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# Venous Invasion and Perineural Invasion as Upstaging and Poor Prognostic Factors in N0 Gastric Cancers

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**Abstract.** *Background/Aim: Lymph node metastasis is an important prognostic factor in gastric cancer patients. In node-negative (N0) gastric cancer patients, additional prognostic factors are needed to reinforce TNM staging. Patients and Methods: We semi-quantitatively recorded the presence of lymphatic, venous, and perineural invasion and evaluated the possibility that they could be used as upstaging factors in N0 gastric cancer by comparing N0 gastric cancer cases with N1 cases. Results: Venous ($p<0.001$) and perineural ($p<0.001$) invasion were important factors in the relapse-free survival of N0 patients, but lymphatic invasion was not. N0 cases with venous or perineural invasion had survival curves similar to those of N1 patients. In addition, the number of invasive features (lymphatic, venous, or perineural) was an important factor in predicting poor patient survival. Conclusion: Venous and perineural invasion were significant prognostic factors in N0 gastric cancer cases. It is necessary to record lymphatic, venous, and perineural invasion separately in the pathology report, especially in cases of N0 gastric cancer.*

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*Key Words:* Gastric cancer, venous invasion, lymphatic invasion, perineural invasion.

Gastric cancer is the fifth-most common cancer and the third most common cause of cancer-related deaths worldwide (1). In Korea, gastric cancer is the second- and third-most common cancer in males and females, respectively (2). Lymph node metastasis is a major factor in TNM staging and is known to be an important indicator for patient survival and gastric cancer recurrence (3). However, in lymph node-negative (N0) gastric cancer cases, few studies have been performed to discover additional prognostic factors. Tumor size, histologic type, patient age, lymphovascular invasion (LVI), and perineural invasion (PNI) have been reported as significant prognostic factors (4-8).

LVI is generally defined as the presence of tumor cells within endothelial-lined lymphatic or vascular spaces. LVI is well-known to predict tumor aggressiveness in N0 gastric cancers, as well as lymph node metastasis irrespective of tumor stage in gastric cancers overall (7, 9-12). In addition, Lu et al. reported that combining LVI and the AJCC staging system could improve accuracy in predicting the prognosis of node-negative gastric cancer patients (13). However, few studies have separately analyzed lymphatic invasion (LI) and vascular invasion (VI) as possible prognostic factors in N0 gastric cancer. Although LI has been reported as an upstaging factor and VI has been reported as a risk factor for hematogenous recurrence after curative surgery, they showed limited significance for gastric cancer only at specific TNM stages (14-16).

Perineural invasion (PNI) is also an independent prognostic factor that affects tumor recurrence and patient survival after curative resection for gastric cancer (17-20). Recently, PNI was reported as a predictive factor for the effectiveness of adjuvant chemotherapy (21). However, for

Table I. *Clinicopathologic features of overall and N0 gastric cancer cases.*

| | Overall cases (%) | N0 cases (%) |
|---|---|---|
| Gender | | |
| Male | 430 (68.5) | 286 (68.6) |
| Female | 198 (31.5) | 131 (31.4) |
| WHO classification | | |
| Tubular | 289 (46.0) | 210 (50.4) |
| Poorly cohesive | 198 (31.5) | 133 (31.9) |
| Mucinous | 8 (1.3) | 2 (0.7) |
| Gastric carcinoma with LS | 23 (3.7) | 18 (4.3) |
| Mixed | 107 (17.0) | 53 (12.7) |
| Location | | |
| Upper | 38 (6.1) | 23 (5.5) |
| Mid | 294 (46.8) | 206 (49.4) |
| Lower | 281 (44.7) | 185 (44.4) |
| Unclassified | 15 (2.4) | 3 (0.7) |
| Gross type | | |
| EGC I | 13 (2.1) | 10 (2.4) |
| EGC IIa | 49 (7.8) | 45 (10.8) |
| EGC IIb | 138 (22.0) | 126 (30.2) |
| EGC IIc | 152 (24.2) | 137 (32.9) |
| EGC III | 9 (1.4) | 8 (1.9) |
| Borrmann type 1 | 11 (1.8) | 6 (1.4) |
| Borrmann type 2 | 58 (9.2) | 22 (5.3) |
| Borrmann type 3 | 137 (21.8) | 39 (9.4) |
| Borrmann type 4 | 28 (4.5) | 7 (1.7) |
| Unclassified | 33 (5.3) | 17 (4.1) |
| T stage | | |
| 1 | 366 (58.3) | 331 (79.4) |
| 2 | 61 (9.7) | 33 (7.9) |
| 3 | 121 (19.3) | 44 (10.6) |
| 4 | 80 (12.7) | 9 (2.2) |
| Lymphatic invasion | | |
| Absent | 413 (65.8) | 364 (87.3) |
| Mild | 112 (17.8) | 35 (8.4) |
| Marked | 103 (16.4) | 18 (4.3) |
| Venous invasion | | |
| Absent | 571 (90.9) | 403 (96.6) |
| Mild | 55 (8.8) | 14 (3.4) |
| Marked | 2 (0.3) | 0 (0) |
| Perineural invasion | | |
| Absent | 483 (76.9) | 385 (92.3) |
| Mild | 89 (14.2) | 17 (4.1) |
| Marked | 56 (8.9) | 15 (3.6) |
| Tumor size (cm) | | |
| Mean | 4.4 | 3.4 |

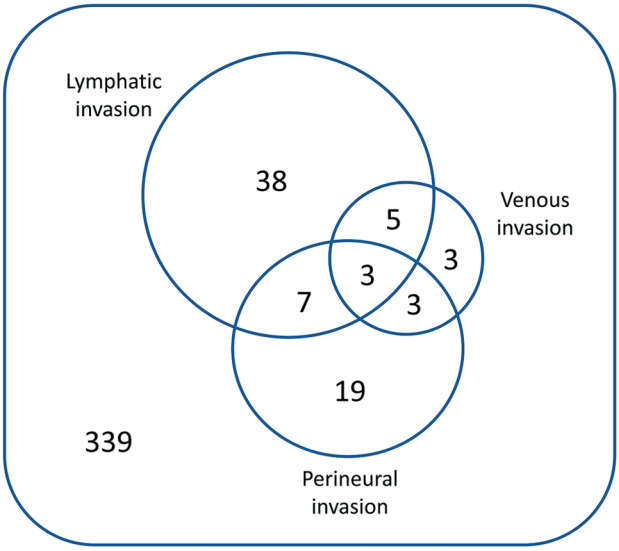


Figure 1. *Venn diagram showing the distribution of lymphatic, venous, and perineural invasion in 417 N0 gastric cancers. Seventy-eight (18.7%) cases showed one or more invasion features, but only three (0.7%) cases showed lymphatic, venous, and perineural invasion.*

N0 gastric cancer patients, the significance of PNI remains unclear. In particular, patients with concurrent PNI and LVI had poorer survival than those with neither or only one of those factors, suggesting that PNI should be analyzed together with LI and VI (22).

Therefore, in this study we examined in detail the prognostic value of LI, VI, and PNI in N0 gastric cancer patients by comparing their relapse-free survival with that of N1 stage patients. In addition, by presenting the clinicopathologic features related to the occurrence of LI, VI, and PNI, we intend to increase the detection rate of LI, VI, and PNI in pathologic examinations.

## Patients and Methods

*Patients and gastric cancer specimens.* This study was approved by the regional Institutional Review Board of Kangbuk Samsung Hospital (approval no. 2020-11-033; Seoul, South Korea). We initially enrolled 673 patients who underwent gastrectomy to treat gastric cancer at Kangbuk Samsung Hospital between January 2011 and December 2014. Among them, 45 cases were excluded due to an insufficient number of dissected lymph nodes, leaving 628 cases to be included in this study. Clinical data, including each patient's age, sex, and follow-up findings, were obtained from the electronic medical records. Disease relapse was defined as cases with local recurrence or distant metastases during the follow-up period after the surgery.

*Gross examination and microscopic review of gastrectomy specimens.* The gastrectomy specimens were fixed in a 10% neutrally buffered formalin solution overnight after opening the lumen. Gross characteristics, including tumor location, tumor size, and gross type, were recorded. Representative tumor sections and all dissected perigastric lymph nodes were embedded in paraffin blocks. In cases of early gastric cancer (EGC), tumor mapping was performed to accurately determine the boundary and extent of the tumor. Two pathologists independently reviewed all glass slides and recorded microscopic features, including histologic type using the WHO (23) and Lauren classifications, pT and pN stages according to the 2018 AJCC Tumor Node Metastasis staging system (24), and LI, VI, and PNI. LI, VI and PNI were classified as mild (1 or 2 foci)

Table II. *Correlation between clinicopathologic features and lymphatic, venous, and perineural invasion in N0 gastric cancer cases.*

| | Lymphatic invasion | | | Venous invasion | | | Perineural invasion | | |
|---|---|---|---|---|---|---|---|---|---|
| | Absent | Present | p-Value | Absent | Present | p-Value | Absent | Present | p-Value |
| Age | | | | | | | | | |
| Older than 45 | 54 (14.8) | 5 (9.4) | 0.399 | 59 (14.6) | 0 (0.0) | 0.235 | 50 (13.0) | 9 (28.1) | 0.031 |
| Younger than 45 | 310 (85.2) | 48 (90.6) | | 344 (85.4) | 14 (100.0) | | 335 (87.0) | 23 (71.9) | |
| Gender | | | | | | | | | |
| Male | 249 (68.4) | 37 (69.8) | 0.876 | 274 (68.0) | 12 (85.7) | 0.242 | 267 (69.4) | 19 (59.4) | 0.241 |
| Female | 115 (31.6) | 16 (30.2) | | 129 (32.0) | 2 (14.3) | | 118 (30.6) | 13 (40.6) | |
| WHO classification | | | | | | | | | |
| Tubular | 178 (48.9) | 32 (60.4) | 0.046 | 204 (50.6) | 6 (42.9) | 0.200 | 202 (52.5) | 8 (25.0) | 0.009 |
| Poorly cohesive | 122 (33.5) | 11 (20.8) | | 127 (31.5) | 6 (42.9) | | 117 (30.4) | 16 (50.0) | |
| Mucinous | 2 (0.5) | 1 (1.9) | | 3 (0.7) | 0 (0.0) | | 3 (0.8) | 0 (0.0) | |
| GCLS | 13 (3.6) | 5 (9.4) | | 16 (4.0) | 2 (14.3) | | 14 (3.6) | 4 (12.5) | |
| Mixed | 49 (13.5) | 4 (7.5) | | 53 (13.2) | 0 (0.0) | | 49 (12.7) | 4 (12.5) | |
| Signet ring cell component | | | | | | | | | |
| Absent | 185 (50.8) | 40 (75.5) | 0.001 | 215 (53.3) | 10 (71.4) | 0.275 | 209 (54.3) | 16 (50.0) | 0.713 |
| Present | 179 (49.2) | 13 (24.5) | | 188 (46.7) | 4 (28.6) | | 176 (45.7) | 16 (50.0) | |
| Lauren classification | | | | | | | | | |
| Intestinal | 172 (47.3) | 30 (56.6) | 0.368 | 196 (48.6) | 6 (42.9) | 0.884 | 195 (50.6) | 7 (21.9) | 0.007 |
| Diffuse | 138 (37.9) | 15 (28.3) | | 147 (36.5) | 6 (42.9) | | 136 (35.3) | 17 (53.1) | |
| Mixed | 54 (14.8) | 8 (15.1) | | 60 (14.9) | 2 (14.3) | | 54 (14.0) | 8 (25.0) | |
| Location | | | | | | | | | |
| Upper | 20 (5.5) | 3 (5.7) | 0.881 | 21 (5.2) | 2 (15.4) | 0.228 | 22 (5.7) | 1 (3.3) | 0.071 |
| Mid | 178 (49.3) | 28 (52.8) | | 199 (49.6) | 7 (53.8) | | 185 (48.2) | 21 (70.0) | |
| Lower | 163 (45.2) | 22 (41.5) | | 181 (45.1) | 4 (30.8) | | 177 (46.1) | 8 (26.7) | |
| T stage | | | | | | | | | |
| 1 & 2 | 330 (90.7) | 34 (64.2) | <0.001 | 358 (88.8) | 6 (42.9) | <0.001 | 357 (92.7) | 7 (21.9) | <0.001 |
| 3 &4 | 34 (9.3) | 19 (35.8) | | 45 (11.2) | 8 (57.1) | | 28 (7.3) | 25 (78.1) | |
| Tumor size (cm) | | | | | | | | | |
| Mean | 3.3 | 3.9 | 0.077 | 3.2 | 6.5 | 0.060 | 3.1 | 6.0 | 0.002 |

or marked (3 or more foci) according to the number of foci observed on one representative tumor section (25). If the two pathologists disagreed, another pathologist was invited to review the slides to achieve diagnostic consensus.

*Statistical analysis*. Data were analyzed using PASW Statistics 18 (SPSS Inc., Chicago, IL, USA) software. Crosstabs, Pearson's chi-square test, and Fisher's exact test were used as needed. For the survival analysis, a Kaplan-Meier survival analysis and Cox regression test were used. Differences were regarded as statistically significant at $p<0.05$.

## Results

The clinicopathologic features of all patients and the N0 patients are presented in Table I. Among all 628 gastric cancer patients, 417 cases (66.4%) were N0, of which 331 were EGC (79.4%) and 86 were advanced gastric cancer (AGC) cases (20.6%). Of the 417 N0 patients, 74 (17.7%), 342 (82.0%), and 1 (0.2%) were treated using total, subtotal, and partial gastrectomy, respectively. At the time of surgery, the patients' median age was 60.0 years (range=29-91 years). During 59.6 months of post-operative follow-up, local recurrence and distant metastasis occurred in 6 (1.4 %) and 6 (1.4 %) patients, respectively, and 10 patients (2.4 %) died from gastric cancer. Among the N0 gastric cancer cases, LI, VI, and PNI were detected in 53 (12.7%), 14 (3.4%), and 32 (7.7%) patients, respectively, and there was no case with marked VI (Table I). Fifteen (3.6%) cases showed two of the three factors (LI, VI, PNI), and only three (0.7%) cases had all of them (Figure 1).

When examining the correlation between the frequency of LI, VI, and PNI and pathologic features, LI, VI, and PNI were all more frequent at higher T stages than at lower stages (Table II). By histologic tumor type, LI was frequent in the tubular subtype ($p=0.046$) and in tumors without a signet ring cell component ($p=0.001$), and PNI was frequent in poorly cohesive carcinoma ($p=0.009$) and diffuse and mixed types of Lauren classification ($p=0.007$), but VI did not show an association with any histologic classification. In addition, PNI was found more often in young patients ($p=0.031$) and in large tumors ($p=0.002$) (Table II).

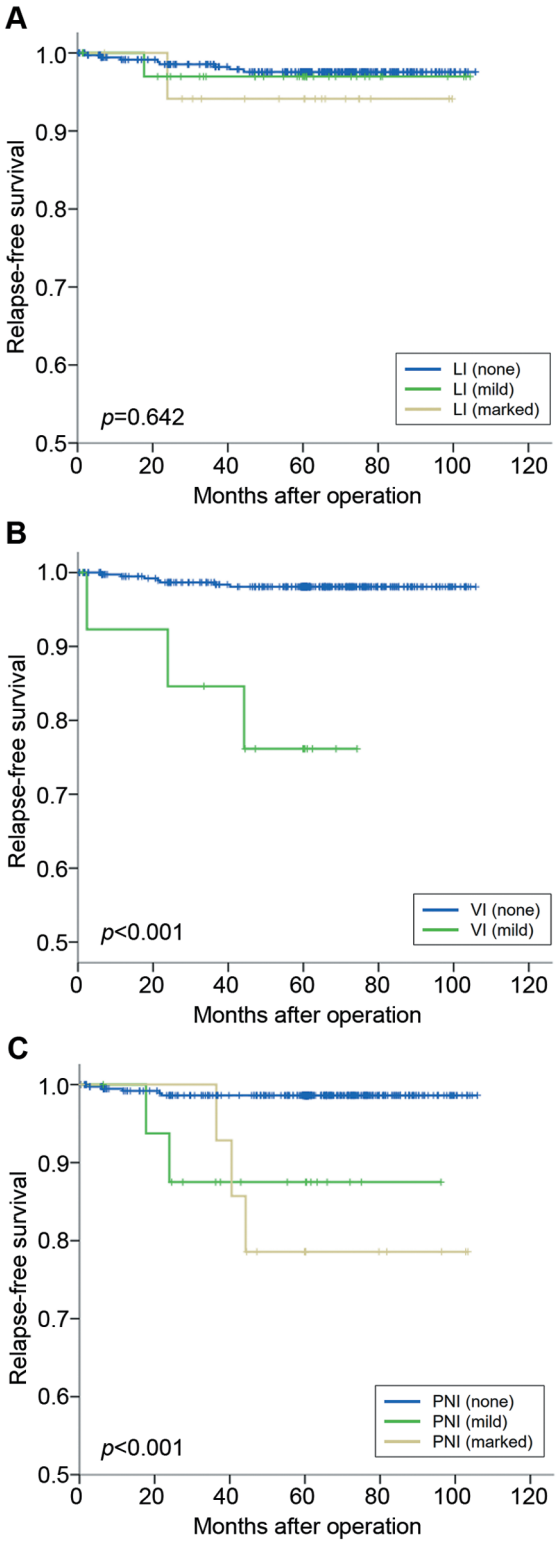


Figure 2. *Comparison of relapse-free survival according to lymphatic (A), venous (B), and perineural (C) invasion using semi-quantitative classification. Although lymphatic invasion did not show statistical significance (A), venous invasion (B) and perineural invasion (C) were associated with a marked decrease in the relapse-free survival rate.*

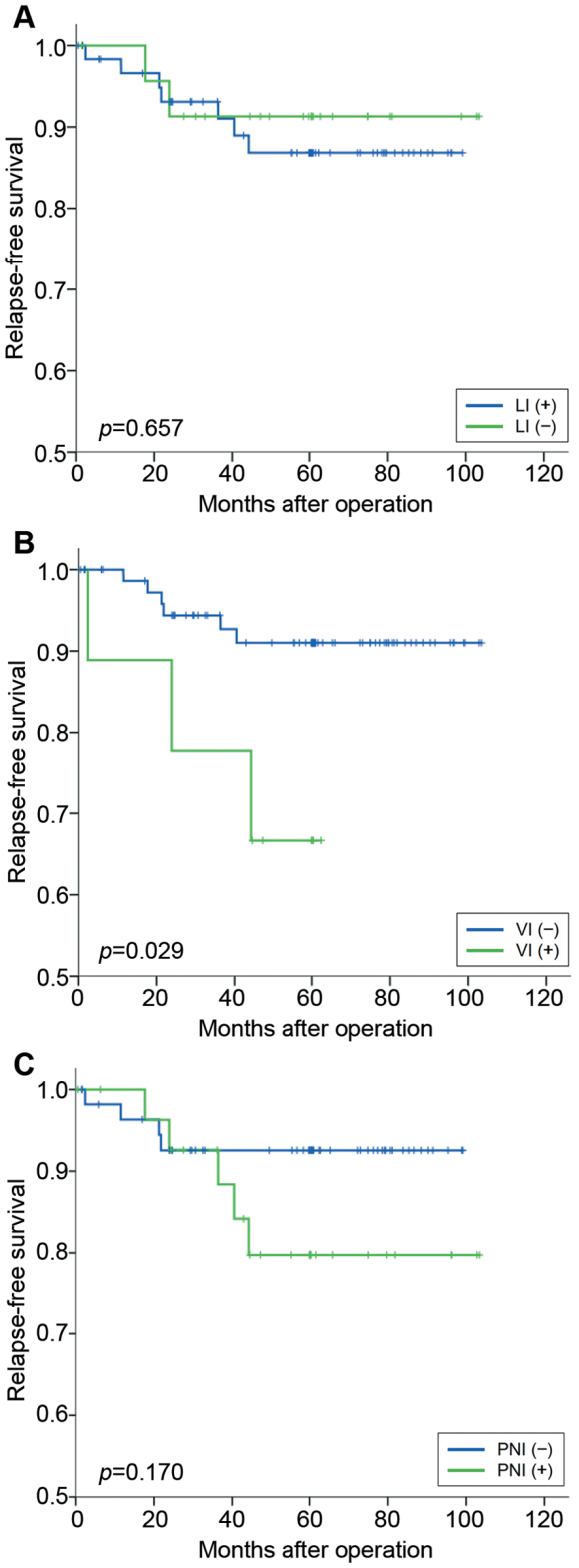


Figure 3. *Comparison of relapse-free survival according to lymphatic (A), venous (B), and perineural (C) invasion in advanced gastric cancers. Only venous invasion correlated significantly with relapse-free survival in advanced gastric cancer cases (B).*

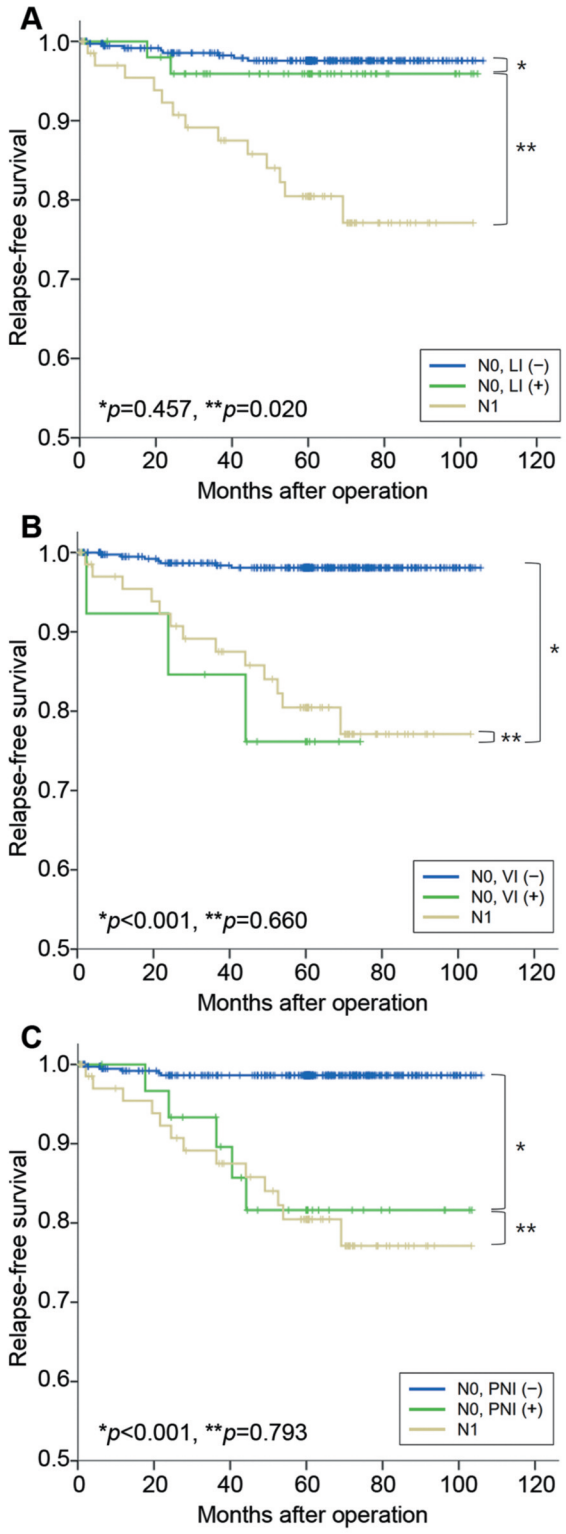


Figure 4. *Comparison of relapse-free survival between cases with lymphatic (A), venous (B), or perineural (C) invasion and N1 cases. The N0/LI(+) survival graph did not differ significantly from that of the N0/LI(–) group (A). However, the survival graphs of the N0/VI(+) and N0/PNI(+) groups showed survival decreases similar to those in the N1 graph (B and C).*

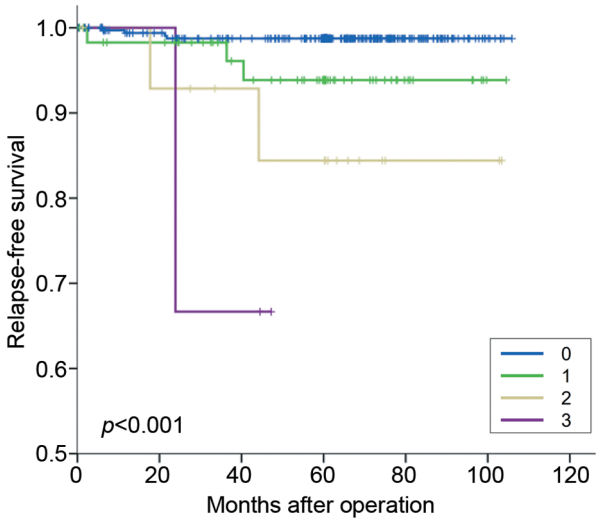


Figure 5. *Comparison of relapse-free survival curves according to the number of invasive factors (lymphatic, venous, and perineural invasion). As the number of invasive features increased, relapse-free survival decreased in a stepwise manner.*

In the survival analysis, VI ($p<0.001$) and PNI ($p<0.001$) were significant factors for relapse-free survival in N0 patients, but LI was not (Figure 2). In the survival analysis, PNI differed quantitatively between mild and marked, but VI showed only two Kaplan-Meier curves of absence and mild because we had no marked VI cases among our N0 gastric cancer patients. When we performed the survival analysis by dividing patients into EGC and AGC, no survival analysis of N0 EGC patients was possible because none of the N0 EGC patients experienced disease relapse or cancer-related death. In the analysis of N0 AGC patients, VI was the only significant factor affecting relapse-free survival (Figure 3). The survival graphs of the N0/VI(+) and N0/PNI(+) patients were similar to those of the N1 stage patients (Figure 4B and C). However, the survival graph of the N0/LI(+) patients did not differ from that of the N0/LI(–) group (Figure 4A). When we analyzed survival according to the number of invasion features (LI, VI, PNI), the relapse-free survival rate decreased in a stepwise manner as the number of invasion features increased (Figure 5). On the Cox regression analysis, VI (HR=13.50, $p<0.001$), PNI (HR=12.50, $p<0.001$), and the pT stage (HR=29.99, $p<0.001$), were significant factors affecting relapse-free survival in the univariate analysis, but only pT stage (HR=21.43, $p=0.001$) remained a significant factor in the multivariate analysis (Table III).

## Discussion

In this study, VI and PNI were significant prognostic factors for relapse-free survival in N0 gastric cancer patients, but LI was not. Furthermore, N0 gastric cancer cases with VI or

Table III. *Cox regression analysis for relapse-free survival in N0 gastric cancer patients.*

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95%CI) | *p*-Value | HR (95%CI) | *p*-Value |
| pT stage (1 and 2 *vs.* 3 and 4) | 29.99 (6.36-141.30) | <0.001 | 21.43 (3.63-126.37) | 0.001 |
| Histologic type (tubular *vs.* poorly cohesive and mixed) | 1.042 (0.302-3.60) | 0.948 | | |
| Lymphatic invasion (absent *vs.* present) | 1.79 (0.38-8.41) | 0.464 | | |
| Venous invasion (absent *vs.* present) | 13.50 (3.49-52.23) | <0.001 | 2.94 (0.65-13.37) | 0.163 |
| Perineural invasion (absent *vs.* present) | 12.50 (3.62-542.22) | <0.001 | 1.19 (0.26-5.42) | 0.823 |

PNI had survival curves similar to those of N1 gastric cancer cases, suggesting that VI and PNI could be used as upstaging factors in N0 gastric cancer. In addition, as the number of invasive features (LI, VI, PNI) increased, the relapse-free survival rate decreased. Therefore, LI, VI, and PNI need to be evaluated and recorded separately on pathologic examinations, especially in N0 gastric cancer.

Although a few previous studies have examined the role of LI or LVI as a prognostic factor in N0 gastric cancer, studies about the prognostic value of VI in N0 gastric cancer have been rare (7, 9, 10, 12-14, 16, 26-29). A Japanese study reported that moderate or marked VI was associated with poor relapse-free and overall survival, but that analysis was only in pT2N0 patients without a comparative analysis with N1 stage patients (16). Another Korean study showed the prognostic significance of VI in N0 gastric cancer, but its significance was valid only in EGC, contrary to our result that VI was significant only in AGC cases (7). The difference between those results is assumed to be due to the low detection rate of VI, which was identified in only 2.4% and 3.4% of N0 cases in the previous Korean study and this study, respectively (7). In our study, 78.6% of VI were accompanied by at least one of LI or PNI, but in the case of LI, 71.7% of cases only had LI, suggesting that VI is a later event than LI. However, this result is limited because this study included a small number of VI positive cases. Therefore, multicenter studies with a larger number of N0 gastric cancers will be needed to use VI as a prognostic factor.

Quantitative measurement of LI or VI has been performed in a few previous studies (16, 25). In the previous Korean study by Park et al., the cut-off value for the number of LVI to predict lymph node metastasis was 1.5, and they proposed dividing by L0 (none), L1 (1-2), and L2 (more than 2), similar to the pN stage used by AJCC (24, 25). Similarly, Araki et al. divided LI and VI into scores from 0 to 3 according to number of foci on the slide (16). In our study, we subclassified LI, VI, and PNI as none, mild (1 or 2), and marked (3 or more) according to the number of foci observed on a representative slide, which is similar to previously reported methods (16, 25). However, this semi-quantitative method also had the limitation that the difference between mild and marked VI could not be analyzed due to the absence of marked VI cases in N0 patients. Therefore, a specific measurement criterion for VI, different from those for LI and PNI, is required.

Several studies previously reported that PNI was a factor indicating a poor prognosis, with frequent recurrence and low efficacy of adjuvant chemotherapy, in gastric cancer (17-21, 30), but little has been reported specifically about N0 gastric cancer cases. Our results show both that PNI was an important prognostic factor and that N0 cases with PNI had prognoses similar to N1 cases. PNI was previously reported to correlate with a worse survival outcome when it appeared simultaneously with LVI (22). In our results, the relapse-free survival rate decreased as the number of invasive features (LI, VI, PNI) increased (Figure 4). Therefore, pathology reports should note the existence of LI, VI, and PNI separately, inducing clinicians to consider active surveillance or adjuvant chemotherapy in patients with a large number of these invasive features, as they do for node-positive gastric cancers. A prospective, randomized, phase III study of adjuvant chemotherapy after curative resection in patients with pathologic stage IB (by AJCC 6th) gastric cancer and at least one additional risk factor (such as the presence of LVI or PNI) is ongoing to compare the efficacy of capecitabine for 6 months to observation alone (NCT01917552).

Another notable point in our study is that the histological subtypes of tumors in which these invasive features were frequently found differed. LI and PNI were frequently identified in the tubular subtype and the poorly cohesive or mixed histology, respectively, suggesting that the sites that tumor cells can easily invade differ depending on the characteristics of the tumor cells, such as cohesiveness. In the case of VI, the detection rate did not differ according to the histologic subtypes in this study, but the frequency of VI was less than that of LI or PNI, so further research is needed with more N0 gastric cancer cases.

This study has a few limitations. First, we included surgically resected gastric cancer specimens from a single institution. Therefore, the prognostic significance of LI, VI,

and PNI obtained in this study should not be applied to endoscopic resection cases. To confirm the prognostic value of VI and PNI, a multicenter study that includes more gastric cases, including endoscopic resection cases, is needed. Second, we reviewed hematoxylin-eosin slides routinely stained for pathologic diagnosis without conducting ancillary tests such as immunohistochemical staining. However, we overcame this disadvantage by having two skillful pathologists meticulously examine all slides and obtaining a third opinion if necessary. Also, given that immunostaining cannot be performed for each case in routine pathology diagnosis, our study design using only routine hematoxylin-eosin slides could be deemed a strength of this study.

In conclusion, VI and PNI were both upstaging and significant prognostic factors in N0 gastric cancer cases, and the number of invasive features (LI, VI, PNI) was also an important factor in relapse-free survival. Therefore, pathologists should evaluate and record LI, VI, and PNI separately in pathology reports, especially in N0 gastric cancer cases, and clinicians should consider active surveillance or adjuvant chemotherapy for N0 gastric cancer depending on the type and number of these invasive features.

## Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

## Authors' Contributions

BS and KK conceived and designed this study. KS, BS, KK and ID participated in pathology review. DHK, BHS and CHY reviewed medical records. KS, BS and HWL analyzed and interpreted the results and prepared the manuscripts. BS, DHK and KK oversaw the entire project and KK approved the final draft submitted. All Authors read and approved the final manuscript.

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