Original Article

# Prognostic significance of the concomitant existence of lymphovascular and perineural invasion in locally advanced gastric cancer patients who underwent curative gastrectomy and adjuvant chemotherapy

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## Abstract

**Objective:** In this study, we evaluated the prognostic significance of the concomitant existence of lymphovascular invasion and perineural invasion in patients with advanced gastric cancer.

**Methods:** A total of 206 consecutive patients with Stage II or III gastric cancer who underwent curative D2 gastrectomy and adjuvant chemotherapy from April 2004 to December 2011 were analyzed. Patients were classified into four groups according to the presence (+) or absence (−) of lymphovascular invasion and perineural invasion: lymphovascular invasion−/perineural invasion− ($n = 33$), lymphovascular invasion+/perineural invasion− ($n = 31$), lymphovascular invasion−/perineural invasion+ ($n = 54$) and lymphovascular invasion+/perineural invasion+ ($n = 88$).

**Results:** A total of 136 patients (66.0%) received 5-fluorouracil plus cisplatin adjuvant chemotherapy and 70 patients (34.0%) received TS-1. During the median follow-up period of 35.18 months, the median disease-free survival times for lymphovascular invasion−/perineural invasion−, lymphovascular invasion+/perineural invasion− and lymphovascular invasion−/perineural invasion+ were not reached at the time of analysis; however, median disease-free survival for lymphovascular invasion+/perineural invasion+ was the worst (36.73 months, $P = 0.001$). The median overall survival in the four groups was also not reached at the time of analysis; however, median overall survival with lymphovascular invasion+/perineural invasion+ was the poorest ($P = 0.002$). In a multivariate analysis, lymphovascular invasion+/perineural invasion+ was an independent prognostic factor for both disease-free survival (hazard ratio = 1.940, 95% confidence interval 1.157–3.252, $P = 0.012$) and overall survival (hazard ratio = 2.973, 95% confidence interval 1.561–5.662, $P = 0.001$).

**Conclusions:** The concomitant existence of lymphovascular and perineural invasion has a significant prognostic impact on disease-free survival and overall survival in patients with Stage II or III gastric cancer.

## Introduction

Gastric cancer is a leading cause of cancer-related mortality in Asian countries. Recently, two clinical trials demonstrated the clinical efficacy of adjuvant chemotherapy after curative gastrectomy using D2 lymph node dissection in Stage II or III gastric cancer patients (1,2). Oral TS-1 monotherapy resulted in improved overall survival (OS) and relapse-free survival of locally advanced gastric cancer (3), and doublet treatment with capecitabine plus oxaliplatin improved survival in patients with locally advanced gastric cancer (2). However, ~30% of these patients develop recurrences even after adjuvant chemotherapy and have a very poor prognosis (4).

Several studies have reported that lymphatic, vascular or perineural invasion (PNI) by cancer cells is associated with poor survival and/or early recurrence in gastric cancer (5–8). However, few studies have compared the prognostic superiority between lymphovascular invasion (LVI) and PNI. The clinical significance of the simultaneous existence of LVI and PNI is unknown in gastric cancer patients, especially in subgroups of patients who have undergone curative gastrectomy and adjuvant chemotherapy.

In this study, we evaluated the prognostic significance of the concomitant existence of LVI and PNI in locally advanced Stage II or III gastric cancer patients who underwent curative D2 resection and adjuvant chemotherapy.

## Patients and methods

### Patients

A total of 206 gastric cancer patients received adjuvant chemotherapy after curative D2 gastrectomy at Chonnam National University Hwasun Hospital in Jeonnam, Korea, between April 2004 and December 2011.

We reclassified the disease stage according to the American Joint Committee on Cancer (AJCC) 7th edition. The eligibility criteria were as follows: histologically confirmed AJCC Stage IIA (T3N0, T2N1, T1N2), IIB (T4aN0, T3N1, T2N2, T1N3), IIIA (T4aN1, T3N2, T2N3), IIIB (T4bN0, T4bN1, T4aN2, T3N3) or IIIC (T4bN2, T4bN3, T4aN3) gastric adenocarcinoma with no evidence of metastatic disease; R0 resection (with no tumor cells at the margin) using D2 lymph node dissection; and no previous cancer treatment except for initial gastric resection of the primary lesion. All data were prospectively recorded, and only the survival data were updated from the cancer registry at the time of analysis. This study was approved by the Institutional Review Board of Chonnam National University Medical School Research Institution. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were followed throughout the study.

### Chemotherapy

Adjuvant chemotherapy was administered using TS-1 (Taiho Pharmaceutical, Tokyo, Japan) or 5-fluorouracil (5-FU) plus cisplatin (FP) according to the physician's judgment and patient's preference. The dose of TS-1 was determined based on the body surface area (BSA). Accordingly, the patients received one of the following doses divided into two and administered daily after meals: 80 mg for patients with BSA < 1.25 $m^2$, 100 mg for those with BSA $\geq$ 1.25 and <1.50 $m^2$ and 120 mg for those with BSA $\geq$ 1.5 $m^2$. TS-1 was administered for 4 weeks, followed by 2 weeks of rest. Treatment was continued for 1 year after surgery. FP chemotherapy was administered as follows: 5-FU 800 mg/$m^2$ per day was administered by continuous intravenous infusion on Days 1–5 of each cycle and cisplatin 80 mg/$m^2$ on Day 1 by intravenous infusion. The FP regimen was administered every 4 weeks for six cycles.

The schedule was repeated until the disease recurred, unacceptable toxicity was reached, or the patient refused treatment. Hematological and non-hematological adverse events were evaluated. The management of adverse events and subsequent dose reductions of chemotherapeutic agents were performed following a conventional protocol.

### Follow-up

For the surveillance of tumor recurrence, abdominal computed tomography was performed every 3 months during the first 2 years after surgery and then every 6 months for 5 years after surgery. Physical examination data, chest radiographs and carcinoembryonic antigen and carbohydrate antigen 19-9 tumor markers were evaluated every 3 months for the first 2 years and then every 6 months for 5 years. If clinical signs or symptoms indicated a possible recurrence or development of a new gastric cancer, investigations were conducted to verify whether the patient was disease-free.

### Pathological examination

A histopathological examination was performed on all radical gastric resection specimens. Resected specimens were dissected and prepared as formalin-fixed paraffin-embedded tissue blocks. The diagnostic criteria for the tumor stages were in agreement with the AJCC 7th edition TNM (tumor, node, metastasis) staging system. Hematoxylin and eosin-stained slides were coded without knowledge of the clinical details. The coded slides were independently reviewed and assessed by two gastrointestinal pathologists (J.H.L. and K.H.L.) to determine the depth of tumor invasion, lymph node involvement, histologic type, LVI and PNI. LVI was defined by the presence of tumor cells within the endothelium-lined space or the destruction of a lymphovascular wall by tumor cells (Fig. 1A) (9). PNI was defined as the observation of extraneural cancer cells (Fig. 1B) (10). The pathologic findings were re-evaluated for cases in which the observers disagreed [for LVI, 13 cases of the 206 (6.3%); for PNI, 7 cases of the 206 (3.4%)]. In these cases, both authors reviewed the cases together and reached a consensus.

### Statistical analysis

The variables for inclusion in the model were age, sex, tumor location, histological grade, Lauren's classification, chemotherapy regimen, T category, N category, LVI and PNI. The Kaplan–Meier method was used to construct disease-free survival (DFS) and OS curves. DFS was defined as the period from the time of surgery to that of documented disease recurrence or death from any cause, whichever occurred first. If neither event occurred at the time of the last record, the patient was censored. OS was calculated from the time of surgery to that of
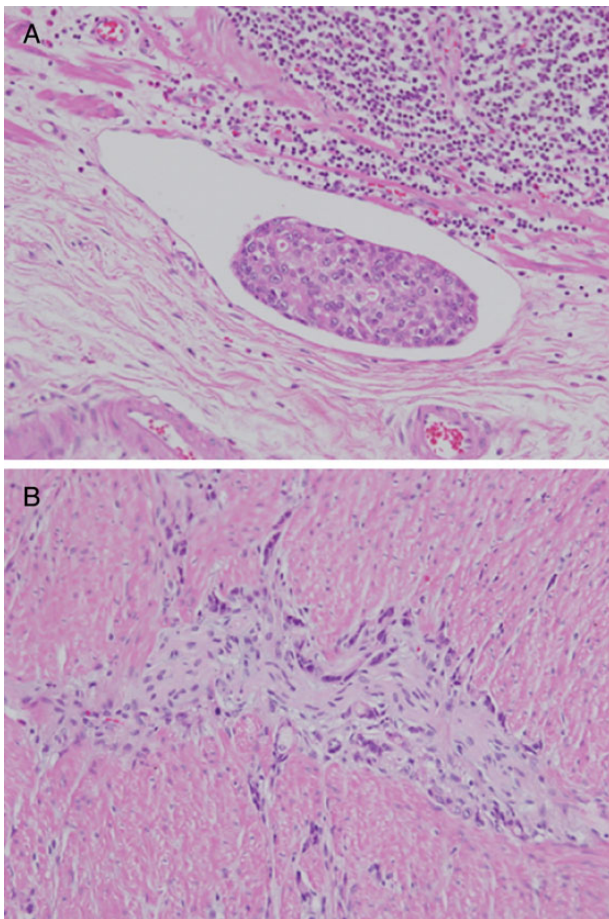
**Figure 1.** Representative microphotographs of lymphovascular invasion (LVI) and perineural invasion (PNI) in a gastric adenocarcinoma. (A) Gastric cancer cells in a vascular channel are shown at a higher magnification [hematoxylin and eosin (H&E) ×200]. (B) Gastric cancer cells can be seen infiltrating along the perineural spaces of a peripheral nerve bundle (H&E ×200).

**Table 1.** Patient characteristics (*n* = 206)

| Characteristics | No. of patients | % |
|---|---|---|
| Age (years) | | |
| <64 | 102 | 49.5 |
| ≥64 | 104 | 50.5 |
| Sex | | |
| Male/female | 145/61 | 70.4/29.6 |
| Tumor location | | |
| GEJ | 19 | 9.2 |
| Body, antrum | 187 | 90.8 |
| Histological grade | | |
| WD/MD | 19/43 | 30.1 |
| PD/signet ring cell | 123/21 | 69.9 |
| Lauren classification | | |
| Intestinal | 95 | 46.1 |
| Diffuse | 79 | 38.4 |
| Mixed | 32 | 15.5 |
| Chemotherapy regimen | | |
| FP | 136 | 66.0 |
| TS-1 | 70 | 34.0 |
| Stage (AJCC 7th edition) | | |
| IIA | 26 | 12.6 |
| IIB | 38 | 18.5 |
| IIIA | 56 | 27.2 |
| IIIB | 47 | 22.8 |
| IIIC | 39 | 18.9 |
| T stage | | |
| T1/T2/T3/T4 | 9/26/83/88 | 4.4/12.6/40.3/42.7 |
| N stage | | |
| N0/N1/N2/N3 | 19/45/75/67 | 9.2/21.8/36.4/32.5 |
| LVI−/PNI−, LVI+/PNI− | 33/31 | 16.0/15.0 |
| LVI−/PNI+, LVI+/PNI+ | 54/88 | 26.2/42.7 |

GEJ, gastrointestinal junction; WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated; FP, cisplatin; AJCC, American Joint Committee on Cancer; LVI, lymphovascular invasion; PNI, perineural invasion.

death from any cause. Differences between survival curves were tested using the log-rank test. A multivariate analysis was performed using a Cox proportional hazards model and a logistic regression analysis. Variables associated with survival (*P* < 0.10) in the univariate analysis were included in the multivariate analysis using the reducing variables methods.

All statistical tests were two sided, and a *P* value < 0.05 indicated statistical significance. All analyses were performed using SPSS software (version 19.0; SPSS, Inc., Chicago, IL, USA).

## Results

### Patient characteristics

The patient demographic characteristics are listed in Table 1. The analysis included 145 males (70.4%), and the median age was 64 years (range 32–82 years); 19 patients (9.2%) had gastroesophageal junction (GEJ) cancer, and 187 patients (90.8%) had body and antrum cancer. Histologically, 95 tumors (46.1%) were intestinal, 79 (38.4%) were diffuse and 32 (15.5%) were mixed-type. LVI was detected in 119 patients (57.8%) and PNI in 142 patients (68.9%); 136 patients (66.0%) received FP chemotherapy, and 70 patients (34.0%) received TS-1. The median numbers of delivered

cycles of FP and TS-1 chemotherapy were 6 (range 1–6, mean 5.43 ± 1.343) and 8 (range 1–8, 6.347 ± 2.240), respectively. Using the AJCC 7th edition TNM staging system, the pathological stage was classified as IIA in 26 patients (12.6%), IIB in 38 (18.5%), IIIA in 56 (27.2%), IIIB in 47 (22.8%) and IIIC in 39 (18.9%).

### Clinicopathological parameters, recurrence and survival

Our results were obtained at a median follow-up of 35.18 months (range 6.3–93.47 months) after surgery. In total, 66 patients (32%) developed recurrent disease: 24 (11.7%) in the S-1 group and 42 (20.3%) in the FP chemotherapy group. A total of 46 patients (22.3%) died: 13 (6.3%) in the S-1 group and 33 (16.0%) in the FP chemotherapy group. The median DFS and OS were not reached at the time of analysis. The 3-year DFS and OS of the patients were 66.7 and 78.1%, respectively. The chemotherapy regimen showed no association with DFS or OS. The 3-year DFS was 63.4% in the TS-1 group and 68.7% in the FP group (*P* = 0.259). The 3-year OS was 76.0% in the TS-1 group and 78.8% in the FP group (*P* = 0.998).

In a subgroup analysis, no chemotherapy regimen was more effective on DFS or OS according to the clinical factors. In DFS, the FP regimen appeared to be more effective than TS-1 in the LVI+/PNI+ group.

The median DFS times of FP and TS-1 in the LVI+/PNI+ group were 46.87 and 29.0 months, respectively, although no statistical significance was detected ($P = 0.391$, Fig. 2).

In a univariate analysis (Table 2), the factors associated with poorer DFS were tumor location, Stage III, advanced T category (T3 + T4), advanced N category (N2 + N3) and LVI + /PNI + . In a multivariate analysis (Table 3), advanced T category (T3 + T4), advanced N category (N2 + N3) and LVI + /PNI+ were independent prognostic factors for DFS. In the univariate analysis (Table 2), the factors associated with a poorer OS were age, male sex, Stage III, advanced T category (T3 + T4), advanced N category (N2 + N3) and LVI+/PNI+. In a multivariate analysis (Table 3), age (≥64 years), male sex, advanced N category (N2 + N3) and LVI+/PNI+ were independent prognostic factors for OS. Advanced T category (T3 + T4) was marginally associated with a poorer OS ($P = 0.058$).

We evaluated the DFS and OS according to the presence (+) or absence (−) of LVI and PNI. We classified the patients into four groups: LVI−/PNI− ($n = 3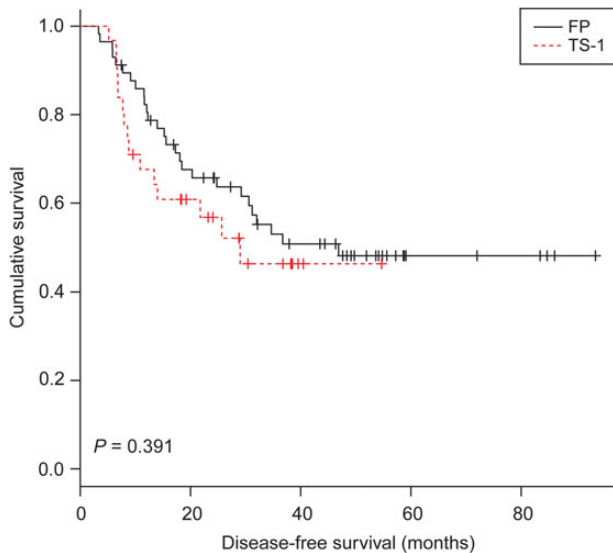3$), LVI+/PNI− ($n = 31$), LVI−/PNI+ ($n = 54$) and LVI+/PNI+ ($n = 88$). During the median follow-up period of 35.18 months, the median DFS times for the LVI−/PNI−, LVI+/PNI− and LVI−/PNI+ groups were not reached at the time of analysis and the DFS curves of the three groups showed no survival differences ($P = 0.885$, Fig. 3). However, the median DFS time for LVI+/PNI+ was the worst (36.73 months, $P = 0.001$, Fig. 3). With regard to OS, the median OS times of the four groups were also not reached at the time of analysis and the OS curves of the LVI−/PNI−, LVI+/PNI− and LVI−/PNI+ groups showed no survival differences ($P = 0.781$). However, the median OS for the LVI+/PNI+ group was the poorest ($P = 0.002$, Fig. 4).

Given the importance of LVI and PNI positivity for survival, we performed a multivariate analysis to identify factors independently associated with positivity of both LVI and PNI (Table 4). Differentiation ($P = 0.047$), advanced T category (T3 + T4, $P = 0.002$) and advanced N category (N2 + N3, $P = 0.016$) were independent predictors of LVI and PNI positivity.

## Discussion

In this study, we identified that the concomitant existence of LVI and PNI is an independent prognostic factor for DFS and OS in Stage II or II gastric cancer patients who have undergone curative D2 gastrectomy and adjuvant chemotherapy. To date, limited studies have focused on recurrence and survival in Stage II or III gastric cancer patients who underwent curative resection and adjuvant chemotherapy. Wada et al. [8] used TS-1 as adjuvant chemotherapy and demonstrated tumor diameter (≥5) as an independent risk factor for recurrence in this patient population. We did not examine the tumor diameter; however, we investigated the pT stage, and a multivariate analysis showed that an advanced T category (T3 + T4) was a poor risk factor for DFS and marginally associated with poor OS.

The detection of cancer cells in peritumoral or intratumoral vascular and lymphatic vessels indicates metastasis, and it is generally considered to be a poor prognostic indicator. Wang et al. [11] reported that peritumoral, but not intratumoral, lymphatics were significantly associated with lymph node metastasis and a poor prognosis in gastric cancer. Angiogenesis is also essential for tumor growth and metastasis. In gastric cancer, intratumoral angiogenesis is significantly associated with vascular invasion, distant metastasis and poor survival [12]. LVI is also considered an independent risk factor for lymph node metastases in gastric cancer [6,13–15].



**Figure 2**. The FP regimen appeared to be more effective than TS-1 in the LVI+/PNI+ group in terms of disease-free survival (DFS).

**Table 2**. Univariate analyses of clinical factors for DFS and OS

| | DFS Hazard ratio (95% CI) | *P* value | OS Hazard ratio (95% CI) | *P* value |
|---|---|---|---|---|
| Age, ≥64 years | 1.373 (0.844–2.234) | 0.202 | 1.976 (1.084–3.604) | 0.026 |
| Male | 1.553 (0.873–2.764) | 0.134 | 2.510 (1.122–5.614) | 0.025 |
| Tumor location (GEJ) | 2.033 (1.005–4.113) | 0.048 | 1.469 (0.580–3.719) | 0.417 |
| Differentiation (PD + signet ring cell) | 1.464 (0.834–2.572) | 0.185 | 1.317 (0.682–2.544) | 0.413 |
| Lauren classification | | 0.591 | | 0.775 |
| Diffuse | 0.957 (0.556–1.648) | 0.875 | 0.993 (0.518–1.904) | 0.983 |
| Mixed | 1.345 (0.700–2.575) | 0.375 | 1.300 (0.595–2.839) | 0.511 |
| TS-1 | 1.335 (0.807–2.210) | 0.261 | 0.999 (0.521–1.917) | 0.998 |
| Stage III | 4.803 (2.191–10.529) | 0.001 | 8.421 (2.608–27.198) | 0.001 |
| T category (T3 + T4) | 5.236 (1.643–16.688) | 0.005 | 5.624 (1.361–23.243) | 0.017 |
| N category (N2 + N3) | 3.291 (1.628–6.650) | 0.001 | 4.290 (1.694–10.864) | 0.002 |
| LVI+/PNI+ | 2.741 (1.659–4.529) | 0.001 | 3.190 (1.719–5.922) | 0.001 |

CI, confidence interval; DFS, disease-free survival; OS, overall survival.

**Table 3.** Multivariate analyses of clinical factors for DFS and OS

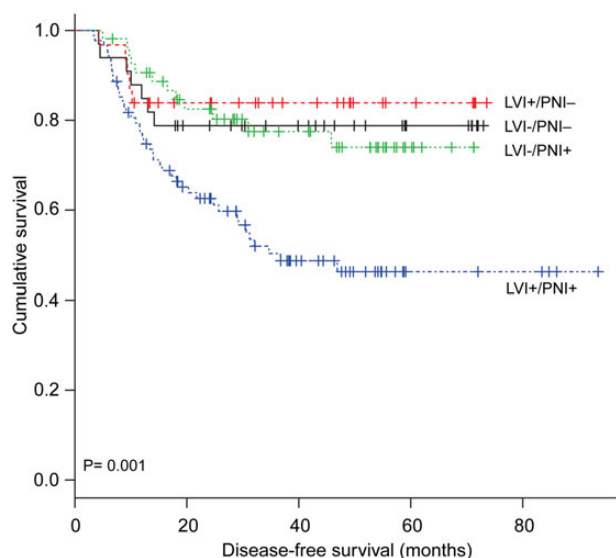|  | Hazard ratio (95% CI) | *P* value |
|---|---|---|
| DFS |  |  |
| Tumor location (GEJ) | 1.570 (0.769–3.205) | 0.215 |
| T category (T3 + T4) | 4.150 (1.280–13.462) | 0.018 |
| N category (N2 + N3) | 3.048 (1.498–6.203) | 0.002 |
| LVI+/PNI+ | 1.940 (1.157–3.252) | 0.012 |
| OS |  |  |
| Age ≥64 years | 2.496 (1.339–4.653) | 0.004 |
| Male | 3.017 (1.334–6.824) | 0.008 |
| T category (T3 + T4) | 4.039 (0.953–17.124) | 0.058 |
| N category (N2 + N3) | 4.727 (1.845–12.111) | 0.001 |
| LVI+/PNI+ | 2.973 (1.561–5.662) | 0.001 |



**Figure 3.** DFS curves according to the presence (+) or absence (−) of LVI and PNI.



**Figure 4.** Overall survival (OS) curves according to the presence (+) or absence (−) of LVI and PNI.

**Table 4.** Multivariate predictors of LVI and PNI positivity in patients with Stage II or III R0 resected gastric cancer

|  | Odds ratio (CI) | *P* value |
|---|---|---|
| Differentiation (PD + signet ring cell) | 2.503 (1.014–6.181) | 0.047 |
| T category (T3 + T4) | 4.466 (1.716–11.624) | 0.002 |
| N category (N2 + N3) | 2.320 (1.166–4.616) | 0.016 |

Although PNI mechanisms are poorly understood, the clear association between PNI and metastasis in several cancers, including prostate and head and neck, suggests a role for PNI in tumor dissemination (16–20). In colorectal cancer, PNI has also been reported as a prognostic factor for recurrence and survival (21,22). A recent meta-analysis suggested PNI to be an independent prognostic factor affecting the OS and DFS of gastric cancer patients who underwent curative resection (5).

We compared the potential prognostic superiority between LVI and PNI in this analysis. We found that LVI only and PNI only had no significant influence on patient survival in this study population. In the three groups studied (LVI–/PNI–, LVI+/PNI– and LVI–/PNI+) similar DFS (*P* = 0.885, Fig. 3) and OS curves (*P* = 0.781, Fig. 4) were observed. Only concomitant LVI+/PNI+ was a strong independent indicator for poor prognosis of both OS and DFS in patients with Stage II or III gastric cancer.

In this study, patients with both LVI– and PNI+ tumors were more likely to have the following clinicopathological factors: poor differentiation, advanced T category (T3 + T4) and advanced N category (N2 + N3). According to these results, patients with concomitant LVI and PNI were more likely to have primary tumors with more aggressive features. Furthermore, the 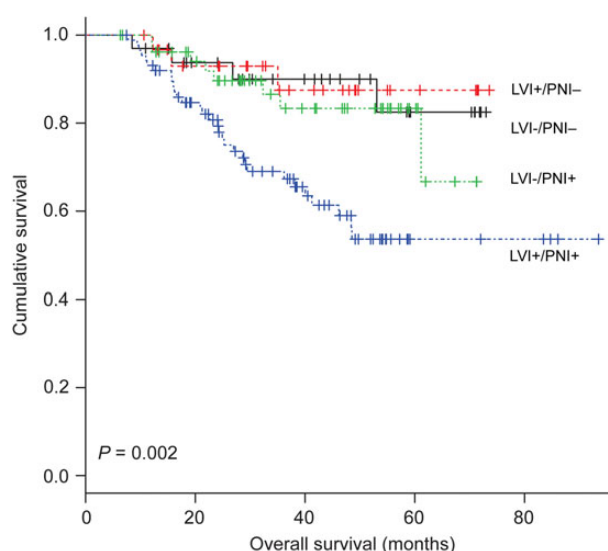hazard ratio of recurrence and survival increased ~2- and 3-fold, respectively, for patients with concomitant LVI+/PNI+ compared with those without.

The SPIRITS trial demonstrated that 5-FU (TS-1) plus platinum is more effective than 5-FU alone (TS-1) as the first-line palliative chemotherapy treatment in advanced gastric cancers (23). In this study, although it was not statistically significant, the FP regimen appeared to be more effective than TS-1 in the LVI+/PNI+ group in terms of DFS. Considering the poor prognostic impact of LVI+/PNI+ on DFS and OS, doublet adjuvant chemotherapy with 5-FU derivatives plus platinum agents might be a better option for patients with LVI+/PNI+. These findings require further investigation to reach a more definitive conclusion.

Although we demonstrated the prognostic significance of the concomitant existence of LVI and PNI, the present study has several limitations. Firstly, this was a retrospective analysis with a relatively small sample size from a single institution. Secondly, this study included a somewhat heterogeneous patient population. We used FP and TS-1 for the adjuvant chemotherapy regimen, and the study population included more patients with Stage III disease (69.0%). Thirdly, our finding that LVI or PNI in isolation is not a prognostic factor for OS and DFS is somewhat in conflict with the results of other studies (5–7,15,21). This could be partly due to the heterogeneous patient population and diversity of diagnostic criteria for LVI and PNI between studies; indeed, there are currently no widely accepted standards for the pathologic evaluation of LVI and PNI (24). This result requires further investigation to reach a firm conclusion.

## Conclusion

The concomitant existence of LVI and PNI can be used as a new significant prognostic factor in Stage II or III gastric cancers. Intensive

follow-up is necessary for LVI+/PNI+ patients because this subgroup has a greater likelihood of recurrence and poor survival.

## Acknowledgements

## Conflict of interest statement

None declared.

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