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Original Article

Risk Factors and Tumor Recurrence in pT1N0M0 Gastric Cancer after Surgical Treatment

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Purpose: This study aimed to evaluate the rate, patterns, and risk factors associated with tumor recurrence in patients with T1N0 gastric cancer.
Materials and Methods: The medical records of 8,753 patients with pathological T1N0M0 gastric cancer who underwent gastrectomy between 1994 and 2014 at Sungkyunkwan University School of Medicine were examined.
Results: Among the 8,753 patients, 95 patients (1.1%) experienced tumor recurrence; this included 31 remnant, 27 hematogenous, 9 lymph nodal, 5 peritoneal, and 23 multiple-site recurrences. When patients were divided into two groups according to the presence of tumor recurrence, the following characteristics were higher in the recurrence group than in the non-recurrence group: older age (≥65 years), male gender, undifferentiated histology, submucosal invasion, and venous invasion. In multivariate analysis, older age, male gender, tumor depth (sm2 and sm3 invasion), and venous invasion were independent risk factors for tumor recurrence. The recurrence rates were 0.7% in patients with less than two risk factors, 1.7% in those with two risk factors, 3.0% in those with three risk factors, and 6.3% in those with four risk factors (P<0.001).
Conclusions: Although tumor recurrence is rare in pT1N0M0 gastric cancer, some patients with certain risk factors demonstrate an increased rate of tumor recurrence. Careful follow-up is required for patients with three or four risk factors.

Key Words: Stomach neoplasms; Recurrence; Risk factors

Introduction

The detection of early gastric cancer (EGC) has increased with advances in diagnostic methods and routine follow-up programs. According to a report from the Korean Gastric Cancer Association, the proportion of T1 cancers increased from 28.6% in 1995 to 57.7% in 2009.[1,2] Patients with EGC generally have a good prognosis after gastrectomy and the 5-year survival rate for patients with EGC can reach up to 90%.[3,4]

Recent studies using large groups of Korean patients reported that the frequency of EGC recurrence was approximately 2.0% to 5.0% after curative resection.[5-7] Given this excellent prognosis, most reports for EGC have focused on risk factors for tumor recurrence and lymph node metastasis; depth of invasion, histological type, and lymphatic or vascular invasion have been reported to be important risk factors.[8,9] Lymph node metastasis, in particular, is an important risk factor for tumor recurrence.[10-12] However, few studies have evaluated EGC without lymph node metastasis because of its excellent prognosis and less aggressive biological behavior.

Therefore, in this study, we aimed to investigate the risk factors, recurrence rates, and recurrence patterns in patients with pT1N0M0 gastric cancer after surgery.

Materials and Methods

Between January 1994 and December 2014, the records of

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8,753 patients who underwent gastrectomy at the Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine and were diagnosed with pathological T1N0M0 gastric cancer were reviewed. Exclusion factors included previous gastric surgery, preoperative chemotherapy or chemoradiotherapy, other malignancy, and follow-up loss after surgery. All patients provided written informed consent before the surgery. This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2016-07-155).

Clinicopathological characteristics included patient age and gender; tumor size, location, histological type, and Lauren classification; the presence of lymphatic, perineural, or venous invasion; and the depth of invasion. Histological type was divided into differentiated-type (including papillary adenocarcinoma and well-to-moderately differentiated tubular adenocarcinoma) and undifferentiated-type (including poorly differentiated tubular adenocarcinoma, mucinous adenocarcinoma, and signet ring cell adenocarcinoma). Tumor recurrence was identified according to standard clinical practices, which consisted of patient evaluation every 6 months for 2 years after surgery, followed by every 12 months thereafter for up to 5 years after surgery, with physical examinations, laboratory tests, imaging (abdomen-pelvis computed tomography and chest x-ray), and endoscopy. Tumor recurrence patterns were classified as remnant stomach, peritoneal, hematogenous, distant lymph node, or multiple type.

Statistical analysis was performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA), and statistically significant differences were defined as those with $P<0.05$. Continuous variables were presented as means±standard deviation, and categorical variables were compared using chi-square or Fisher's exact test. Kaplan-Meier curves and a Cox regression hazard model were adopted for the analysis of tumor recurrence. The hazard ratio and 95% confidence interval were calculated using Cox regression models.

Results

The clinicopathological features of 8,753 EGC patients with pT1N0M0 are shown in Table 1. Compared with the non-recurrence group, the recurrence group was older, had a larger percentage of male patients, and demonstrated higher incidence rates of venous invasion, differentiated histology, intestinal-type Lauren classification, and deeper penetration into the submucosal area. There were no significant differences in tumor location, type of surgery, resection margin length, or lymphatic and perineural invasion between the recurrence and non-recurrence groups.

Table 1. Comparison of clinicopathological characteristics between patients in the recurrence group and the non-recurrence group

Clinicopathological characteristic	Recurrence group (n=95)	Non-recurrence group (n=8,658)	P-value
Age (yr)			0.006
<65	60 (63.2)	6,526 (75.4)	
≥65	35 (36.8)	2,132 (24.6)	
Sex			<0.001
Female	15 (15.8)	2,992 (34.6)	
Male	80 (84.2)	5,666 (65.4)	
Tumor size (cm)	3.04±1.83	2.85±1.80	0.307
Tumor location			0.413
Upper	11 (11.6)	837 (9.7)	
Middle	23 (24.2)	2,621 (30.3)	
Lower	61 (64.2)	5,200 (60.1)	
Histologic type			0.010
Differentiated	61 (64.2)	4,411 (50.9)	
Undifferentiated	34 (35.8)	4,247 (49.1)	
Lauren type			0.011
Intestinal	65 (68.4)	4,604 (53.2)	
Diffuse	27 (28.4)	3,508 (40.5)	
Mixed	3 (3.2)	546 (6.3)	
Type of surgery			0.140
STG	80 (84.2)	7,351 (84.9)	
TG	12 (12.6)	1,215 (14.0)	
PG	3 (3.2)	92 (1.1)	
Depth of invasion*			0.002
Mucosa	46 (48.4)	5,346 (61.7)	
Sm1	9 (9.5)	1,150 (13.3)	
Sm2	18 (18.9)	996 (11.5)	
Sm3	22 (23.2)	1,166 (13.5)	
Lymphatic invasion	13 (13.7)	809 (9.3)	0.149
Perineural invasion	0 (0.0)	119 (1.4)	0.250
Venous invasion	4 (4.2)	77 (0.9)	0.001
Resection margin			
PRM	5.85±3.51	5.26±3.40	0.093
DRM	6.02±4.96	5.98±3.98	0.942

Values are presented as number (%) or mean±standard deviation. The sum of the percentages does not equal 100% because of rounding. STG = subtotal gastrectomy; TG = total gastrectomy; PG = proximal gastrectomy; Sm = submucosa; PRM = proximal resection margin; DRM = distal resection margin. *Classification according to the Japanese Gastric Cancer Association guideline.

The mean follow-up period was 69.1 months (6.0~232.0 months). Of the 8,753 patients, 95 patients (1.1%) showed tumor recurrence: 31 patients experienced remnant recurrences, 27 patients experienced hematogenous recurrences (as detected in liver, lung, brain, or bone), 9 patients experienced lymphatic recurrences, 5 patients experienced peritoneal recurrence, and 23 patients had multiple sites of recurrence (Table 2). The mean time to tumor recurrence was 49 months (6~135 months): 60 months (7~116 months) for remnant recurrences, 38 months (6~135 months) for hematogenous recurrences, 40 months (8~67 months) for lymphatic recurrences, 60 months (22~117 months)

Table 2. Site of first recurrence in patients with T1N0M0 early gastric cancer

Recurrence mode	No. of patients	Time to tumor recurrence (mo)
Remnant	31	60±29
Lymphatic	9	40±21
Hematogenous	27	38±30
Peritoneal	5	60±38
Multiple	23	47±35
Total	95	49±32

Values are presented as number only or mean±standard deviation.

Table 3. Univariate and multivariate analysis of factors associated with recurrence in T1N0M0 early gastric cancer (Cox's proportional hazard model)

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age (yr)						
<65						
≥65	2.143	1.411~3.255	<0.001*	1.909	1.238~2.944	0.003*
Sex						
Female						
Male	2.801	1.613~4.861	<0.001*	2.586	1.478~4.524	0.001*
Tumor location						
Upper						
Middle	0.573	0.279~1.176	0.129	0.706	0.343~1.455	0.346
Lower	0.762	0.401~1.448	0.406	0.897	0.468~1.717	0.742
Tumor size (cm)						
<2						
2~5	1.065	0.686~1.654	0.779	0.947	0.603~1.485	0.811
>5	1.306	0.715~2.385	0.385	1.212	0.652~2.252	0.544
Histologic type						
Differentiated						
Undifferentiated	0.656	0.431~0.999	0.050*	1.290	0.554~3.002	0.555
Lauren type						
Intestinal						
Diffuse	0.582	0.371~0.911	0.018*	0.646	0.261~1.595	0.343
Mixed	0.688	0.215~2.199	0.528	0.622	0.173~2.236	0.467
Depth of invasion†						
Mucosa, Sm1						
Sm2, Sm3	2.204	1.467~3.313	<0.001*	1.940	1.248~3.045	0.003*
Lymphatic invasion						
Negative						
Positive	1.786	0.994~3.211	0.053	1.032	0.544~1.956	0.924
Venous invasion						
Negative						
Positive	6.019	2.209~16.405	<0.001*	3.944	1.384~11.237	0.010*

HR = hazard ratio; CI = confidence interval; Sm = submucosa. *Statistically significant data (P<0.05). †Classification according to the Japanese Gastric Cancer Association guideline.

for peritoneal recurrences, and 47 months (8~105 months) for multiple recurrence sites.

Univariate analysis revealed that older age (P<0.001), male gender (P<0.001), undifferentiated-type (P=0.050), diffuse-type (P=0.018), tumor depth with sm2 and sm3 invasion (P<0.001), and venous invasion (P<0.001) were significant risk factors for recurrence (Table 3). Multivariate analysis using the significant factors identified by univariate analysis demonstrated that older age, male gender, tumor depth, and venous invasion were independent prognostic factors for recurrence.

As shown in Fig. 1, the recurrence rates were 0.7% (42/5,990) in patients with less than two risk factors, 1.7% (38/2,282) in patients with two risk factors, 3.0% (14/461) in patients with three risk factors, and 6.3% (1/16) in patients with four risk factors. The recurrence-free survival rate was significantly different according to the number of risk factors, using the log-rank test (P<0.001). The 5- and 10-year recurrence-free survival rates were 99.5% and 98.6%, respectively, in patients with less than two risk factors; 98.4% and 96.7%, respectively, in patients with two risk factors; and 97.1% and 92.1%, respectively, in patients with three risk factors. Notably, for patients with four risk factors, only the 5-year recurrence-free survival rate was available (91.7%).

Discussion

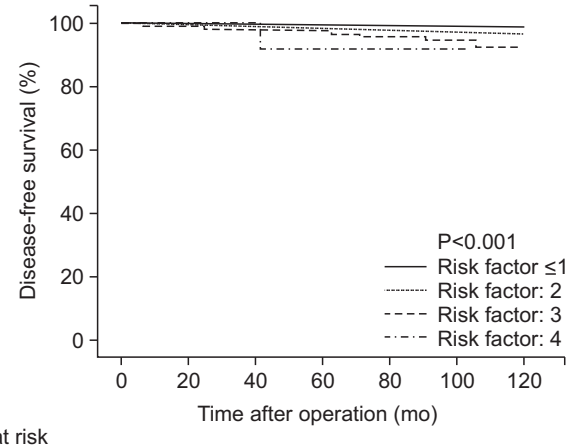
Recent studies using large groups of Korean patients have reported that the frequency of EGC recurrence was approximately 3.0% after curative resection.[5,7] Many studies have confirmed that the presence of lymph node metastasis indicates a higher probability of tumor recurrence. There has been minimal evaluation of tumor recurrence in EGC without lymph node metastasis, because it demonstrates a very low incidence of recurrence after surgery. As expected, this study found tumor recurrence in only 1.1% of patients with pT1N0M0 gastric cancer after gastrectomy. Older age (≥65 years), male gender, deeper submucosal invasion, and venous invasion were identified as significant risk factors for tumor recurrence.

Previous investigations have reported that recurrence in node-negative gastric cancer is most commonly classified as locoregional recurrence with peritoneal seeding.[13,14] However, our study showed that the most common recurrence patterns for lymph node-negative EGC were remnant (32.6%) and hematogenous (28.4%) recurrences. Interestingly, in nine cases of local lymphatic recurrence, no lymph node metastases were detected at the time of the initial surgery. One possible explanation for this finding is micrometastasis.[12] Maehara et al.[15] reported that among 34 patients with pT1N0M0 EGC who died due to tumor recurrence, micrometastasis was eventually confirmed by cytokeratin staining in eight cases.

Hematogenous EGC recurrence could theoretically arise indirectly due to the seeding of lymphovascular tissue during submucosal invasion of cancer cells.[14,16] However, in the case of mucosal EGC invasion, the mechanism for hematogenous recurrence has yet to be adequately described. In our study, 11 of the 27 hematogenous recurrences showed mucosal invasion and 16 had submucosal invasion (Sm1, n=1; Sm2, n=7; Sm3, n=8).

A multicenter longitudinal study of the recurrence patterns of the two main gastric cancer histological types after radical surgery revealed that 41% of cases were intestinal-type tumors, while 65% were diffuse-type tumors (P<0.001).[17] Our study reported that the incidence of intestinal-type tumors was higher in the recurrence group (68.4%) than in the non-recurrence group (53.2%). Lauren classification was a significant factor for EGC recurrence, but it was not an independent risk factor (P=0.381).

Risk factors related to EGC recurrence have been discussed in several reports. Shiozawa et al.[18] considered factors such as submucosal invasion and tumor size >40 mm. This study included 3,883 patients who had undergone gastrectomy for EGC. It revealed that older age (>60 years), larger tumor size, and the presence of multiple tumors were significant factors for recur-



No. at risk							
Risk factor ≤1	5,990	5,355	4,408	3,034	2,091	1,421	903
Risk factor: 2	2,282	2,018	1,555	1,058	709	458	241
Risk factor: 3	461	390	298	174	92	53	24
Risk factor: 4	16	14	11	3	1	0	0

Fig. 1. Recurrence-free survival curves for T1N0MO early gastric cancer according to the number of risk factors (Kaplan-Meier analysis with log-rank test).

rence.[5] Our study revealed that older age, male gender, tumor depth (sm2 and sm3 invasion), and venous invasion were all independent risk factors for pT1N0M0 EGC recurrence.

Node-negative EGC has a better prognosis than node-positive EGC, which may be explained by the less aggressive biological behavior of node-negative tumors.[14] Thus, lymph node metastasis remains a risk factor for EGC recurrence.[10-12] Nonetheless, pT1N0M0 EGC does recur, and additional studies are needed. After curative gastrectomy for EGC, a rigorous follow-up program of at least 5 years should be employed.

We aimed to evaluate the rate, as well as recurrence and prognostic patterns, of pT1N0M0 EGC recurrence. Our study revealed that older age (P=0.003), male gender (P=0.001), sm2 and sm3 invasion (P=0.003), and venous invasion (P=0.010) were independent risk factors for pT1N0M0 recurrence on multivariate analysis.

This study has several limitations. First, the inherent features of a nonrandomized retrospective cohort study were inevitable. Secondly, this study is limited by its use of a single center and a Korean population; therefore, the results may not be applicable to other races or populations.

However, this study has several strengths. First, to the best our knowledge, this is the largest single-center study to present long-term follow-up data characterizing EGC recurrence. Furthermore, we utilized multivariate analyses of many clinicopathological factors to adjust for confounding factors.

In conclusion, although recurrence is rare in pT1N0M0 gastric cancer, some patients with select risk factors showed a high recurrence rate. Follow-up with close monitoring is required for patients with three or four risk factors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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