancer in China and the US appears to be more similar in terms of location of the tumor, Lauren's classification and histology. Previous work has shown, however, that for all tumors, Chinese gastric cancer patients demonstrate worse survival than US gastric cancer patients¹². The underlying reasons for these differences must be further evaluated.

In our study of node negative gastric cancer patients who underwent curative intent gastrectomy 7% of all patients recurred. These recurrences, which overall were quite similar in our US and Chinese cohorts, most frequently occurred at distant locations. The time of earliest recurrence differed by T-stage: no patients recurred before six months and no T1a patients recurred before a year. Overall, 80% of all patients who did recur did so within three years of resection. Surveillance for recurrence in these patients should be focused on this

short period when they are at highest risk of recurrence, as screening outside of this timeframe is low yield.

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Abbreviations

CT Computerized Tomography

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Synopsis

We describe recurrent patterns and location in a large cohort of T1-2N0 gastric cancer patients treated in the United States and China. Recurrences predominantly occur between 6 – 36 months and distant recurrences are more common than locoregional or peritoneal recurrences.

Figure 1.
Recurrence – free survival according to T stage.

Table 1

Clinicopathological data for the entire cohort.

	United States (n = 414)	China (n = 644)
Gender		
Male	255 (62)	450 (70)
Female	159 (38)	194 (30)
Age	67 (25–95)	60 (25–84)
Race		
White	344 (83)	-
Black	28 (7)	-
Asian	42 (10)	644 (100)
Tumor Location		
Upper	177 (43)	60 (9)
Middle	102 (25)	119 (19)
Lower	131 (32)	463 (72)
Diffuse	4 (1)	2 (0.3)
Depth of invasion		
T1a	151 (37)	209 (33)
T1b	196 (47)	187 (29)
T2	67 (16)	248 (38)
Tumor Size	2 (0.1–10)	3 (0.1–10)
Lymphovascular invasion	72 (17)	240 (37)
Lauren's classification		
Intestinal	273 (66)	446 (69)
Diffuse	107 (26)	188 (29)
Mix	34 (8)	10 (2)
Differentiation		
Well	69 (17)	126 (20)
Moderate	150 (36)	187 (29)
Poor	195 (47)	331 (51)
Lymph node retrieval	19 (3–66)	26 (2–68)
Operation		
Subtotal	314 (76)	508 (79)
Total	100 (24)	136 (21)
Extent of lymphadenectomy		
D1	65 (16)	162 (25)
D2	342 (83)	472 (73)
D2+	7 (2)	10 (2)
Follow up (months)	81 (2–226)	63 (10–215)

Continuous variables are expressed as median (IQR) and categorical variables as N (%).

Table 2

Clinicopathological Factors Associated with Recurrence for Individual Cohorts

	United States n = 414 patients		China n = 644 patients	
	Recurrence n=25 (6%)	p- value	Recurrence n=51 (8%)	p-value
Gender		0.497		0.088
Male	17 (7)		41 (9)	
Female	8 (5)		10 (5)	
Age:	68 (41–84)	0.463	58 (41–79)	0.887
Race		0.374		-
White	22 (6)		-	
Black	0 (0)		-	
Asian	3 (7)		51 (8)	
Tumor Location		0.333		0.575
Upper	15 (8)		4 (7)	
Middle	4 (4)		13 (11)	
Lower	6 (5)		34 (7)	
Diffuse	0 (0)		0 (0)	
T-Stage		0.023		<0.001
T1a	3 (2)		4 (2)	
T1b	14 (7)		12 (6)	
T2	8 (12)		35 (14)	
Tumor size (cm)	2.9 (1–7)	0.119	3.5 (1–10)	<0.001
Lymphovascular invasion	8 (11)	0.047	35 (15)	<0.001
Lauren's classification		0.495		0.029
Intestinal	19 (7)		32 (7)	
Diffuse	4 (4)		16 (8)	
Mix	2 (6)		3 (30)	
Differentiation		0.191		0.003
Well	2 (3)		1 (1)	
Moderate	7 (5)		16 (9)	
Poor	16 (8)		34 (10)	
Lymph node retrieval	18 (3–39)	0.398	20 (2–52)	0.020
Operation		0.985		0.062
Subtotal	19 (6)		35 (7)	
Total	6 (6)		16 (12)	
Lymphadenectomy		0.419		0.113
D1	2 (3)		8 (5)	
D2	23 (7)		41 (9)	
D2+	0 (0)		2 (20)	

Continuous variables are expressed as median (IQR) and categorical variables as N (%).

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Table 3

Specific sites of recurrence

Recurrence	Entire Cohort n = 1,058	United States n = 414	China n = 644
Total	76 patients, 93 specific sites	25 patients, 29 specific sites	51 patients, 64 specific sites
Locoregional	16 (17)	8 (28)	8 (13)
Lymph node	9 (10)	4 (14)	5 (8)
Anastomosis	7 (8)	4 (14)	3 (5)
Peritoneal	15 (16)	2 (7)	13 (20)
Distant	62 (67)	19 (65)	43 (67)
Liver	40 (43)	7 (24)	33 (51)
Lung	7 (8)	4 (14)	3 (5)
Bone	2 (2)	1 (3)	1 (2)
Brain	3 (3)	1 (3)	2 (3)
Distant lymph node	4 (4)	1 (3)	3 (5)
Others	6 (7)	5 (17)	1 (2)

Table 4

Clinicopathological Factors Associated with Recurrence for the Entire Cohort

	Recurrence n = 76	Univariate p-value	Multivariate p-value	Multivariate HR (95% CI)
Gender		0.063		
Male	58 (8)			
Female	18 (5)			
Age, year		0.653		
60	36 (8)			
>60	40 (7)			
Race		0.226		
White	22 (6)			
Black	0 (0)			
Asian	54 (8)			
Tumor size (cm)		<0.001	0.001	2.820 (1.572–5.060)
4	53 (6)			
>4	23 (21)			
Location		0.807		
Upper	19 (8)			
Middle	17 (8)			
Lower	40 (7)			
Diffuse	0 (0)			
Depth of invasion		<0.001	0.010	
T1a	7 (2)			1 (reference)
T1b	26 (7)		0.009	3.133 (1.328–7.392)
T2	43 (14)		0.002	3.811 (1.601–9.070)
Lymphovascular invasion	43 (14)	<0.001	0.001	2.397 (1.412–4.070)
Lauren's classification		0.540		
Intestinal	51 (7)			
Diffuse	20 (7)			
Mix	5 (11)			
Differentiation		0.001	0.022	
Well	3 (2)			1 (reference)
Moderate	23 (7)		0.059	3.278 (0.956–11.247)
Poor	50 (10)		0.010	4.792 (1.453–15.801)
Lymph node retrieval	18 (2-52)	0.123		
Operation		0.149		
Subtotal	54 (7)			
Total	22 (9)			
Lymphadenectomy		0.155		
D1	10 (4)			
D2	64 (8)			

	Recurrence n = 76	Univariate p-value	Multivariate p-value	Multivariate HR (95% CI)
D2+	2 (12)			

Continuous variables are expressed as median (IQR) and categorical variables as N (%).

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