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ORIGINAL ARTICLE

Evaluation of the prognostic factors in patients with pT3N0 or pT1N2–3 gastric cancer: a single institutional retrospective cohort study

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Abstract
Purpose The impact of adjuvant chemotherapy on the survival of patients with the pT3N0/pT1N2–3 subset of Stage II gastric cancer is unclear. The aim of this study was to evaluate the survival rate of pT3N0/pT1N2–3 patients who were treated by surgery alone and to identify a high-risk group within this cohort.
Methods A total of 258 patients with pT3N0/pT1N2–3 gastric cancer who underwent gastrectomy alone in our hospital between January 1992 and December 2012 were enrolled in the present study. Their medical records were retrospectively reviewed to evaluate the survival rates and investigate prognostic factors.
Results The 3- and 5-year recurrence-free survival rates of this cohort were 84 and 80%, respectively. The 3- and 5-year overall survival rates were 89 and 83%, respectively. A multivariate analysis revealed that pathological venous infiltration was an independent prognostic factor. The survival of patients with pathological venous infiltration was significantly worse than that of those without (5-year recurrence-free survival, 75 vs. 90%, $p = 0.0005$; 5-year overall survival, 78 vs. 91%, $p = 0.0062$).
Conclusions The prognosis of pT3N0/pT1N2–3 gastric cancer patients treated by surgery alone was relatively good; however, patients with pathological vessel infiltration may be at high risk of recurrence and could be candidates for adjuvant chemotherapy.

Keywords Gastric cancer · Adjuvant chemotherapy · Gastrectomy · T3N0

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Introduction

Gastric cancer is the fifth most common form of cancer and the third leading cause of cancer death worldwide [1]. Japan is known to have a high incidence of this disease and many treatment modalities have been developed to improve the prognosis of patients. Nevertheless, gastric cancer remains the third leading cause of cancer death for both men and women in Japan [2]. Radical surgery with D2 dissection is still a mainstay in the treatment of localized advanced gastric cancer in Japan, and adjuvant chemotherapy after curative resection plays an important role in increasing the survival rate for pathological stage II or III disease [3].

The standard strategy of upfront surgery followed by adjuvant chemotherapy is based on evidence obtained from the ACTS-GC trial in Japan, which compared surgery alone to surgery plus adjuvant S-1 monotherapy in patients with pathological stage II or III disease. The results of this trial, which were published in 2007 revealed that adjuvant chemotherapy had a significant impact on survival [4]; subsequently, S-1 adjuvant therapy has become a standard treatment for pathological Stage II or III gastric cancer patients in Japan, as mentioned in the guidelines. However, it seems confusing that although patients with T3N0M0, T1N2M0, and T1N3M0 disease are classified as Stage II in the third English edition of the Japanese classification of gastric carcinoma (JCGC) [5], they are excluded from the indications for adjuvant chemotherapy. This is because the ACTS-GC

was designed according to the second English edition of the JCGC [6], in the second edition, current T3(SS)N0 was classified as T2N0, Stage IB. Additionally, patients with T1 disease were excluded from the ACTS-GC regardless of their N status. Thus, it is questionable whether it can truly be said that adjuvant chemotherapy does not benefit patients with pT3N0 or pT1N2–3 disease (classified as Stage II in the current staging system). Moreover, the identification of predictive factors that indicate an unfavorable prognosis in this population may aid in the selection of appropriate candidates for adjuvant chemotherapy.

The aim of the current study was to evaluate the survival rate of patients with pT3N0 or pT1N2–3 gastric cancer who were treated by surgery alone, and to identify a high-risk group within this cohort who may be appropriate candidates for adjuvant chemotherapy.

Methods

This study is a retrospective single-institutional cohort study. Out of 4328 gastric cancer patients who underwent radical resection at National Cancer Center Hospital East between January 1992 and December 2012, consecutive patients who were diagnosed with pT3N0M0, T1N2M0, or T1N3M0, according to the third English edition of the JCGC [5], were enrolled in this study. The clinical factors and long-term outcomes were retrospectively reviewed using our electronic medical records. Patients who received preoperative chemotherapy in registered clinical trials were excluded from the present study. During this period, in principle, no adjuvant chemotherapy was given to pT3N0M0, pT1N2M0, or pT1N3M0 patients. The only exceptions were patients who indicated that they wished to receive adjuvant chemotherapy; these patients were excluded from the present study. Patients with other concurrent cancer were also excluded from this study. For eligible patients, clinicopathological data including gender, age, tumor location, tumor size, histological type, lymphatic invasion, venous invasion, surgical procedures, range of lymph node dissection, intraoperative blood loss, operation time, postoperative complications (according to Clavien–Dindo Classification) [7, 8], the presence of recurrence, site of recurrence, and survival status were retrospectively collected from the patients' electronic medical records. The survival rates were calculated and the factors that were potentially associated with the prognosis were examined.

The surgical procedures were decided according to tumor size, location, and consideration of the resection margin. In 2010, laparoscopic surgery was introduced for patients with cStage I. In terms of the range of lymph node dissection, D2 was performed for patients with potentially curable cT2–T4 tumors as well as cT1 N + tumors, in accordance with the guidelines at that time. Limited dissection, D1 + beta or D1 + (as defined in the guidelines at that time) was indicated for patients with cT1N0 tumors other than those for whom endoscopic mucosal resection or endoscopic submucosal dissection was recommended [3]. After surgery, the patients were followed every 4 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. The routine follow-up assessment included a physical examination, laboratory tests, the measurement of tumor marker levels (carcinoembryonic antigen and carbohydrate antigen 19-9), and chest to abdominopelvic computed tomography. In principle, upper gastrointestinal endoscopy was performed every 2 years after surgery.

The tumors were classified histopathologically into the differentiated and undifferentiated types. The former included papillary adenocarcinoma, well-differentiated adenocarcinoma, and moderately differentiated adenocarcinoma; the latter included poorly differentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma. The descriptions of T factor, N factor, and staging were in accordance of the third English edition of JCGC [5].

The Chi-squared test, an independent t test, the Kaplan–Meier method with a log-rank test, and a Cox regression hazards model were used to analyze the factors associated with survival and the prognostic factors. p values of <0.05 were considered to indicate statistical significance. The variables that were found to be significantly associated with survival ($p < 0.10$) in the univariate analysis were included in the multivariate analysis. Overall survival (OS) was defined as the period from the date of surgery to the date of death from any cause, and recurrence-free survival (RFS) was defined as the period from the date of surgery to the date of recurrence or death, whichever occurred first. Cases in which the patient did not experience an event before the date of the final observation were censored. The JMP® software program (version 11; SAS Institute, Cary, NC, USA) was used to perform the statistical analyses.

This study was approved by the Institutional Review Board of National Cancer Center Hospital East (Approval No. 2016-083).

Results

A total of 258 patients were eligible for this study. The median age of the patients was 64 years (range 34–87). This cohort included 204 pT3N0M0, 43 pT1N2, and 11 pT1N3 cases; thus 79% of the patients had pT3N0M0 disease. The clinicopathological characteristics of these patients are shown in Table 1. The number of patients who underwent laparoscopic gastrectomy was 11 (4.3%) and the rest of 247 (95.7%) patients underwent open gastrectomy. The comparison of patients with pT3N0 and pT1N2–3 disease revealed

Table 1 The characteristics of pT3N0/pT1–2 gastric cancer patients treated by surgery alone

	Total ($n = 258$)	T1N2–3 ($n = 54$)	T3N0 ($n = 204$)	p value
Gender				0.9
Male	174 (67%)	36 (67%)	138 (68%)	
Female	84 (33%)	18 (33%)	66 (32%)	
Age (years)				0.4
≥65	121 (47%)	22 (41%)	99 (49%)	
<65	137 (53%)	32 (59%)	105 (51%)	
Tumor location				0.005
Upper	76 (29%)	7 (13%)	69 (34%)	
Middle	100 (39%)	24 (44%)	76 (37%)	
Lower	82 (32%)	23 (43%)	59 (29%)	
Tumor major axis (mm)				0.06
≥50	100 (39%)	19 (35%)	81 (40%)	
<50	158 (61%)	35 (65%)	123 (60%)	
Histological type				0.7
Differentiated	131 (51%)	29 (54%)	102 (50%)	
Undifferentiated	127 (49%)	25 (46%)	102 (50%)	
Lymphatic invasion				0.006
Absent	139 (54%)	20 (37%)	119 (58%)	
Present	119 (46%)	34 (63%)	85 (42%)	
Venous invasion				0.007
Absent	96 (37%)	29 (54%)	67 (33%)	
Present	162 (63%)	25 (46%)	137 (67%)	
Surgical procedure				0.007
DG	156 (60%)	40 (74%)	116 (57%)	
TG	89 (34%)	11 (20%)	78 (38%)	
PG	10 (4%)	1 (2%)	9 (4%)	
PPG	2 (1%)	2 (4%)	0 (0%)	
Other	1 (1%)	0 (0%)	1 (1%)	
Lymph node dissection				0.9
≥D2	235 (91%)	49 (91%)	186 (91%)	
<D2	23 (9%)	5 (9%)	18 (9%)	
Intraoperative blood loss (g)				0.01
≥350	141 (55%)	21 (39%)	120 (59%)	
<350	117 (45%)	33 (61%)	84 (41%)	
Operation time (min)	218 ± 69	195 ± 51	224 ± 72	0.0007
Postoperative complications				0.2
≥CD 3	22 (9%)	2 (4%)	20 (10%)	

DG distal gastrectomy, *TG* total gastrectomy, *PG* proximal gastrectomy, *PPG* pylorus-preserving gastrectomy, *CD* Clavien–Dindo Classification

that pT1N2–3 disease was more frequently localized in the lower stomach, and was associated with a higher incidence of pathological lymphatic invasion. In contrast, pT3N0 disease was associated with a higher incidence of pathological venous invasion. The median follow-up period was 61 months (range 2–222). During this period, 55 (21.3%) patients died of any cause (T3N0, $n = 45$; T1N2–3, $n = 10$) and 35 (13.6%) patients developed recurrence (T3N0, $n = 25$; T1N2–3, $n = 10$). The most common primary site of recurrence was the lymph nodes ($n = 12$; 34.3%), followed by the peritoneum ($n = 10$; 28.6%), liver ($n = 8$; 22.9%), locoregional recurrence ($n = 4$; 11.4%), brain ($n = 3$; 8.6%), and lung ($n = 2$; 5.7%) (Table 2). Lymphatic recurrence was detected in 5 (20%) patients with T3N0 disease and 7 (70%) patients with T1N2–3 disease; the difference was statistically significant ($p = 0.004$). Peritoneal recurrence was only detected in patients with T3N0 disease. In the overall cohort, the 3- and 5-year RFS rates were 84 and 80%, respectively, while the 3- and 5-year OS rates were 89 and 83%, respectively (Fig. 1a, b). When the cohort was divided

Table 2 The sites of recurrence in patients with pT3N0 and pT1N2–3 gastric cancer

	Total (n = 258)	T1N2–3 (n = 54)	T3N0 (n = 204)	p value
Recurrence	35 (13.6%)	10 (18.5%)	25 (12.2%)	0.25
Lymph node	12 (34.3%)	7 (70%)	5 (20%)	0.004
Peritoneum	10 (28.6%)	0	10 (40%)	0.03
Liver	8 (22.9%)	2 (20%)	6 (24%)	0.78
Local	4 (11.4%)	1 (10%)	3 (12%)	0.84
Lung	2 (5.7%)	0	2 (8%)	0.33
Brain	3 (8.6%)	2 (20%)	1 (4%)	0.09
Others	2 (5.7%)	2 (20%)	0	0.01

Some recurrence sites are overlapped

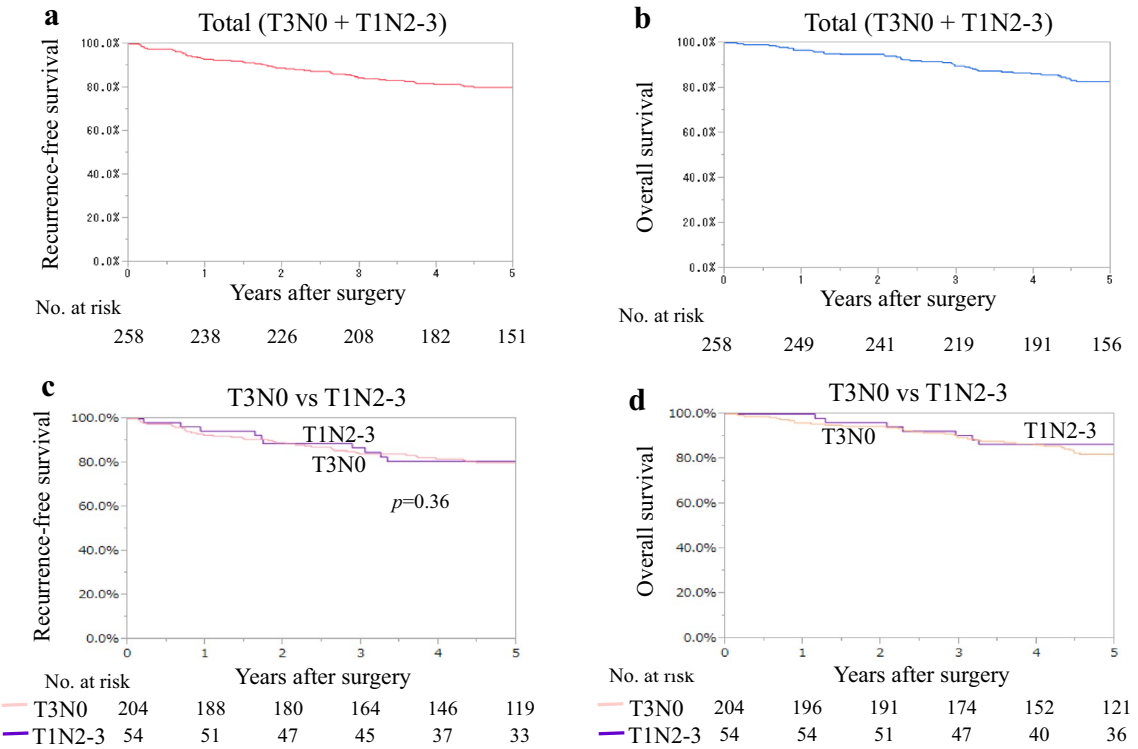

Fig. 1 The Kaplan–Meier estimates of recurrence-free survival (**a** T3N0 + T1N2–3, **c** T3N0 vs. T1N2–3) and overall survival (**b** T3N0 + T1N2–3, **d** T3N0 vs. T1N2–3)

into T3N0 and T1N2–3 groups, the 3- and 5-year RFS rates of the T3N0 cases were 84 and 80%, respectively, while the 3- and 5-year OS rates were 89 and 82%, respectively. Similarly, the 3- and 5-year RFS rates of the T1N2–3 cases were 87 and 81%, respectively, while the 3- and 5-year OS rates were 90 and 86%, respectively (Fig. 1c, d). There was no significant difference between the T3N0 and T1N2–3 disease subgroups.

Regarding the prognostic factors for RFS, a univariate analysis revealed that venous infiltration was significantly associated with RFS in this cohort. Additionally, the variables with p values of ≤ 0.10 in the univariate analysis were included in the subsequent multivariate analysis. A Cox regression hazards model showed that pathological venous infiltration was an independent risk factor for RFS [hazards ratio (HR) 2.829; $p = 0.0009$ (95% confidence interval 1.502–5.814)] (Table 3).

When we compared the RFS and OS curves of the groups with or without pathological venous infiltration (v+ or v−), the prognosis of the v+ group was significantly worse than that of the v− group. The 5-year RFS rates of the v+ and v− groups were 75 and 90%, respectively (log-rank test, $p = 0.0005$). The 5-year OS rates of the v+ and v− groups were 78 and 91%, respectively (log-rank test, $p = 0.006$) (Fig. 2). When the cohort was divided into the T3N0 and T1N2–3 subgroups, 5-year

Table 3 The univariate and multivariate Cox proportional hazards analyses of the clinicopathological factors

Factors	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)			0.575			
<65	1					
≥65	1.158	0.690–1.934				
ASA PS			0.118			
1	1					
2–3	1.507	0.901–2.536				
BMI			0.343			
<23	1					
≥23	0.78	0.462–1.300				
Tumor location			0.057			0.306
U	1			1		
M	0.495	0.269–0.899		0.647	0.346–1.190	
L	0.58	0.303–1.076		0.674	0.351–1.258	
Tumor major axis (mm)			0.665			
<50	1					
≥50	1.121	0.664–1.865				
Macroscopic tumor appearance			0.472			
Type 0	1					
Type 1–5	1.241	0.700–2.344				
Histological type			0.141			
Differentiated	1					
Undifferentiated	0.682	0.404–1.135				
Lymphatic invasion			0.558			
Absent	1					
Present	1.164	0.699–1.937				
Venous invasion			0.0003			0.0009
Absent	1			1		
Present	3.015	1.629–6.113		2.829	1.502–5.814	
Lymph node dissection			0.059			0.054
<D2	1			1		
≥D2	0.473	0.245–1.031		0.462	0.236–1.013	
Postoperative complications			0.212			
<CD 3	1					
≥CD 3	1.712	0.709–3.519				

HR hazard ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *CD* Clavien–Dindo classification

RFS rates of the v− and v+ cases in the T3N0 subgroup were 87 and 76%, respectively (log-rank test, $p = 0.03$), while the 5-year OS rates of the v− and v+ cases were 89 and 79%, respectively (log-rank test, $p = 0.09$) (Fig. 3a, b). The 5-year RFS rates of the v− and v+ cases in the T1N2–3 subgroup were 97 and 61%, respectively (log-rank test, $p = 0.005$), while the 5-year OS rates of the v− and v+ cases were 96 and 75%, respectively (log-rank test, $p = 0.01$) (Fig. 3c, d).

Discussion

In the current study, we confirmed that the prognosis of pT3N0/pT1N2–3 patients treated by surgery alone was relatively good, with 5-year OS and RFS rates of 83 and 80%, respectively. Ahn et al. [9] reviewed a database of 9998 patients who were treated at Seoul National University Hospital between 1986 and 2006 to evaluate the survival rates with the 7th TNM classification. They showed that the

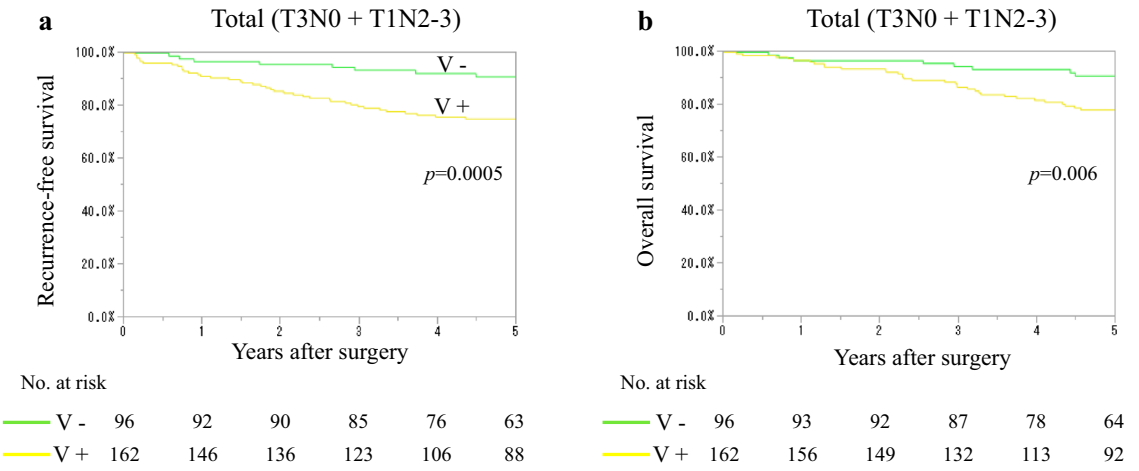

Fig. 2 The Kaplan–Meier estimates of recurrence-free survival (**a**) and overall survival (**b**) in patients (T3N0 + T1N2–3) without venous invasion (v−) vs. patients with venous invasion (v+)

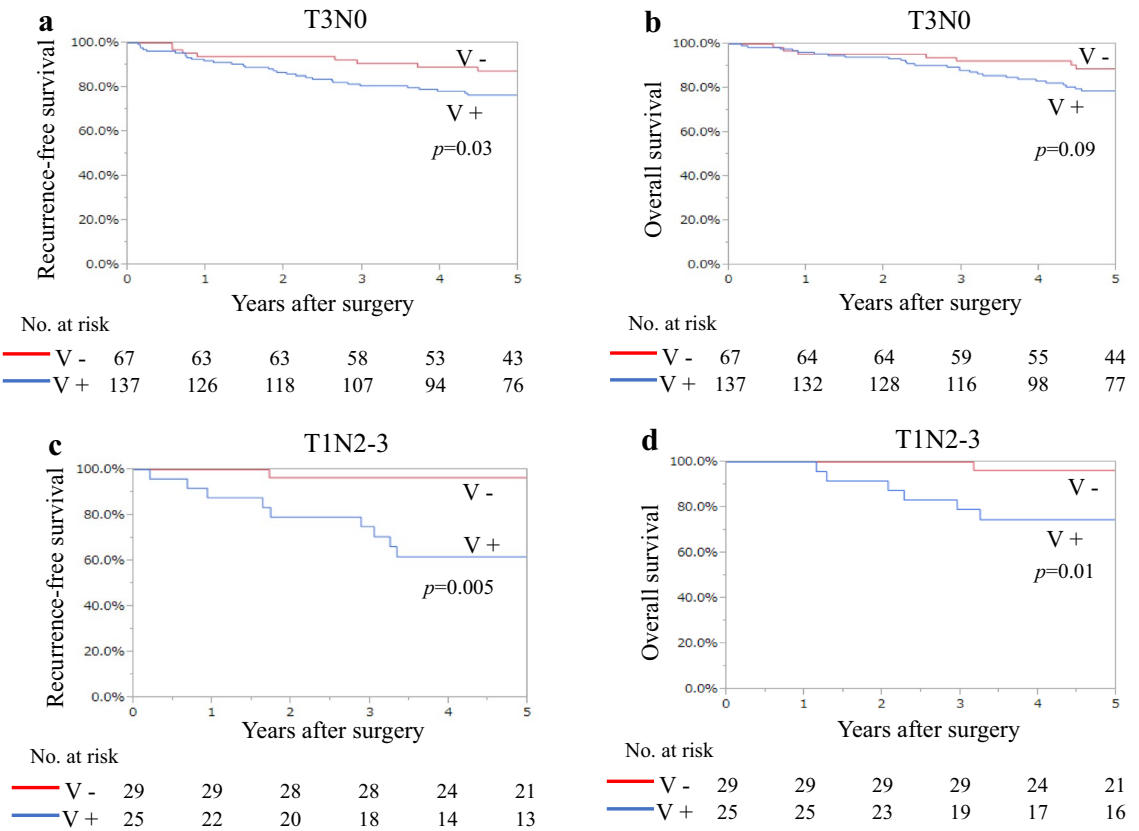

Fig. 3 The Kaplan–Meier estimates of recurrence-free survival (**a** T3N0, **c** T1N2–3) and overall survival (**b** T3N0, **d** T1N2–3) in patients without venous invasion (v−) vs. patients with venous invasion (v+)

5-year OS rates of patients with T3N0 and T1N2 disease were 82.1 and 84.0%, respectively, which seems comparable with results of the current study. Meanwhile, they reported that the 5-year OS of patients with T1N3 disease was 71.1%, which was worse than that of the former groups. In the current study, T1N2 and T1N3 were unified into one group for the analysis due to the small sample size; thus, it was not possible to fully compare our results to the results of

the Korean study. In this context, it seems unnecessary to administer adjuvant chemotherapy to all pT3N0/pT1N2–3 patients. However, as approximately 20% of patients encounter recurrence after surgery, it is important to identify the high-risk subgroup of patients who may be appropriate candidates for adjuvant chemotherapy.

In the current study, venous infiltration was revealed as an independent prognostic factor in pT3N0/pT1N2–3 patients. The prognoses of patients with this factor (5-year OS and RFS: 78 and 75%) were significantly worse than of those without it. Although pT3N0 and pT1N2–3 patients were excluded from the ACTS-GC trial, the results of the current study may indicate the necessity of adjuvant chemotherapy for selected patients. Interestingly, the difference in the survival of the v− and v+ subgroups was more obvious in patients with pT1N2–3 disease (5-year OS and RFS: 75 and 61%, respectively). We hypothesized that the presence of multiple nodal metastases combined with micro-cancerous infiltration into the vessel structure is indicative of very aggressive oncological behavior. In fact, the primary pattern of recurrence in most of these patients (70%) was lymphatic. As mentioned above, the Korean group suggested that the prognosis of T1N3 patients did not seem favorable. Thus, adjuvant chemotherapy may be strongly recommended, specifically for patients with pT1N2–3 gastric cancer with venous infiltration. In the ACTS-GC trial [10], the incidence of lymphatic recurrence was particularly decreased in patients who received S-1. From this viewpoint, adjuvant chemotherapy using S-1 may be a reasonable treatment for this subpopulation.

Although this was a retrospective study that was performed in a single-institution, our cohort represented the largest sample size of any study on this topic to date. Some previous publications have evaluated prognostic factors in patients with pathological stage II gastric cancer. Imamura et al. retrospectively analyzed the clinical outcomes of 116 patients with pStage IIA gastric cancer (T3N0, T2N1, and T1N2) who underwent curative gastrectomy. They reported that the 5-year OS rate of those patients was 77%, and concluded that pathological lymphatic infiltration was independently associated with a poor prognosis in pT3N0 gastric cancer [11]. Toyokawa et al. conducted a retrospective study of 201 patients with stage IB gastric cancer (according to the second JCGC; T2N0, T3N0, and T1N1–3 according to the third JCGC), and concluded that patients with large tumors might be candidates for adjuvant chemotherapy [12]. Aoyama et al. retrospectively examined 52 patients with pathological stage II disease according to the third JCGC (T1N2–3, T3N0), and identified that a small tumor diameter was an independent prognostic factor in patients with T1N2–3 disease [13]. Due to the limited sample sizes, it may not be possible to reach a consistent conclusion. In the current study, around 80% of the patients were diagnosed with T3N0 disease, and hematogenous recurrence was the predominant pattern of recurrence in patients with T3N0 disease. Thus, it is hypothesized that venous infiltration rather than lymphatic infiltration was a strong prognostic factor due to this bias. However, it seems rational—from an oncological point of view—to regard pathological vessel (lymphatic or venous) infiltration as a pivotal indicator of a high-risk subpopulation of pT3N0/T1N2–3 disease, as a similar discussion has already taken place in relation to the management of pathological Stage II colorectal cancer, in which vessel infiltration was suggested to be a crucial prognostic indicator [14].

Moreover, it is still unclear whether the prognosis of this high-risk subpopulation is really improved by adjuvant chemotherapy. In this regard, Lee et al. retrospectively evaluated 630 patients who were diagnosed with pStage II disease according to the third JCGC, and reported that adjuvant chemotherapy provided a survival benefit for patients with pT2N1 but that it did not affect the survival of patients with T3N0 or T1N2 disease [15]. Of course, there might have been a selection bias in the present study because of its retrospective nature; thus, a well-designed prospective study should be conducted to validate the results.

The current study is associated with several limitations due to its retrospective design and the fact that it was performed in a single institution. In addition, we only evaluated the outcomes patients who were treated with surgery alone, and there was no comparable analysis of patients who received surgery combined with adjuvant chemotherapy. A multi-institutional prospective study should be performed to overcome this limitation and reach a conclusion.

Conclusions

The prognosis of patients with pT3N0/pT1N2–3 gastric cancer was relatively favorable, even when they were treated with surgery alone. However, patients with pathological vessel infiltration, especially those with pT1N2–3 disease, may have a high risk of recurrence and could be appropriate candidates for adjuvant chemotherapy.

Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

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