Original Article

Reappraise role of lymph node status in patterns of recurrence following curative resection of gastric adenocarcinoma

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Abstract

Objective: To examine the association between lymph node status and recurrence patterns in completely resected gastric adenocarcinoma.

Methods: We retrospectively assessed 1,694 patients who underwent curative gastrectomy from January 2010 to August 2014. Patients stratified according to lymph node status and recurrence patterns among different subgroups were compared.

Results: Of all, 517 (30.5%) patients developed recurrent disease, and complete data of recurrence could be obtained in 493 (95.4%) patients. For pN0 patients, the patterns of recurrence were different according to pT stage: locoregional recurrence was most common in patients with pT1−2 disease (57.1%), distant recurrence was most common in patients with pT3 disease (57.1%), and peritoneal recurrence was most common in patients with pT4a disease (66.7%). For pN+ patients, distant metastasis was most common pattern irrespective of pT stage. The site-specific trend of recurrence showed that locoregional recurrence increased within 5 years in patients with pN0−2 disease but plateaued 3 years after surgery in patients with pN3 disease. Time to recurrence was significantly longer for the pN0 patients compared with the pN+ patients (median: 25 *vs.* 16 months, P=0.001). Moreover, post-recurrence survival was significantly better for the pN0 patients than for the pN+ patients (median: 12 *vs.* 6 months, P<0.001), especially in patients with non-peritoneal recurrence, late recurrence, single recurrence, and receipt of potential curative treatment.

Conclusions: Among clinicopathologic factors, lymph node status is the most important factor associated with recurrence patterns after curative gastrectomy. Lymph node status may be used as an adjunct in clinical decision-making about postoperative therapeutic and follow-up strategies.

Keywords: Recurrence patterns; lymph node status; post-recurrence survival; recurrence-free survival; gastric cancer

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Introduction

There were over 1,000,000 new cases of gastric cancer (GC) and an estimated 783,000 deaths caused by GC (equating to 1 in every 12 deaths globally) in 2018, making it the fifth most frequently diagnosed cancer and the third

leading cause of cancer death (1,2). Although improving surgical techniques and perioperative care have led to decreased operative mortality and morbidity (3,4), the long-term prognosis of GC remains poor (5,6). Moreover, adjuvant chemotherapy or radiochemotherapy is less effective against GC than other solid malignancies because of the heterogeneity of tumor biology (7). As a main cause of GC-related death, recurrence after curative gastrectomy was reported to occur in 20%–50% of patients (5,6,8-10). Therefore, early detection of recurrence as well as positive treatment is critical in achieving a good prognosis (11,12).

In practice, treatment and follow-up strategies for patients with GC after curative-intent resection are generally conducted based on the pathologic stage (13). However, patterns of recurrence always vary among patients with GC who had the same pathologic stage and similar treatment regimens (5,6,9,10). Thus, clinicopathologic factors associated with recurrence patterns have been extensively investigated (9,10). To our knowledge, data on the timing and site(s) of recurrence are helpful in conducting effective follow-up examinations. For example, Seo *et al*. proposed a risk-scoring system based on the extragastric recurrence of early GC to stratify postsurgical computed tomography (CT) surveillance, which can reduce the possible risk associated with radiation exposure as well as additional cost and time (14).

Lymph node status is one of the most important prognostic factors in patients with various malignancies, including GC (15-17). Several studies have demonstrated that lymph node status greatly affects patterns of recurrence in several cancers (18,19). However, patterns of recurrence in node-negative versus node-positive patients with GC have not been well characterized. In this study, using a prospectively collected database from a high-volume center, we sought to examine the impact of lymph node status on the patterns of recurrence and to identify potential factors predicting overall survival (OS) after recurrence.

Materials and methods

Study population and data collection

We retrospectively reviewed patients undergoing curative resection for GC at the Fujian Medical University Union Hospital (FMUUH) between January 2010 and August 2014. Patients who met the following criteria were included: 1) no evidence of peritoneal dissemination or distant metastasis at diagnosis; 2) gastric adenocarcinoma confirmed by histopathology; 3) D2 lymph node dissection; and 4) R0 resection. Patients were excluded if they met the following criteria: 1) concurrent malignant disease of other organs (n=16); 2) preoperative chemotherapy (n=58); 3) previous gastrectomy (n=46); 4) T4b disease (n=22); 5) postoperative death within 30 d (n=14); or 6) incomplete medical records or follow-up data (n=20). Patients with incomplete data on recurrence (n=26) were also excluded. Finally, a total of 1,694 patients were enrolled in this study (*Supplementary Figure S1*). All surgical procedures, including D2 lymph node dissection, were performed according to the guidelines of the Japanese Research Society for the Study of Gastric Cancer (13), while staging was performed according to the TNM classification [American Joint Committee on Cancer (AJCC), 8th edition] (20). Patients with advanced GC were routinely recommended to receive 6–8 cycles of 5-fluorouracil (5-FU)-based adjuvant chemotherapy [Oxaliplatin plus Capecitabine or S-1 (XELOX/SOX)] after surgery every 3 weeks. The regimen consisted of an intravenous infusion of Oxaliplatin 130 mg/m^2 on d 1 and the oral administration of Capecitabine 1,000 mg/m^2 twice daily on d 1–14 or the the oral administration of S-1 40–60 mg twice daily on d 1–14 (21). Drug toxicities were routinely recorded before the initiation of each cycle. Data on demographics and clinicopathologic results were obtained from a large-scale prospective database. Patients were divided into pN0, pN1, pN2, pN3a, and pN3b groups according to the number of positive lymph nodes. Additionally, patients with pT1–2 disease were only divided into pN0 and pN+ groups due to a small simple size. This study was reviewed and approved by the FMUUH Institutional Review Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Follow-up investigation

All patients were followed up postoperatively by physical examination, laboratory tests [including carcinoembryonic antigen (CEA), cancer antigen (CA) 19-9, and CA 72-4], and imaging examination [including chest radiography or chest CT, abdominal ultrasonography or abdominopelvic CT/magnetic resonance imaging (MRI), if necessary] every

3 months for 2 years, every 6 months during the 3rd–5th year, and annually thereafter. In addition, annual endoscopy was recommended annually. Postoperative follow-up strategies in FMUUH are detailed in *Supplementary Table S1*. The follow-up period was completed in August 2019. The median follow-up time was 68 (range, 2–113) months. OS was defined as the time interval from surgery to death from any cause or to the last follow-up. Recurrence-free survival (RFS) was defined as the time interval from surgery to recurrence or to the last follow-up.

Definition and categorization of recurrence

Recurrences were categorized as locoregional, peritoneal, or distant recurrence (5,9). Locoregional recurrence included anastomotic or gastric remnant recurrence, and regional lymph nodes. Peritoneal recurrence was indicated by positive cytology in ascitic fluid or by a convincing presence of peritoneal nodules on cross-sectional imaging as determined by the radiology report. Distant metastasis was further defined according to the specific organ involved. Cervical lymph nodes or abdominal nodes beyond the upper retroperitoneum were considered distant metastases. Mediastinal lymph node recurrence was considered locoregional for gastroesophageal junction tumors and distant metastasis for all other tumors. Tumors involving the ovaries were considered peritoneal recurrence. The presence of recurrent disease in two or more sites was defined as multiple recurrences. Multiple recurrent lesions in the same area (e.g., liver) were not classified as having multiple recurrences. Although some patients had multiple recurrence episodes, this study analyzed the initial recurrence episode as defined above. According to our previous study, recurrence within 12 months after surgery was defined as early recurrence, and recurrence more than 12 months after surgery was defined as late recurrence (22).

Treatment of recurrent disease

At FMUUH, patients with recurrent disease were treated by a professional multidisciplinary team (MDT) including surgical oncologists, medical oncologists, radiologists, pathologists, and nutritionists. Curative-intent resections were performed only when recurrent tumors could be completely resected. Systemic chemotherapy was routinely recommended for patients with good performance status and adequate organ functions. For patients with bad performance status or inadequate organ functions, best supportive treatment like pain relief and nutritional support would be performed to improve the quality of life.

Statistical analysis

The primary endpoint of the present study was the patterns of initial recurrence. The secondary endpoints were RFS, OS, and post-recurrence survival (PRS). Continuous variables were compared using Student's *t* test, and categorical variables were assessed using the χ^2 test or Fisher's exact test. Logistic regression was used for multivariate analysis of clinicopathologic factors associated with sites of initial recurrence. When exploring risk factors for sites of initial recurrence, the case group comprised all patients who experienced recurrence at the certain site (locoregional, peritoneum, or distant), including those who had multiple recurrences, while the control group comprised the remaining patients. Pearson's correlation test was performed to identify variables associated with time to recurrence at univariate analysis, then multiple linear regression analysis was developed by using enter method (23). The Kaplan-Meier method was used to analyze OS and DFS, and the differences were assessed with log-rank tests. Univariate and multivariate analysis were performed using the Cox proportional hazards model to identify predictors of survival. Variables with a value of $P<0.1$ in the univariate analysis were included in the subsequent multivariate analysis. Two-tailed $P<0.05$ was considered statistically significant. All statistical analyses were conducted with SPSS software (Version 18.0; SPSS Inc., Chicago, IL, USA).

Results

Clinicopathologic and treatment characteristics

In the present study, we reviewed 1,694 patients with gastric adenocarcinoma who underwent curative-intent resection and met our inclusion criteria between January 2010 and August 2014 at FMUUH. Of these, 1,269 patients (74.9%) were males, and 425 (25.1%) were females. The mean age at the time of surgery was 60.7 years [standard derivation (SD) 11.3 years]. According to the pathologic results, 521 (30.8%) patients were classified as stage I, 404 (23.8%) as stage II, and 769 (45.4%) as stage III; 655 patients (38.7%) had node-negative disease, and 1,039 (61.3%) had node-positive disease (*Supplementary Table S2*). After a median follow-up of 68 [interquartile

range (IQR), 41–86] months, 517 patients (30.5%) developed recurrent disease. Complete data on recurrence could be obtained in 493 (95.4%) patients. The clinicopathological and treatment characteristics for these 493 patients are summarized in *Table 1*.

OS and RFS

For all patients (excluding 24 patients with incomplete data on recurrence), the 5-year OS was 70.9%, and the 5-year RFS was 71.9%. The 5-year OS rates in the pN0 and pN+ groups were 87.9% and 52.9%, respectively, and the 5-year RFS rates were 93.7% and 55.7%, respectively (log-rank P<0.001). In multivariate analysis, more advanced pN stage, more advanced pT stage, larger tumors, and no adjuvant chemotherapy were significantly associated with disease recurrence (all P<0.05; *Supplementary Table S3*).

Pattern of recurrence according to pN stage

Figure 1 illustrates the pattern of initial recurrence for all patients. Overall, 406 (82.4%) patients experienced recurrence involving a single area, 79 (16.0%) patients experienced recurrence involving two areas, and 8 (1.6%) patients experienced recurrence involving all three areas. Distant metastasis occurred in 312 (63.3%) patients, peritoneal recurrence in 147 (29.8%) patients, and locoregional recurrence in 129 (26.2%) patients. *Figure 2* presents the sites of initial recurrence in detail. Distant metastasis was the most common site of initial recurrence in the pN+ group (including pN1, pN2, pN3a, and pN3b groups, all P<0.01), whereas the proportion in the three (locoregional, peritoneal, and distant) sites was similar in the pN0 group (*Figure 2A*). Compared with pN+ patients, pN0 patients had a significantly higher proportion of locoregional recurrence [40.9% *vs.* 24.7%, odds ratio (OR): 2.108, 95% confidence interval (95% CI), 1.114–3.990, P=0.020], a significantly lower proportion of distant metastasis (43.2% *vs.* 65.3%, OR: 0.405, 95% CI, 0.216–0.758, P=0.004), and a comparable proportion of peritoneal recurrence (29.5% *vs.* 29.8%, OR: 0.986, 95% CI, 0.500–1.943, P=0.967). We next performed a stratified analysis according to pT stage. The proportion of distant metastasis was higher than that of locoregional or peritoneal recurrence in pN+ patients irrespective of pT stage (significant difference was not found only in pT4aN1 patients). For the pN0 patients, locoregional recurrence was the most common site of initial recurrence in patients with pT1–2 disease (57.1%), followed by distant recurrence (42.9%) and peritoneal recurrence (14.3%); distant metastasis was the most common site in patients with pT3 disease (57.1%), followed by locoregional recurrence (38.1%) and peritoneal recurrence (23.9%); peritoneal recurrence was the most common site in patients with pT4a disease (66.7%), followed by locoregional recurrence (22.2%) and distant recurrence (11.1%) (*Figure 2B–D*). We next investigated the impact of adjuvant chemotherapy on sites of initial recurrence in *Supplementary Figure S2*. There was no significant difference in the sites of recurrence between the pN0 and pN+ patients.

Then we performed the univariate and multivariate analysis of clinicopathologic factors associated with sites of initial recurrence in *Supplementary Table S4*. The results showed that patients with pN0 disease and tumors located in lower 1/3 had a significantly increased risk of locoregional recurrence. Predictive factors for distant recurrence included older age, well/moderate differentiation, pN+ disease, and lack of neural invasion. Several factors were associated with an increased risk of peritoneal recurrence including younger age, female sex, poorly differentiation/signet ring cell, more advanced T stage, and neural invasion (all P<0.05).

Trends of recurrence according to pN stage

Time-varying distributions of recurrence patterns are depicted in *Supplementary Figure S3*. Distant metastasis was the most common site of initial recurrence in different periods. *Figure 3* shows the trends of the initial recurrence pattern over time in each pN stage. The number of patients with distant metastasis continued to increase within 5 years after surgery, irrespective of pN stage. Most peritoneal recurrence occurred within 3 years after surgery. Notably, the number of locoregional recurrence continued to increase within 5 years after surgery in patients with pN0–2 disease but plateaued 3 years after surgery in patients with pN3 disease.

Time to recurrence according to pN stage

The median time to initial recurrence for all patients was 16 (IQR, 9–28) months. The time to recurrence was significantly longer for the pN0 group compared with the pN+ group (median: 25 *vs.* 16 months, P=0.001). Patients with advanced pN stage were likely to experience recurrence early (P<0.001 for linear trend, *Figure 4*). For patients with pT1–2 disease, the pN0 group had a longer recurrence time than the pN+ group (median: 26 *vs.* 18

Table 1 Clinicopathological characteristics of patients with recurrence according to lymph node status (N=493)

Variables	n (%)			P
	Total	pN0	pN+	
Age at recurrence (year) ($\bar{x}\pm s$)	63.5±11.7	65.2±13.9	63.3±11.5	0.295
Gender				0.470
Male	370 (75.1)	35 (79.5)	335 (74.6)	
Female	123 (24.9)	9 (20.5)	114 (25.4)	
Differentiation				0.051
Well/moderate	180 (36.5)	22 (50.0)	158 (35.2)	
Poorly/signet ring cell	313 (63.5)	22 (50.0)	291 (64.8)	
T stage				<0.001
T1	17 (3.4)	11 (25.0)	6 (1.3)	
T2	23 (4.7)	3 (6.8)	20 (4.5)	
T3	175 (35.5)	21 (47.7)	154 (34.3)	
T4a	278 (56.4)	9 (20.5)	269 (59.9)	
N stage				–
N0	44 (8.9)	44 (100)	–	
N1	45 (9.1)	–	45 (10.0)	
N2	93 (18.9)	–	93 (20.7)	
N3a	176 (35.7)	–	176 (39.2)	
N3b	135 (27.4)	–	135 (30.1)	
Tumor size (mm) ($\bar{x}\pm s$)	58.3±24.0	43.5±30.9	59.8±22.7	<0.001
Tumor location				0.497
Lower	180 (36.5)	16 (36.4)	164 (36.5)	
Middle	110 (22.3)	7 (15.9)	103 (22.9)	
Upper	116 (23.5)	10 (22.7)	106 (23.6)	
Mixed	87 (17.6)	11 (25.0)	76 (16.9)	
Lymphovascular invasion				0.075
No	285 (57.8)	31 (70.5)	254 (56.6)	
Yes	208 (42.2)	13 (29.5)	195 (43.4)	
Neural invasion				0.281
No	346 (70.2)	34 (77.3)	312 (69.5)	
Yes	147 (29.8)	10 (22.7)	137 (30.5)	
Adjuvant chemotherapy				<0.001
No	132 (26.8)	22 (50.0)	110 (24.5)	
Yes	361 (73.2)	22 (50.0)	339 (75.5)	
Time to recurrence (month) [median (IQR)]	16 (9–28)	26 (14–41)	15 (9–27)	0.001
Symptom(s) of recurrence				0.304
Asymptomatic	146 (29.6)	16 (36.4)	130 (29.0)	
Symptomatic	347 (70.4)	28 (63.6)	319 (71.0)	
Number of metastasis site(s)				0.552
1 site	339 (68.8)	32 (72.7)	307 (68.4)	
≥2 sites	154 (31.2)	12 (27.3)	142 (31.6)	
Treatment of recurrence				0.215
Support treatment only	150 (30.4)	17 (38.6)	133 (29.6)	
Potential curative treatment	343 (69.6)	27 (61.4)	316 (70.4)	

IQR, interquartile range.

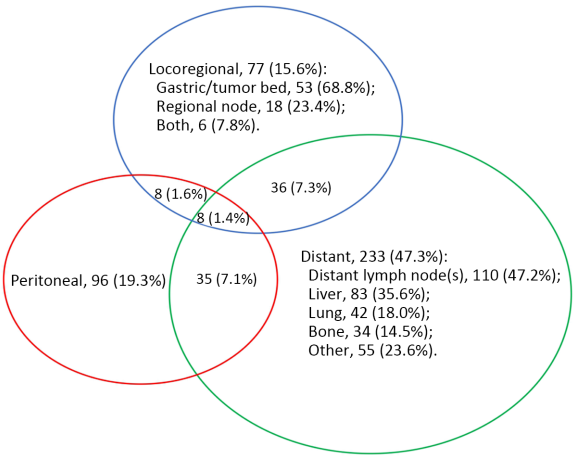

Figure 1 Venn diagram of recurrence patterns in 493 patients.

months), but the difference was not statistically significant (P=0.163). For patients with pT3–4a disease, more advanced pN disease was significantly associated with a shorter time to recurrence (P<0.001 for linear trend, P=0.006, respectively). Moreover, the time to recurrence was similar between patients who receive adjuvant chemotherapy and those who did not (all P>0.05, *Supplementary Figure S4*). In the multivariate linear regression model, only lymph node status was an independent factor for recurrence time (B: −7.054, 95% CI, −12.643, −1.465, P=0.013, *Supplementary Table S5*).

PRS after recurrence according to pN stage

The median PRS was 6 (IQR, 3–15) months. PRS was significantly better for pN0 patients compared to pN+ patients (median: 12 *vs*. 6 months, P<0.001). We next analyzed clinicopathologic and treatment factors associated with PRS. In univariate analysis, older age at recurrence, more advanced pT disease, more advanced pN disease, larger tumors, the presence of symptoms, early recurrence, multiple recurrences, and support treatment only were associated with poorer survival. After adjusting for these factors, advanced pN disease, the presence of symptoms, early recurrence, multiple recurrences, and support treatment only remained independent risk factors for PRS (all P<0.05, *Table 2*). A forest plot was further established to perform a subgroup analysis. The results revealed that pN0 disease exhibited a significant OS benefit among patients with non-peritoneal recurrence, late recurrence, single recurrence, and receipt of potential curative treatment (all P<0.05, *Supplementary Figure S5*).

Discussion

In the present study, we compared recurrence patterns and PRS between pN0 and pN+ groups after curative resection for GC. Patients in the pN+ group had a significantly lower

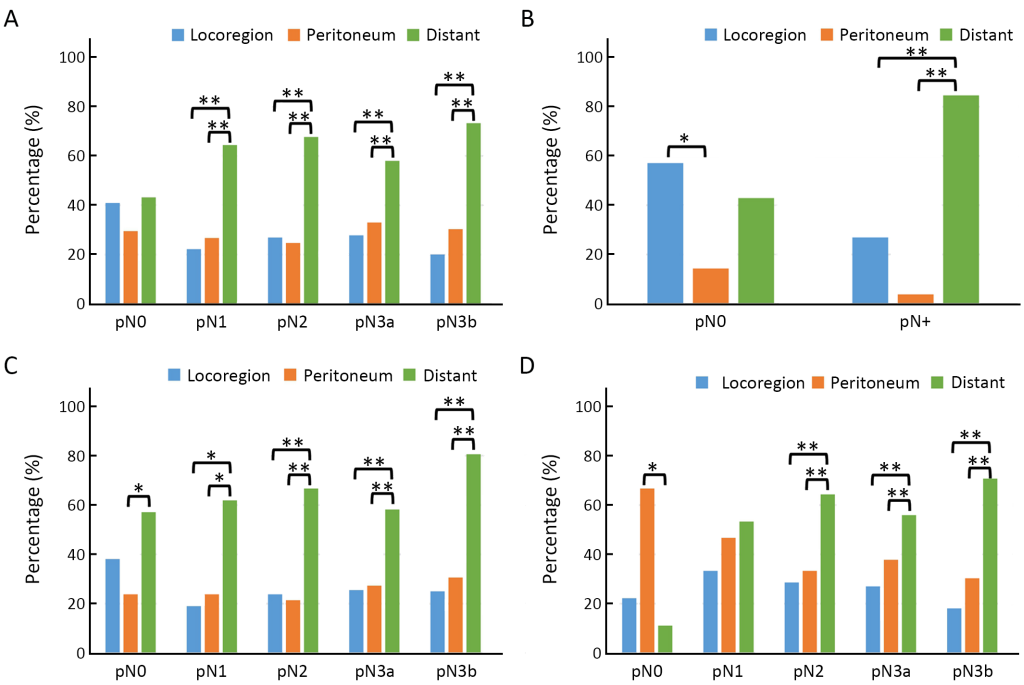

Figure 2 Patterns of initial recurrence according to pN stage in (A) all; (B) pT1–2; (C) pT3; (D) pT4a patients. **, P<0.01; *, P<0.05.

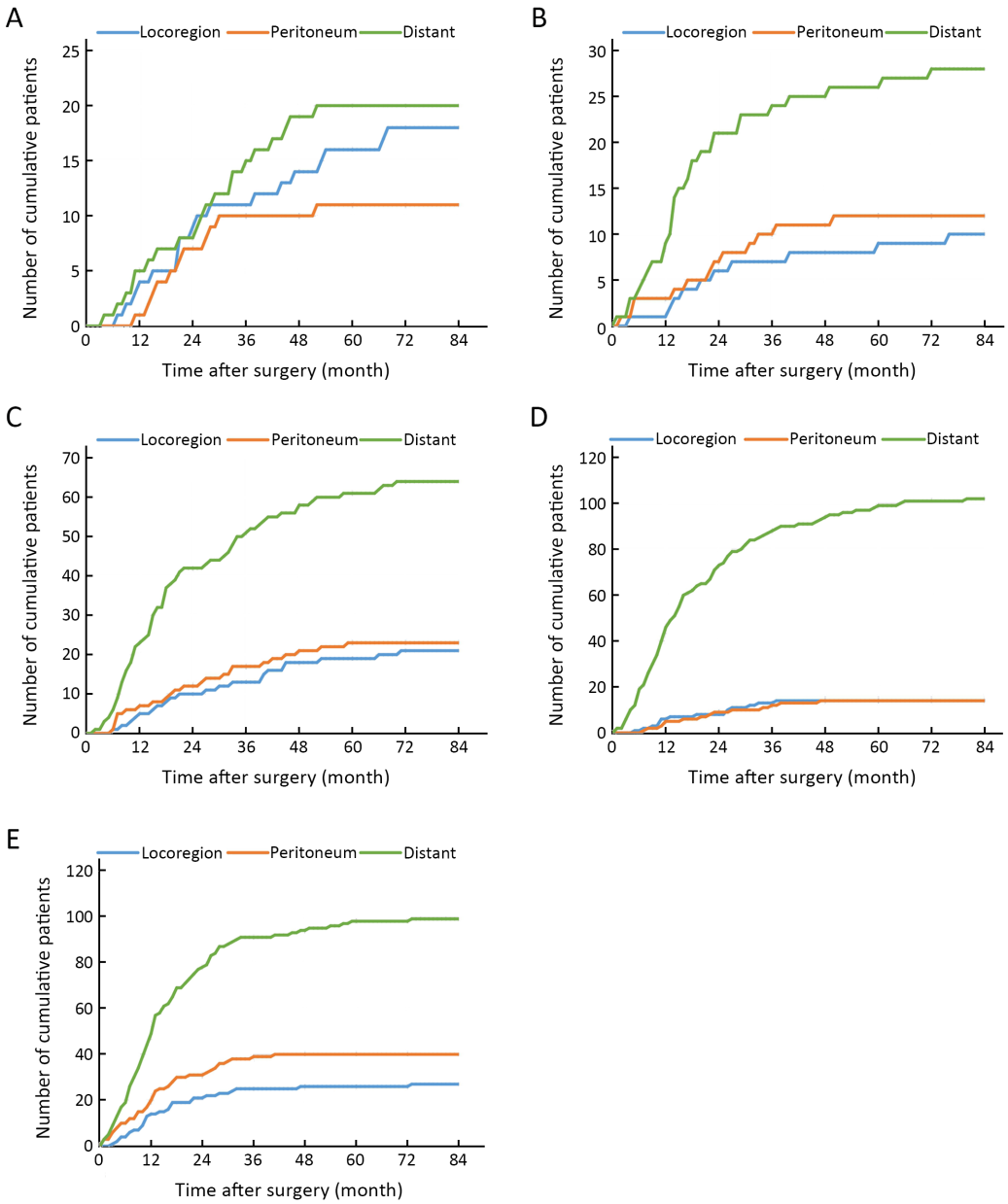

Figure 3 Cumulative numbers of patients with locoregional, peritoneal, and distant recurrence according to pN stage. (A) pN0; (B) pN1; (C) pN2; (D) pN3a; (E) pN3b.

risk of locoregional recurrence but a significantly higher risk of distant metastasis. For the pN+ group, the proportion of distant metastasis was higher than that of locoregional or peritoneal recurrence irrespective of pT stage. In contrast, the patterns of recurrence depended on pT stage for the pN0 group. Distant metastasis increased within 5 years after surgery in both the pN0 and pN+ groups; peritoneal recurrence mostly occurred within 3 years; locoregional recurrence increased within 5 years in patients with pN0–2 disease but plateaued 3 years after surgery in patients with pN3 disease. The time to recurrence was significantly longer for the pN0 group compared with the pN+ group. Moreover, PRS in the pN0 group was significantly better for the pN+ group, especially in patients with non-peritoneal recurrence, late recurrence, single recurrence, and receipt of potential curative treatment. These results can assist in the clinical decision-making about individualized therapeutic and follow-up

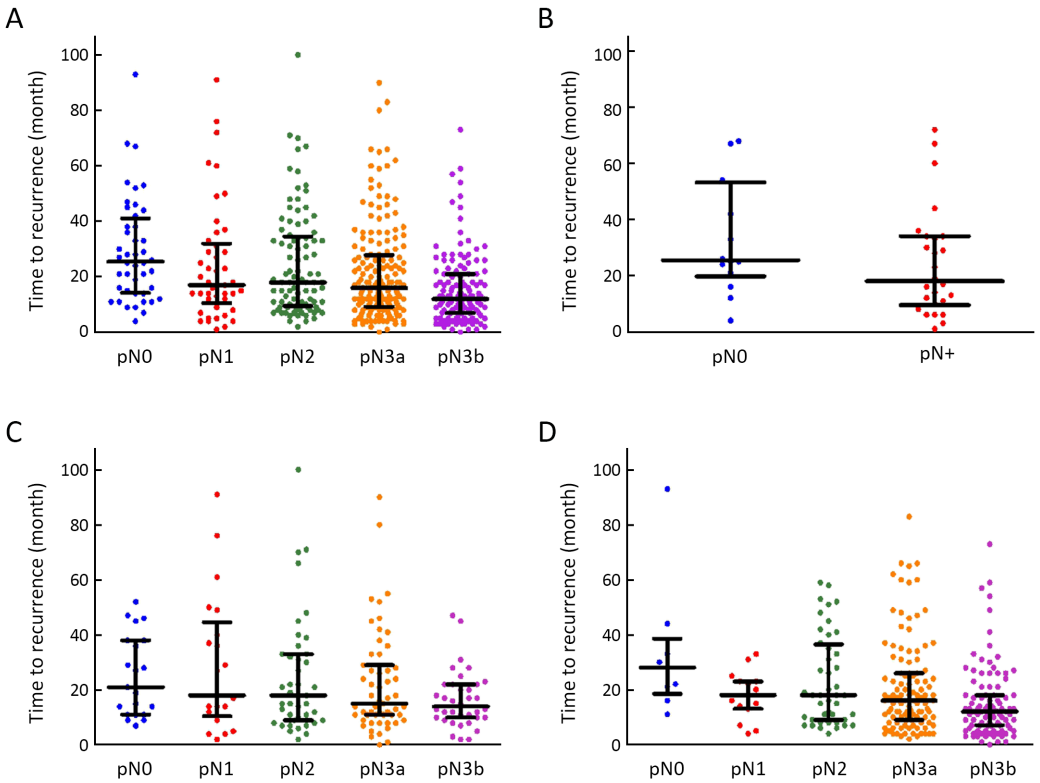

Figure 4 Timing of initial recurrence after surgery in (A) all (P<0.001); (B) pT1–2 (P=0.163); (C) pT3 (P<0.001); (D) pT4a patients (P=0.006).

strategies.

Many previous studies have attempted to demonstrate the patterns of initial recurrence after curative resection for GC (5,6,9,10). However, the results were quite different because of the heterogeneity of the study population. Thus, the identification of specific clinicopathologic factors associated with recurrence patterns has become a hot topic. Lee *et al.* examined patients with gastric and gastroesophageal junction Siewert II or III adenocarcinoma who underwent potentially curative resection at the Memorial Sloan Kettering Cancer Center (MSKCC). In this study, Lauren histologic type proved the only significant factor that was associated with both peritoneal recurrence and distant metastasis (9). In a retrospective study of 656 patients with recurrent GC, Kim *et al.* found that the pattern of initial recurrence was also different according to the pathologic stage. Among patients with stage I GC, more than half had distant organ metastasis; distant metastasis was the most common pattern in patients with stage III GC (10). However, the effects of lymph node status and depth of tumor invasion on recurrence patterns after surgery appear to be inconsistent in clinical practice. It was reported that T stage and N stage may have a significant interaction effect on patterns of recurrence (9). As a critical prognostic factor for disease recurrence and survival in resected GC, the impact of lymph node status itself on recurrence patterns remains unclear. Thus, the present study investigated the association between lymph node status and recurrence patterns. Compared with pN+ patients, pN0 patients had a significantly greater proportion of locoregional recurrence (40.9% *vs.* 24.7%; OR: 2.108; 95% CI, 1.114–3.990; P=0.020) and a significantly lower proportion of distant metastasis (43.2% *vs.* 65.3%; OR: 0.405; 95% CI, 0.216–0.758; P=0.004). According to the previous studies, tumor cells exit through lymph node blood vessels for systemic dissemination (24-26). Thus, for pN+ patients, the presence of lymph node metastasis is related to a higher risk of distant metastasis, which may lead to a relatively lower risk of locoregional recurrence. For pN+ patients, distant metastasis was the most common pattern irrespective of pT stage. In contrast, patterns of initial recurrence differed by pT stage for pN0 patients: locoregional recurrence was most common in patients with pT1–2 disease (57.1%), distant metastasis was

Table 2 Univariate and multivariate analyses for OS after recurrence

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age at recurrence	1.009 (1.001–1.017)	0.035	1.003 (0.994–1.012)	0.521
Gender		0.827		
Male	Reference			
Female	1.024 (0.830–1.263)			
Differentiation		0.322		
Well/moderate	Reference			
Poorly/signet ring cell	1.100 (0.911–1.329)			
T stage		0.005		0.300
T1–2	Reference		Reference	
T3	1.510 (1.032–2.209)		1.358 (0.910–2.028)	
T4a	1.777 (1.229–2.571)		1.261 (0.830–1.915)	
N stage		<0.001		0.004
N0	Reference		Reference	
N1	1.371 (0.872–2.156)		1.535 (0.970–2.429)	
N2	1.749 (1.179–2.595)		1.933 (1.281–2.918)	
N3a	1.886 (1.307–2.721)		1.845 (1.245–2.736)	
N3b	2.329 (1.597–3.396)		2.235 (1.476–3.386)	
Tumor size	1.005 (1.001–1.008)	0.008	1.001 (0.997–1.006)	0.572
Tumor location		0.605		
Lower	Reference			
Middle	1.127 (0.882–1.441)			
Upper	1.070 (0.842–1.361)			
Mixed	1.183 (0.908–1.543)			
Lymphovascular invasion		0.160		
No	Reference			
Yes	1.141 (0.949–1.372)			
Neural invasion		0.676		
No	Reference			
Yes	1.043 (0.856–1.270)			
Adjuvant chemotherapy		0.025		0.881
No	Reference		Reference	
Yes	0.793 (0.648–0.971)		0.983 (0.784–1.233)	
Symptom(s) of recurrence		<0.001		<0.001
Asymptomatic	Reference		Reference	
Symptomatic	2.044 (1.666–2.507)		2.027 (1.637–2.510)	
No. of metastasis site(s)		0.002		<0.001
1 site	Reference		Reference	
≥2 sites	1.375 (1.129–1.675)		1.544 (1.257–1.896)	
Time of recurrence		0.018		0.037
Within 1 years	Reference		Reference	
≥1 years	0.795 (0.657–0.961)		0.808 (0.661–0.987)	
Treatment of recurrence		<0.001		<0.001
Support treatment only	Reference		Reference	
Potential curative treatment	0.288 (0.234–0.355)		0.265 (0.211–0.333)	

OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval.

most common in patients with pT3 disease (57.1%), and peritoneal recurrence was most common in patients with pT4a disease (66.7%). A possible explanation is that a low peritoneal recurrence rate led to relatively high locoregional and distant recurrence rates in patients with pT1–2 disease, while a high peritoneal recurrence rate led to relatively low locoregional and distant recurrence rates in patients with serosal invasion (pT4a disease). Therefore, for node-negative patients, follow-up strategies should be considered according to pathologic T stage, while the key to follow-up for node-positive patients is distant metastasis. Furthermore, since adjuvant therapies focus on specific disease patterns (e.g. intraperitoneal chemotherapy for patients at high risk of peritoneal recurrence), understanding the pattern of recurrence is critical to the planning of adjuvant strategies.

It has been reported that the majority of GC recurrence develops within the first 2 years after surgery (27). Kang *et al*. investigated predictors of early recurrence (within 2 years) after surgery for GC and found that the proportion of early recurrence of pN+ patients was significantly higher than that of pN0 patients in both early and advanced GC (28). Sawayama *et al*. also demonstrated that early recurrence (within 12 months) was associated with a high lymph node ratio (metastasis/dissected lymph nodes) (29). In the present study, the time to recurrence was significantly longer for pN0 patients compared with pN+ patients (median: 25 *vs.* 16 months, P=0.001). In the multivariate analysis, only lymph node status was an independent predictor of time to recurrence. The prolonged duration between surgery and recurrence in node-negative tumors may be attributed to less aggressive disease biology. Thus, intensive follow-up in the early postoperative period may be unnecessary for node-negative patients. Furthermore, we found that distant metastasis increased within 5 years after surgery; peritoneal recurrence mostly occurred within 3 years; locoregional recurrence increased within 5 years after surgery in patients with pN0–2 disease but plateaued 3 years after surgery in patients with pN3 disease. This finding provides valuable information on follow-up strategies. First, more attention should be paid to distant metastasis in patients without disease recurrence 3 years after surgery. Second, more attention should also be paid to locoregional recurrence in patients with N0–2 disease.

Survival after recurrence of surgically resected GC remains poor in both Eastern and Western countries (9-12). Most patients succumbed within 1 year after receiving a diagnosis of recurrence. The median OS after a diagnosis of recurrence was 6 months in this study, which is similar to previous studies. Notably, PRS in pN0 patients was significantly better than that in pN+ patients (median: 12 *vs.* 6 months, P<0.001), especially in patients with non-peritoneal recurrence, late recurrence, single recurrence, and receipt of potential curative treatment (all P<0.05). Positive therapies are needed to treat recurrent disease in node-negative patients following curative surgical resection for GC.

Our study has several limitations. First, as a retrospective, single-institution study, it may have been subject to selection bias, and the validity and generalizability of our findings need to be established by testing it in other institutions. Second, although the probability is low, misdiagnosis of recurrence patterns may lead to deviations in results. Third, not all patients performed the follow-up strategies provided by the clinicians. Last, we did not perform the same analysis in patients receiving neoadjuvant chemotherapy (only 58 cases), which must be analyzed in the future.

Conclusions

Among clinicopathologic factors, lymph node status is the most important factor associated with recurrence patterns after curative gastrectomy. Lymph node status may be used as an adjunct in clinical decision-making about post-operative therapeutic and follow-up strategies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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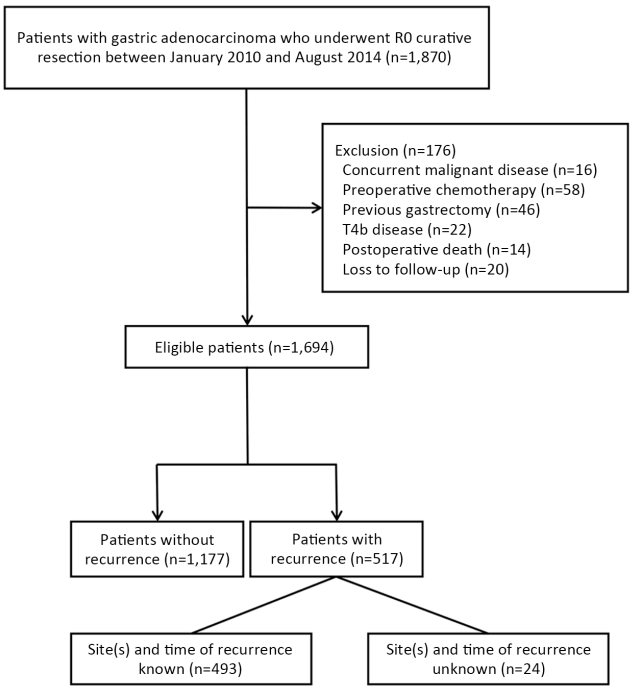

Figure S1 Diagram of study population.

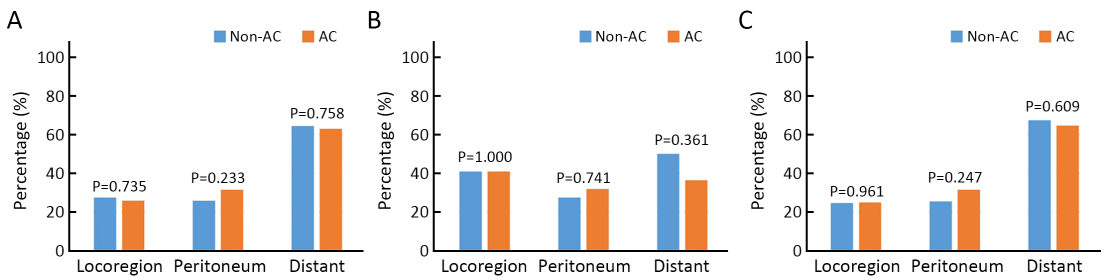

Figure S2 Patterns of initial recurrence according to receipt of AC in (A) all; (B) pN0; and (C) pN+ patients. AC, adjuvant chemotherapy.

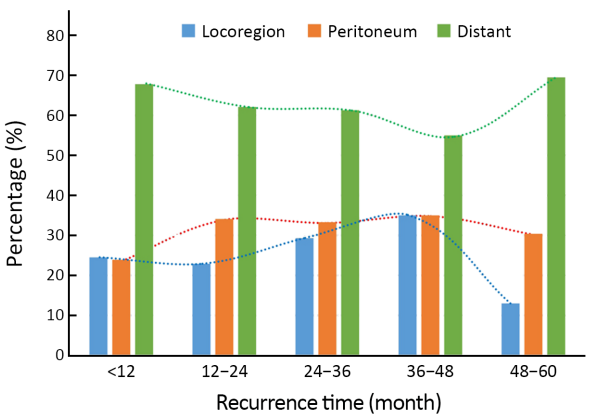

Figure S3 Time-varying distributions of recurrence pattern.

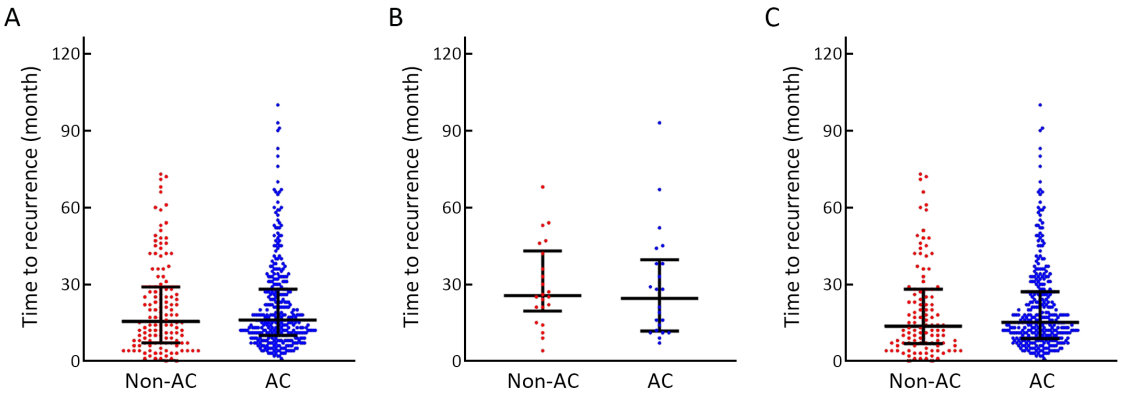

Figure S4 Timing of initial recurrence after surgery according to receipt of AC in (A) all; (B) pN0; and (C) pN+ patients. AC, adjuvant chemotherapy.

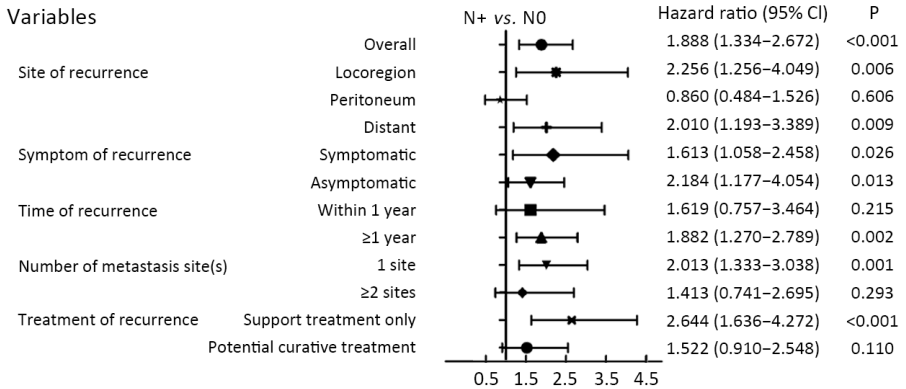

Figure S5 Forest plot showing the impact of lymph node status on post-recurrence survival stratified by different clinicopathological factors. Hazard ratios with 95% CI are shown for pN+ cohort *vs*. pN0 cohort. 95% CI, 95% confidence interval.

Table S1 Postoperative follow-up strategies

Examinations	Duration after surgery (month)														
	1	3	6	9	12	15	18	21	24	30	36	42	48	54	60
Medical examination, PS, body weight	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Blood test including tumor markers	O	O	O	O	O	O	O	O	O	O	O	O	O	O	O
Chest and abdominopelvic CT			O		O		O		O		O		O		O
Chest radiography and abdominal US		O		O		O		O		O		O		O	
Endoscopy					O				O		O		O		O

Examinations to be considered when needs arise: MRI, bone scintigram, PET scan, etc. PS, performance status; CT, computed tomography; US, ultrasonography; MRI, magnetic resonance imaging; PET, positron emission tomography; O, the time points at which the specific examinations are performed after surgery.

Table S2 Clinicopathological characteristics of patients according to lymph node status

Variables	Total	pN0	pN+	P
Age at diagnosis (year) ($\bar{x}\pm s$)	60.7±11.3	60.2±11.2	61.0±11.3	0.133
Gender				0.338
Male	1,269 (74.9)	499 (76.2)	770 (74.1)	
Female	425 (25.1)	156 (23.8)	269 (25.9)	
Differentiation				<0.001
Well/moderate	821 (48.5)	412 (62.9)	409 (39.4)	
Poorly/signet ring cell	873 (51.5)	243 (37.1)	630 (60.6)	
Surgical procedure				<0.001
Total gastrectomy	831 (49.1)	253 (38.6)	578 (55.6)	
Distal gastrectomy	823 (48.6)	373 (56.9)	450 (43.3)	
Proximal gastrectomy	40 (2.4)	29 (4.4)	11 (1.1)	
T stage				<0.001
T1	450 (26.6)	376 (57.4)	74 (7.1)	
T2	195 (11.5)	95 (14.5)	100 (9.6)	
T3	548 (32.3)	125 (19.1)	423 (40.7)	
T4a	501 (29.6)	59 (9.0)	442 (42.5)	
N stage				–
N0	655 (38.7)	655 (100)	–	
N1	269 (15.9)	–	269 (25.9)	
N2	272 (16.1)	–	272 (26.2)	
N3a	307 (18.1)	–	307 (29.5)	
N3b	191 (11.3)	–	191 (18.4)	
Tumor stage				–
I	521 (30.8)	471 (71.9)	50 (4.8)	
II	404 (23.8)	184 (28.1)	220 (21.2)	
III	769 (45.4)	–	769 (74.0)	
Lymph node retrieved (n) ($\bar{x}\pm s$)	35.3±13.7	32.4±12.3	37.1±14.2	<0.001
Tumor size (mm) ($\bar{x}\pm s$)	43.1±24.5	28.4±17.7	52.4±23.6	<0.001
Tumor location				<0.001
Lower	742 (43.8)	327 (49.9)	415 (39.9)	
Middle	352 (20.8)	115 (17.6)	237 (22.8)	
Upper	391 (23.1)	145 (22.1)	246 (23.7)	
Mixed	209 (12.3)	68 (10.4)	141 (13.6)	
Lymphovascular invasion				<0.001
No	1,229 (72.6)	588 (89.8)	641 (61.7)	
Yes	465 (27.4)	67 (10.2)	398 (38.3)	
Neural invasion				<0.001
No	1,374 (81.1)	613 (93.6)	761 (73.2)	
Yes	320 (18.9)	42 (6.4)	278 (26.8)	
Postoperative complications				0.924
No	1,352 (79.8)	522 (79.7)	830 (79.9)	
Yes	342 (20.2)	133 (20.3)	209 (20.1)	
Adjuvant chemotherapy				<0.001
No	695 (41.0)	482 (73.6)	213 (20.5)	
Yes	999 (59.0)	173 (26.4)	826 (79.5)	

Table S3 Univariate and multivariate analyses of factors associated with recurrence

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age at diagnosis	1.012 (1.004–1.021)	0.003	1.007 (0.999–1.015)	0.104
Gender		0.985		
Male	Reference			
Female	0.998 (0.813–1.225)			
Differentiation		<0.001		0.430
Well/moderate	Reference		Reference	
Poorly/signet ring cell	1.849 (1.539–2.221)		0.923 (0.758–1.125)	
T stage		<0.001		<0.001
T1	Reference		Reference	
T2	3.396 (1.825–6.322)		2.423 (1.273–4.615)	
T3	10.350 (6.288–17.035)		4.135 (2.354–7.264)	
T4a	22.650 (13.874–36.978)		6.670 (3.758–11.837)	
N stage		<0.001		<0.001
N0	Reference		Reference	
N1	2.698 (1.780–4.088)		1.866 (1.200–2.902)	
N2	6.063 (4.235–8.679)		3.123 (2.092–4.663)	
N3a	13.314 (9.560–18.542)		6.096 (4.127–9.003)	
N3b	21.329 (15.144–30.039)		8.528 (5.586–13.018)	
Tumor size	1.025 (1.022–1.027)	<0.001	1.006 (1.002–1.011)	0.002
Tumor location		<0.001		0.760
Lower	Reference		Reference	
Middle	1.393 (1.099–1.767)		0.880 (0.690–1.122)	
Upper	1.318 (1.043–1.664)		0.918 (0.722–1.168)	
Mixed	2.007 (1.554–2.593)		0.936 (0.708–1.237)	
Lymphovascular invasion		<0.001		0.640
No	Reference		Reference	
Yes	2.336 (1.953–2.793)		1.049 (0.859–1.280)	
Neural invasion		<0.001		0.450
No	Reference		Reference	
Yes	2.217 (1.826–2.692)		1.084 (0.879–1.337)	
Adjuvant chemotherapy		<0.001		<0.001
No	Reference		Reference	
Yes	2.104 (1.723–2.570)		0.642 (0.514–0.801)	

HR, Hazard ratio; 95% CI, 95% confidence interval.

Table S4 Univariate and multivariate analysis of clinicopathologic factors associated with sites of initial recurrence

Variables	Locoregional		Peritoneal		Distant	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age at diagnosis	0.999 (0.982–1.017)		**0.960 (0.944–0.977)**	**0.970 (0.953–0.989)**	**1.025 (1.009–1.042)**	**1.022 (1.004–1.040)**
Gender						
Male	Reference		Reference	Reference	Reference	Reference
Female	0.883 (0.551–1.415)		**2.444 (1.595–3.744)**	**1.673 (1.045–2.679)**	**0.668 (0.441–1.012)**	0.876 (0.555–1.383)
Differentiation						
Well/moderate	Reference		Reference	Reference	Reference	Reference
Poorly/signet ring cell	1.265 (0.827–1.934)		**2.308 (1.493–3.568)**	**1.672 (1.046–2.674)**	**0.557 (0.375–0.826)**	**0.585 (0.383–0.894)**
T stage						
T1–2	Reference		Reference	Reference	Reference	
T3–4	0.847 (0.345–2.080)		**5.748 (1.743–18.951)**	**3.536 (1.025–12.206)**	0.720 (0.357–1.454)	
N stage						
N0	Reference	Reference	Reference		Reference	Reference
N+	**0.474 (0.251–0.898)**	**0.456 (0.232–0.896)**	1.014 (0.515–1.999)		**2.471 (1.320–4.628)**	**3.222 (1.656–6.269)**
Tumor size	**0.991 (0.983–1.000)**	0.999 (0.989–1.008)	**1.010 (1.002–1.018)**	**1.007 (0.997–1.016)**	0.999 (0.992–1.007)	
Tumor location						
Lower	Reference	Reference	Reference	Reference	Reference	Reference
Middle	**0.589 (0.344–1.008)**	0.608 (0.351–1.054)	1.498 (0.910–2.465)	1.227 (0.713–2.111)	1.096 (0.676–1.776)	1.120 (0.676–1.856)
Upper	**0.577 (0.340–0.980)**	**0.581 (0.339–0.996)**	**0.546 (0.311–0.959)**	0.617 (0.338–1.126)	**1.918 (1.160–3.173)**	1.656 (0.978–2.802)
Mixed	**0.365 (0.191–0.699)**	**0.359 (0.178–0.723)**	1.107 (0.638–1.922)	0.789 (0.420–1.483)	1.462 (0.856–2.495)	1.733 (0.986–3.049)
Lymphovascular invasion						
No	Reference		Reference		Reference	
Yes	1.216 (0.812–1.823)		0.999 (0.676–1.477)		1.089 (0.751–1.578)	
Neural invasion						
No	Reference		Reference		Reference	Reference
Yes	0.977 (0.629–1.517)		**1.801 (1.196–2.713)**	**1.784 (1.149–2.770)**	**0.587 (0.395–0.870)**	**0.549 (0.364–0.829)**
Adjuvant chemotherapy						
No	Reference		Reference		Reference	
Yes	0.925 (0.590–1.451)		1.313 (0.838–2.058)		0.937 (0.618–1.419)	

Significant results are indicated in bold.

Table S5 Multivariate linear regression model predicting time to recurrence

Variables	Univariate analysis		Multivariate analysis	
	Pearson's correlation	P	B (95% CI)	P
Age at diagnosis	−0.024	0.445		
Gender (female *vs.* male)	−0.024	0.589		
Differentiation (poorly *vs*. well/moderate)	−0.017	0.714		
T stage (T3−4 *vs.* T1−2)	−0.106	0.018	−3.054 (−9.062, 2.954)	0.318
N stage (N+ *vs.* N0)	−0.146	0.001	−7.054 (−12.643, −1.465)	0.013
Tumor size	−0.125	0.005	−0.064 (−0.131, 0.003)	0.060
Tumor location (proximal *vs.* distal)	0.005	0.918		
Lymphovascular invasion (yes *vs.* no)	−0.045	0.314		
Neural invasion (yes *vs.* no)	−0.042	0.347		
Adjuvant chemotherapy (yes *vs.* no)	0.002	0.969		

95% CI, 95% confidence interval.