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Clinicopathologic factors associated with recurrence and long-term survival in node-negative advanced gastric cancer patients

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ABSTRACT

Background: despite a better prognosis in node-negative advanced gastric cancer (GC), a proportion of patients have a tumor recurrence within five years and eventually die due to cancer-related causes. The present study aimed to evaluate the predictive factors of tumor recurrence and long-term survival in node-negative advanced GC.

Methods: a total of 646 node-negative advanced GC patients who underwent a curative gastrectomy in our institution were included in the study. The impact of different clinicopathologic factors on tumor recurrence and overall survival were analyzed.

Results: tumor recurrences were observed in 181 patients and the cumulative recurrence rate at two-years and five-years were 50.8% and 86.2%, respectively. Lymphovascular invasion, advanced T stage (T3-T4) and an inadequate number of

retrieved lymph nodes (LNs) were independent predictive factors of tumor recurrence in node-negative advanced GC. Older age, an upper 1/3 tumor, lymphovascular invasion, infiltration growth pattern (INFγ) and the depth of tumor invasion (T4 stage) were independently associated with long-term survival. With regard to node-negative patients with ≥ 15 retrieved LNs, infiltration growth pattern (INFγ) and advanced T stage (T3-T4) were independent risk factors for both tumor recurrence and long-term survival.

Conclusion: in addition to lymphovascular invasion, inadequate RLNs and advanced T stage, the prognostic significance of infiltration growth pattern in node-negative advanced GC was especially emphasized. These risk factors should be considered when selecting candidates for adjuvant chemotherapy and postoperative surveillance.

Key words: Gastric cancer. Node negative. Recurrence. Survival. Prognostic factor.

INTRODUCTION

Gastric cancer (GC) is one of the most common malignant diseases in the world and the third leading cause of cancer-related deaths (1). GC patients are usually diagnosed at an advanced stage of disease due to the vague clinical manifestation and signs. A curative resection with adequate lymphadenectomy was regarded as the only potentially curable treatment for advanced GC patients. However, the long-term survival of these patients was still unsatisfactory due to the high rate of recurrence and metastasis (2,3). The lymphatic system is an important pathway for the spread of gastric cancer cells and lymph node (LN) metastasis is the most important prognostic factor for tumor recurrence and survival in resectable GC (4,5). Although node-negative GC patients had a significantly better prognosis than node-positive patients, a high proportion of these patients still experience tumor recurrence and metastasis after a curative resection (6,7). Recently, increased evidence has shown that postoperative adjuvant chemotherapy in advanced GC patients could have a survival benefit (8,9). The identification of clinicopathologic factors associated with tumor recurrence and long-term survival is indispensable for

node-negative advanced GC patients in order to better predict tumor recurrence and select patients eligible for adjuvant chemotherapy.

Previous studies have uniformly reported that the depth of tumor invasion (T stage) was a significant and independent predictor of tumor recurrence and metastasis in node-negative GC patients (10-13). However, there was no consensus opinion with regard to the prognostic significance of other clinicopathologic factors, including age, tumor size, Lauren type, signet ring histology, the number of retrieved lymph nodes (RLNs), lymphovascular invasion and perineural invasion (7,10-16). The present study aimed to evaluate the predictive factors of tumor recurrence and long-term survival in node-negative advanced GC.

PATIENTS AND METHODS

Patients

A total of 2,634 consecutive GC patients who underwent a curative gastrectomy at the Department of Surgical Oncology, in the First Affiliated Hospital of China Medical University, between January 1990 and January 2010 were reviewed. The inclusion and exclusion criteria were as follows:

1. All cases were pathologically diagnosed with advanced GC via hematoxylin-eosin staining after surgery. Advanced gastric cancer was defined as an invasion depth of tumor deeper than the submucosa (≥ T2 stage), according to the pathological evaluation of the surgically resected tissues.
2. A curative resection with LN dissection had been performed and no positive LNs were detected in the pathological examination.
3. The patients who developed distant metastasis before the curative surgery should be excluded, including liver metastasis, peritoneal metastasis and extraregional lymph node metastasis.
4. Patients who were treated with neo-adjuvant chemotherapy and those with a history of other malignant tumors were excluded from the study.
5. The clinicopathologic information of all patients was complete.

In accordance with the eligibility criteria described above, 364 early GC patients and 1,624 node-positive advanced GC patients were excluded. A total of 646 node-

negative advanced GC patients who underwent a curative resection in our institution during the same period were enrolled in the study. The percentage of node-negative advanced GC patients was 24.5% in all patients and 28.5% in advanced GC patients, respectively. The study was approved by the Ethics Committee of the China Medical University and all patients were provided with a written informed consent prior to surgery.

Surgical procedures and postoperative treatment

The following information was collected: gender, age, tumor location, tumor size, Lauren type, signet ring histology, postoperative complications, intraoperative blood transfusion, lymphovascular invasion, infiltration growth pattern, the number of retrieved LNs, the depth of tumor invasion (T stage) and adjuvant chemotherapy. The performance of a distal gastrectomy, proximal gastrectomy or total gastrectomy was mainly determined by tumor size, tumor location and resection margins. The Billroth-I, Billroth-II or Roux-en-Y esophagojejunostomy was performed to reconstruct the alimentary tract. The extent of LN dissection was based on the Japanese gastric cancer treatment guidelines (17). The standard procedure included the spleen and pancreas-preserving D1+ or D2 lymph node dissection. The following lymphatic tissues should be removed for a curative resection with D1+ lymphadenectomy: No.1 (right pericardial), No.2 (left pericardial), No.3 (along the lesser curvature), No.4 (along the short gastric and gastroepiploic vessels), No.5 (suprepyloric), No.6 (infrapyloric), No.7 (along the left gastric artery), No.8a (along the common hepatic artery) and No.9 LNs (around the celiac artery). When lymph node dissection was extended to the proximal splenic artery (No.11p) and hepatic artery (No.12a), the procedure was defined as a D2 lymphadenectomy. A combined organ resection was performed when the spleen or the body and tail of pancreas was directly invaded by tumor or suspicious lymph node involvement was detected in the splenic hilum (No.10). In addition to lymph node dissection, the surgeons continued to retrieve as many lymph nodes as possible from the resected specimens after curative resection. The histopathological examination of surgically resected specimens and retrieved lymph nodes was independently performed by two

pathologists. Non-concordance was resolved via a discussion with a third expert. All patients were staged according to the pathological TNM staging of the American Joint Commission on Cancer (AJCC) (7th edition) (18). Stage II-III patients were recommended postoperative adjuvant chemotherapy and the regimens were fluorouracil- or cisplatin/oxaliplatin-based systemic chemotherapy.

In the present study, blood transfusion was defined as the transfusion of red blood cells that were filtered to remove leukocytes during the curative resection. The intraoperative blood transfusion was performed according to the amount of intraoperative blood loss, hemoglobin concentration of GC patients before the operation (< 70 g/l) or hemodynamic changes during the surgery. The severity of postoperative complications was assessed according to the Clavien-Dindo classification (19) and ≥ grade II were identified as postoperative complications. The most common postoperative complications included intraperitoneal hemorrhage, anastomotic leakage, pulmonary infection, catheter-related infection, wound infection, postoperative bowel obstruction, intraperitoneal infection or abscess, pancreatic fistula, reflux esophagitis and cholecystitis.

With regard to the Lauren type, papillary adenocarcinoma, tubular adenocarcinoma and mucinous adenocarcinoma were included in the intestinal type, and signet-ring cell carcinoma and other poorly cohesive carcinomas were included in the diffuse type (20). Infiltration growth pattern (INF) can be classified into three categories according to the Japanese Classification of Gastric Cancer (JCGC): INFα, INFβ and INFγ (21). INFα pattern was described as the expanding growth and a distinct border with the surrounding tissue and INFγ pattern was described as the infiltrating growth and an indistinct border with the surrounding tissue. The intermediate pattern between INFα and INFγ was defined as the INFβ pattern (22).

Follow-up

All GC patients who underwent a curative resection in our institution were followed up every three months for the first two years, every six months for the next two years and annually thereafter until death or the follow-up cut-off date. U ltrasonography, abdominal CT, upper digestive endoscopy and tumor biomarker

tests were performed during the follow-up period in order to monitor postoperative recurrence. Tumor recurrences included local relapse (gastric remnant or anastomotic site), regional lymph node metastasis and distant metastasis (peritoneal seeding, hematogenous dissemination or extraregional lymph node metastasis). All p ostoperative recurrences were diagnosed according to the clinical findings, imaging and pathological results. The primary outcome in this study was recurrence-free survival (RFS) and overall survival (OS). The RFS was defined as the time between the date of surgery to the date of postoperative recurrence and OS was defined as the time from the date of surgery to death due to any cause or the date of the last follow-up in live patients. The median follow-up periods were 49 months (range, 1-3 12 months) in our cohort.

Statistical analysis

The categorical variables were compared using the Pearson's Chi-square test or Fisher's exact test and continuous variables were compared using the Student's t test. The univariate analysis was performed using the Kaplan-Meier method and survival data was presented as five-year RFS rate or five-year OS rate. The differences between different patient groups were compared using the log-rank test. The Cox proportional hazard model was used in the multivariate analysis to identify independent prognostic factors; hazard ratios (HR) and 95% confidence intervals (CI) were also calculated. All statistical analyses were performed using the SPSS19.0 statistical package (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered to be statistically significant.

RESULTS

Clinicopathologic characteristics of GC patients

The clinicopathologic features of 646 node-negative advanced GC patients are summarized in table 1; 25.5% patients were female and 74.5% were male, and the median age was 60 years (range, 25-83). A total of 10,853 LNs were retrieved from 646 GC patients and the median number of retrieved LNs was 15 (range, 1-67). Among these patients, the proportion of the patients with at least 15 retrieved LNs

was 54.2% (n = 350). There were no significant differences between the recurrence and recurrence-free group in terms of gender, age, postoperative complications, Lauren classification, signet ring histology and infiltration growth pattern. Compared with the recurrence-free group, patients who experienced tumor recurrence had a larger tumor size, upper 1/3 stomach, more frequent intraoperative blood transfusions, lymphovascular invasion, fewer number of retrieved LNs and more advanced T stage (Table 1). In addition, a lower proportion of adjuvant chemotherapy was observed in the recurrence group.

The cumulative RFS rates of node-negative advanced GC patients at two-years and five-years were 84.5% and 71.1%, respectively. The corresponding overall survival rates at two-years and five-years were 81.1% and 63.5%, respectively (Fig. 1). Tumor recurrences were observed in 181 patients (overall recurrence rate was 28.0%), and the cumulative recurrence rates of these patients at two-years and five-years were 50.8% and 86.2%, respectively. According to the recurrence pattern, 27.1% of patients (n = 49) experienced locoregional recurrence and 72.9% of patients (n = 132) experienced distant metastasis after a curative resection. The two-year and five-year RFS rates of the patients with locoregional recurrence were 51.0% and 26.5%, respectively. In addition, the two-year and five-year RFS rates of patients with distant metastasis were 48.5% and 9.1%, respectively. A significantly longer survival time was observed in patients with locoregional recurrence compared to those with distant metastasis (five-year OS rate: 32.2% *vs* 9.4%, p = 0.002) (Fig. 2).

Univariate and multivariate analysis of prognostic factors for tumor recurrence and overall survival

The following six factors were significantly associated with tumor recurrence of node-negative patients according to the univariate analysis as shown in table 2: tumor location ($p < 0.001$), tumor size ($p = 0.002$), lymphovascular invasion ($p < 0.001$), infiltration growth pattern ($p = 0.041$), T stage ($p < 0.001$) and the number of retrieved LNs ($p = 0.012$). The multivariate analysis showed that lymphovascular invasion, advanced T stage (T3-T4) and the number of retrieved LNs were independently associated with tumor recurrence in node-negative advanced GC. In

addition, the univariate analysis indicated that the following factors significantly affected the overall survival of node-negative advanced GC patients: age ($p = 0.002$), tumor location ($p < 0.001$), tumor size ($p = 0.002$), intraoperative blood transfusion ($p = 0.004$), lymphovascular invasion ($p < 0.001$), infiltration growth pattern ($p = 0.015$), T stage ($p < 0.001$) and the number of retrieved LNs ($p = 0.004$). The multivariate analysis showed that age (> 60 years), tumor location (upper 1/3), lymphovascular invasion, infiltration growth pattern (INFγ) and the depth of tumor invasion (T4 stage) were independent prognostic factors (Table 3).

It has been reported that lymph node staging was significantly affected by the number of retrieved LNs and the prognosis of GC patients may be underestimated due to the inadequate LN retrieval (23,24). Therefore, those node-negative patients with an inadequate number of retrieved LNs should be termed as “node-negative” patients. In view of the limitation in this study, we also evaluated the predictive factors for recurrence and overall survival in node-negative patients with ≥ 15 retrieved LNs. According to the univariate and multivariate analysis, infiltration growth pattern (INFγ) and advanced T stage (T3-T4) were two independent predictive factors for recurrence and long-term survival in these patients (Tables 4 and 5).

DISCUSSION

Although the prognosis of node-negative GC patients was significantly better than that of node-positive patients, a proportion of these patients experienced tumor recurrence within five years and eventually died due to a cancer-related cause (7,10,11). A total of 181 (28.0%) node-negative advanced GC patients in the present study experienced tumor recurrence during the follow-up period. The cumulative recurrence rates of these patients at two-years and five-years were 50.8% and 86.2%, respectively. Consistent with previous reports (10,11), tumor recurrence in GC frequently occurred within two years after curative resection. In view of the high recurrence rate, it is necessary to identify predictive factors for tumor recurrence in order to further guide postoperative therapeutic strategies. To date, some studies have reported that patient age, T stage, tumor size, differentiation type, the number

of retrieved LNs, lymphovascular invasion and perineural invasion are associated with tumor recurrence and long-term survival of node-negative GC patients (7,10-16) . However, there was no consensus opinion with regard to the prognostic significan ce of these clinicopathologic factors, except for the depth of tumor invasion (T stage). In the present study, the impact of different clinicopathologic factors on tumor recurrence and long-term survival of node-negative advanced GC patients was evaluated. The results indicated that lymphovascular invasion, advanced T stage (T3-T4) and an inadequate number of retrieved LNs were independent predictive factors for tumor recurrence. On the other hand, overall survival of node-negative patients was independently affected by patient age (> 60 years), tumor location (upper 1/3), the presence of lymphovascular invasion, INF pattern and a deeper tumor invasion (T4 stage).

Lymphovascular invasion was regarded as the initial step of LN metastasis and distant metastasis. Some studies reported on the negative association between lymphovascular invasion and the prognosis of node-negative GC patients (10,16,25,26). Jin et al. collected and reviewed survival data of 317 node-negative patients from seven high-volume academic institutions and the results showed that lymphovascular invasion was an independent prognostic factor (10). Furthermore, some studies indicated that lymphovascular invasion was a risk factor that correlated with lymph node micrometastasis (27,28), which may provide further evidence for the association between lymphovascular invasion and tumor recurrence.

Despite the increased postoperative complications, D2 lymph node dissection has been shown to be associated with improved survival of GC patients (29,30). In our study, the number of retrieved LNs was identified as an independent predictive factor for tumor recurrence. Similarly, some studies reported that a greater number of retrieved LNs could confer a survival benefit in node-negative GC patients (31,32). N-stage migration may occur if the number of retrieved LNs was inadequate, which may explain why a poorer prognosis was observed in patients with an inadequate number of retrieved LNs (23,24). Recently, Yuan et al. proposed a novel staging system which incorporated the information on the 8th edition of TNM staging and the number of retrieved LNs (33). In this study, the patients with < 15 retrieved LNs were

upgraded correspondingly compared to those patients in the same TNM stage. The new staging system was proved to be superior to the 8th edition staging (33). Similarly, Li et al. suggested that node-negative GC patients should be classified as N1 stage when the number of RLNs was inadequate (34). These results indicated that the TNM staging system should be revised in the future according to the number of retrieved LNs. On the other hand, inadequate lymph node harvesting may be regarded as an indication to receive adjuvant therapy.

With regard to node-negative patients with ≥ 15 retrieved LNs, we found that infiltration growth pattern (INFγ) and advanced T stage (T3-T4) were independent predictive factors for recurrence and long-term survival. In previous studies, the depth of tumor invasion (T stage) has been consistently identified as a risk factor for both tumor recurrence and long-term survival (10-13). The present study further confirmed that advanced T stage (T3-T4) had a negative impact on the prognosis of node-negative GC patients, suggesting that in T3N0 and T4N0 stage cases adjuvant chemotherapy should be strongly recommended. The other consistent risk factor for both tumor recurrence and long-term survival in this study was INF pattern. According to the Japanese Classification of Gastric Cancer (JCGC), INF pattern was further classified into three categories: INFα (expanding growth and a distinct border with the surrounding tissue), INFβ (intermediate pattern between INFα and INFγ) and INFγ (infiltrating growth and an indistinct border with the surrounding tissue) (22). The Japanese Gastric Cancer Association (JGCA) recommended that the INF pattern should be described in T1b or a tumor with deeper invasion, but it was not widely used and accepted worldwide. There were only few studies that evaluated the prognostic significance of the INF pattern in GC patients (22,35-38). Saito et al. reported that node-negative patients with an INFγ pattern had a poorer prognosis than those with an INFα/β pattern (35). In previous studies, the INFγ pattern was a significant predictive factor for peritoneal metastasis in GC without serosal invasion (22). Furthermore, Song et al. reported that peritoneal recurrence was more frequent in T3 stage patients with an INFγ pattern than in those with an INFα/β pattern (36). The exact mechanism behind the INF pattern and tumor recurrence remains unclear. Kanda et al. speculated that the INFγ pattern may represent a

higher penetration ability of cancer cells, which provides a larger probability for peritoneal dissemination (37). Despite the limited studies and reports, we believe that the prognostic significance of the INF pattern should not be ignored in advanced GC patients. Further studies with larger patient cohorts are necessary to confirm its prognostic value.

Unlike breast cancer and other solid tumors, there is no unanimous opinion of the prognostic significance of tumor size in GC patients. Some studies reported that tumor size was an independent prognostic factor for node-negative GC (7,11,39), but this finding was not reproduced in other studies (10,12). In the present study, tumor size was proved to be a potential prognostic factor according to the univariate analysis, although this was not significant in the multivariate analysis. In addition, Lauren type and signet ring histology were reported as significant prognostic factors in node-negative GC (7,10,12). However, we found that these clinicopathologic factors were not associated with tumor recurrence and survival outcome. The conflicting results may be attributed to different inclusion and exclusion criteria. In some studies, early GC patients were also enrolled in the study cohort, which might affect the prognostic assessment. Over the last decade, adjuvant chemotherapy following a curative resection has been performed in our institution. However, the proportion of patients receiving adjuvant chemotherapy was relatively low due to economic reasons, personal willingness, comorbidities and poor physical status. Although we did not find a statistically significant association between adjuvant chemotherapy and improved survival, we still believe that node-negative GC patients with a high recurrence risk could gain a survival benefit from adjuvant chemotherapy.

Some limitations should be emphasized in the present study. Firstly, in view of the retrospective nature of this study, all results and conclusions could have been influenced by some confounding or unknown factors. Secondly, the proportion of patients with < 15 retrieved LNs accounted for 45.8% of all cases. Thus, N stage may be underestimated in some patients. In view of the limitation in this study, we also evaluated the predictive factors for tumor recurrence and overall survival in node-negative patients with ≥ 15 retrieved LNs. In addition, immunohistological

examination was not routinely performed in our research institution. The possibility of lymph node micrometastasis or isolated tumor cells was not completely excluded. Therefore, our study cohort may not represent a realistic N0 stage cohort. In the future, immunohistological staining may provide a more reliable method for the identification of node-negative patients.

In summary, our results indicated that lymphovascular invasion, advanced T stage (T3-T4) and an inadequate number of retrieved LNs were independent predictive factors for tumor recurrence in node-negative advanced GC. Older age, upper 1/3 tumor, lymphovascular invasion, INFγ pattern and serosal invasion (T4 stage) were independently associated with long-term survival. With regard to node-negative patients with ≥ 15 retrieved LNs, INF pattern (INFγ) and advanced T stage (T3-T4) were independent risk factors for both tumor recurrence and long-term survival. To further improve the survival of node-negative patients, these risk factors should be considered when selecting candidates for adjuvant chemotherapy and postoperative surveillance.

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Table 1. Clinicopathological characteristics of node-negative advanced GC patients according to tumor recurrence

		Recurrence		
Factor	*Patients (%)*	*No (n = 465)*	*Yes (n = 181)*	*p value*
Age(years)				0.251
≤ 60	341 (52.8%)	252 (54.2%)	89 (49.2%)	
> 60	305 (47.2%)	213 (45.8%)	92 (50.8%)	
Gender				0.293
Female	165 (25.5%)	124 (26.7%)	41 (22.7%)	
Male	481 (74.5%)	341 (73.3%)	140 (77.3%)	
Tumor location				0.007
Lower 1/3	349 (54.0%)	267 (57.4%)	82 (45.3%)	
Middle 1/3	78 (12.1%)	59 (12.7%)	19 (10.5%)	
Upper 1/3	116 (18.0%)	72 (15.5%)	44 (24.3%)	
≥ 2/3 stomach	103 (15.9%)	67 (14.4%)	36 (19.9%)	
Tumor size				0.004
< 5 cm	290 (44.9%)	225 (48.4%)	65 (35.9%)	
≥ 5 cm	356 (55.1%)	240 (51.6%)	116 (64.1%)	
Lauren classification				0.671
Intestinal	337 (52.2%)	245 (52.7%)	92 (50.8%)	
Diffuse	309 (47.8%)	220 (47.3%)	89 (49.2%)	
Signet ring histology				0.654
No	565 (87.5%)	405 (87.1%)	160 (88.4%)	
Yes	81 (12.5%)	60 (12.9%)	21 (11.6%)	
Postoperative complications				0.336
No	586 (90.7%)	425 (91.4%)	161 (89.0%)	
Yes	60 (9.3%)	40 (8.6%)	20 (11.0%)	
Intraoperative blood transfusion				
No	380 (58.8%)	293 (63.0%)	87 (48.1%)	< 0.001
Yes	266 (41.2%)	172 (37.0%)	94 (51.9%)	
Lymphovascular invasion				
No	585 (90.6%)	430 (92.5%)	155 (53.6%)	
Yes	61 (9.4%)	35 (7.5%)	26 (14.4%)	0.008
Infiltration growth pattern				
α/β	385 (55.5%)	380 (56.3%)	380 (53.6%)	

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Table 2. Univariate and multivariate analysis of risk factors associated with tumor recurrence in node-negative advanced GC

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	Univariate analysis		*Multivariate analysis*	
Factor	*5-year RFS (%)*	*p value*	*HR (95% CI)*	*p value*
Age (years)		0.095	-	-
≤ 60	73.6%			
> 60	68.1%			
Gender		0.390	-	-
Female	72.5%			
Male	68.1%			
Tumor location		< 0.001		0.135
Lower 1/3	75.2%		1	
Middle 1/3	78.4%	0.903	0.986 (0.595-1.636)	0.371
Upper 1/3	60.3%	< 0.001	1.505 (1.026-2.207)	0.047
≥ 2/3 stomach	62.4%	0.017	1.132 (0.741-1.730)	0.449
Tumor size		0.002		0.073
< 5 cm	77.6%		1	
≥ 5 cm	65.7%		1.289 (0.920-1.806)	
Lauren classification		0.478	-	-
Intestinal	72.5%			
Diffuse	69.5%			
Signet ring histology		0.549	-	-
No	74.8%			
Yes	70.2%			
Postoperative complications		0.869	-	-
No	70.4%			
Yes	76.3%			
Intraoperative blood transfusion		0.120	-	-
No	72.6%			
Yes	68.7%			
Lymphovascular invasion		< 0.001		0.010
No	73.0%		1	
Yes	53.3%		1.729 (1.136-2.632)	
Infiltration growth pattern		0.041		0.136

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Table 3. Univariate and multivariate analysis of prognostic factors (overall survival, OS) for node-negative advanced GC patients

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	Univariate analysis		*Multivariate analysis*	
Factor	*5-year OS (%)*	*p value*	*HR (95% CI)*	*p value*
Age (years)		0.002		< 0.001
≤ 60	69.0%		1	
> 60	57.2%		1.560 (1.210-2.012)	
Gender		0.699	-	-
Female	63.9%			
Male	63.3%			
Tumor location		< 0.001		< 0.01
Lower 1/3	68.9%		1	
Middle 1/3	74.4%	0.674	1.059 (0.723-1.550)	0.768
Upper 1/3	47.9%	< 0.001	1.653 (1.218-2.245)	< 0.001
≥ 2/3 stomach	53.9%	0.002	1.323 (0.946-1.849)	0.102
Tumor size		0.002		0.428
< 5 cm	66.8%		1	
≥ 5 cm	59.1%		1.107 (0.828-1.481)	
Lauren classification		0.213	-	-
Intestinal	66.2%			
Diffuse	60.5%			
Signet ring histology		0.453	-	-
No	64.5%			
Yes	56.9%			
Postoperative complications		0.716	-	-
No	62.9%			
Yes	67.5%			
Intraoperative blood transfusion		0.004		0.196
No	67.5%		1	
Yes	58.0%		1.142 (0.865-1.507)	
Lymphovascular invasion		0.002		0.009
No	65.2%		1	
Yes	43.6%		1.656 (1.133-2.422)	
Infiltration growth pattern		0.015		0.011

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Table 4. Univariate and multivariate analysis of risk factors associated with tumor recurrence in node-negative advanced GC (RLNs ≥ 15 nodes)

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	Univariate analysis		*Multivariate analysis*	
Factor	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age (> 60 years)	1.001 (0.634-1.580)	0.996	-	-
Gender (male)	1.390 (0.822-2.352)	0.220	-	-
Tumor location (upper 1/3; ≥ 2/3 stomach)	1.035 (0.856-1.253)	0.721	-	-
Tumor size (≥ 5 cm)	1.090 (0.699-1.701)	0.703	-	-
Lauren classification (diffuse type)	1.506 (0.958-2.367)	0.076	-	-
Signet ring histology (yes)	1.056 (0.558-1.997)	0.868	-	-
Postoperative complications (yes)	1.045 (0.521-2.095)	0.901	-	-
Intraoperative blood transfusion (yes)	0.915 (0.577-1.451)	0.706	-	-
Lymphovascular invasion (yes)	1.762 (0.880-3.531)	0.110	-	-
Infiltration growth pattern (IFNγ)	1.751 (1.126-2.722)	< 0.05	1.680 (1.080-2.615)	< 0.05
T stage (T3-T4)	1.909 (1.116-3.266)	< 0.05	1.828 (1.067-3.130)	< 0.05
Chemotherapy (yes)	0.748 (0.410-1.365)	0.748	-	-

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Table 5. Univariate and multivariate analysis of prognostic factors (overall survival, OS) of node-negative advanced GC patients (RLNs ≥ 15 nodes)

	Univariate analysis		*Multivariate analysis*	
Factor	*HR (95% CI)*	*p value*	*HR (95% CI)*	*p value*
Age (> 60 years)	1.239 (0.848-1.809)	0.268	-	-
Gender (male)	1.165 (0.763-1.780)	0.479	-	-
Tumor location (upper 1/3; ≥ 2/3 stomach)	1.068 (0.913-1.250)	0.412	-	-
Tumor size (≥ 5 cm)	1.070 (0.735-1.558)	0.723	-	-
Lauren classification (diffuse type)	1.303 (0.925-1.835)	0.130	-	-
Signet ring histology (yes)	1.429 (0.881-2.319)	0.148	-	-
Postoperative complications (yes)	1.058 (0.592-1.889)	0.849	-	-
Intraoperative blood transfusion (yes)	1.195 (0.815-1.752)	0.361	-	-
Lymphovascular invasion (yes)	1.647 (0.904-3.001)	0.103	-	-
Infiltration growth pattern (IFNγ)	1.510 (1.040-2.193)	< 0.05	1.461 (1.005-2.123)	< 0.05
T stage (T3-T4)	1.620 (1.050-2.501)	< 0.05	1.568 (1.014-2.422)	< 0.05
Chemotherapy (yes)	0.668 (0.391-1.143)	0.141	-	-

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Fig.1

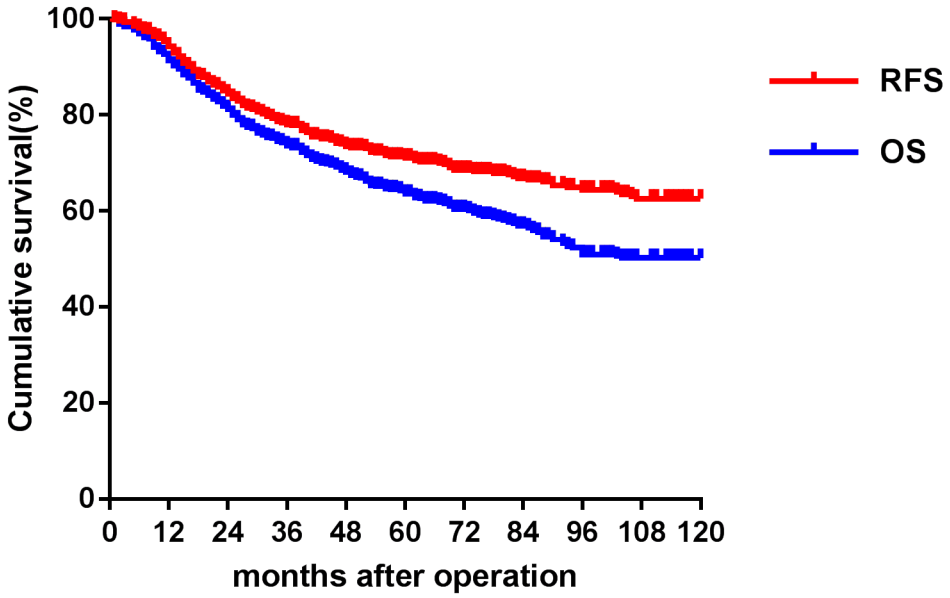

Fig. 1. Cumulative recurrence-free survival (RFS) and overall survival (OS) of node-negative advanced GC patients.

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Fig.2

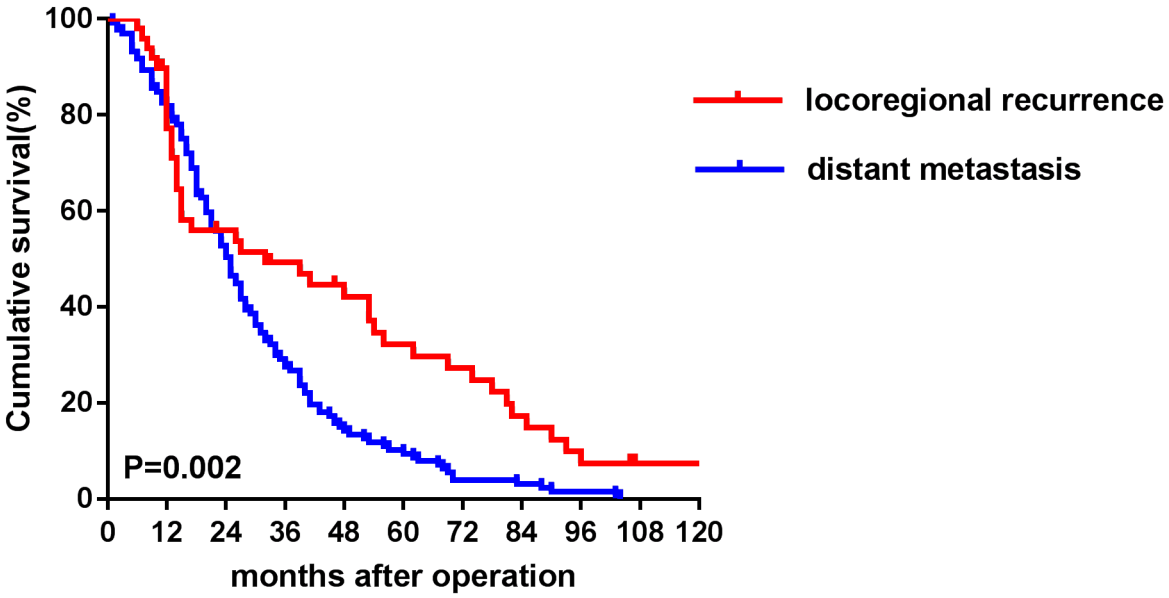

Fig. 2. Cumulative overall survival of node-negative advanced GC patients according to the recurrence pattern.