Reevaluating Significance of Perineural Invasion in Gastric Cancer Based on Double Immunohistochemical Staining

Zhi-Hua Zhou, MD; Gui-Fang Xu, MD, PhD; Wei-Jie Zhang, MD; Hai-Bin Zhao, MD; Yao-Yi Wu, MD

**Context.**—In gastric cancer, the significance of perineural invasion remains controversial. Detecting perineural invasion with hematoxylin-eosin staining often leads to misdiagnosis. Labeling nerves by immunohistochemistry greatly assists perineural invasion detection, but it might also be misdiagnosed, because scattered cancer cells are difficult to recognize.

**Objective.**—To reevaluate the significance of perineural invasion in gastric cancer by double immunohistochemical staining that labels both nerves and cancer cells, and to examine agreements on perineural invasion detection between double immunohistochemical staining and single immunochemical staining (to label nerves) or hematoxylin-eosin staining.

**Design.**—We evaluated perineural invasion in 160 cases of gastric cancer with double immunohistochemical staining, single immunochemical staining, and hematoxylin-eosin staining, respectively; then we investigated the prognostic significance of perineural invasion.

**Results.**—Perineural invasion was detected in 65.0% (104 of 160), 38.1% (61 of 160), and 56.9% (91 of 160) of cases with double immunohistochemical staining, hematoxylin-eosin staining, and single immunohistochemical staining, respectively. Agreement was low between double staining and hematoxylin-eosin staining ($\kappa = .34$), and most false reports occurred in diffuse gastric cancer. Agreement between single immunochemical staining and double staining was good ($\kappa = .67$), but it declined in diffuse gastric cancer ($\kappa = .28$). Perineural invasion was closely associated with other clinicopathologic variables. Although perineural invasion–positive patients had a worse outcome than perineural invasion–negative patients, it was not an independent prognostic factor ($P = .11$; hazard ratio, 0.637; 95% confidence interval, 0.366–1.110).

**Conclusions.**—Double immunohistochemical staining could improve accuracy of perineural invasion detection in gastric cancer, particularly in the diffuse type. Moreover, perineural invasion predicts a poor outcome in gastric cancer, but it cannot provide more information than traditional clinicopathologic variables.

_Gastric cancer is the fourth most common malignancy, and for the year 2008, globally 990,000 new cases were diagnosed._ Although the incidence of gastric cancer has declined in recent decades, it remains the second leading cause of cancer-related death worldwide, with an overall 5-year survival rate of approximately 25%. Radical surgery is currently the main therapy method for gastric cancer, and adjuvant chemotherapy can improve overall survival. So it is crucial to select patients who would potentially benefit from aggressive chemotherapy after surgery. Traditional clinicopathologic variables such as depth of tumor invasion and lymph node metastasis have significant prognostic value and are regarded as determinants for patient selection for adjuvant therapy, but for more accurate prognosis and patient selection, new clinicopathologic factors need to be identified.

Perineural invasion (PNI) is a pathologic feature defined as tumor cell infiltration in, around, and through the nerves. Increasing evidence indicates that PNI could reflect a high invasive capability of cancer cells, and its prognostic significance has been remarked in head and neck cancer, prostate cancer, pancreatic cancer, and colorectal cancer. In gastric cancer, although most previous studies suggest PNI corresponds to cancer progression, whether PNI could provide more information than traditional clinicopathologic variables and serve as an independent prognostic factor remains controversial.

Determining PNI is tedious and difficult, and in this process, nerves and cancer cells should be recognized correctly. In tissue sections stained by hematoxylin-eosin (H&E), a considerable proportion of cases with PNI can be identified by pathologists. Because nerves may be obscure in H&E-stained slides, previous studies have immunohistochemically stained nerves by labeling S-100 or laminin to assist the detection of PNI. Despite enhanced visualization of...
nerves, determining PNI remains a difficult task, because invading cancer cells are especially difficult to recognize when they are small and scattered, morphologically resembling inflammatory cells. Therefore, to detect PNI precisely and rapidly, it is necessary to label both nerves and cancer cells in the same slides. In this study, for the purpose of reevaluating the significance of PNI in gastric cancer, we doubly labeled nerves and cancer cells to enhance diagnostic accuracy of PNI.

**MATERIALS AND METHODS**

**Patients and Database**

A total of 160 patients with gastric cancer underwent surgical resection in our hospital between January 2001 and December 2006. Specimens and data were obtained with institutional review board approval, and all patients gave written informed consent for the use of these materials. All surgical specimens were confirmed R0 resection histologically, and patients with remote metastasis (M1) or those who had received chemotherapy before operation were excluded from our study. Clinical data including sex, age, tumor location, tumor size, differentiation, Lauren classification, invasion depth of tumor, lymph node metastasis, and clinical stage were reviewed. Lauren classification of gastric cancer was determined as below: if cancer cells formed glandular structure, the case was classified as intestinal type; if cancer cells were diffuse and did not form glandular structure, the case was classified as diffuse type.\(^1\) Clinical staging was determined according to the 2010 7th edition of the American Joint Commission on Cancer TNM staging system.\(^2\) All patients were followed by telephone, mail, or outpatient service. The duration of follow-up was the interval between surgical resection date and the last contact (death or last follow-up).

**Immunohistochemistry**

Archival tumor tissue blocks were serially cut in 3-μm sections for H&E staining, single S100 staining, and double staining, respectively. For each of the 160 cases, 2 representative tissue blocks that included whole gastric wall and comprised widespread cancer invasion were selected in this study, and tissue blocks with extensive necrosis and hemorrhage were excluded. Immunohistochemical double staining was performed to label nerves and cancer cells. S100 antibody was used to stain nerves specifically, and AE1/AE3 antibody. Using H&E staining, we observed PNI in 61 cases (38.1%), and many PNI lesions could be easily identified with this staining method (Figure 1, A), as well as immunohistochemical staining (Figure 1, B and C). With single S-100 staining, we found that the positive rate of PNI was 56.9% (91 of 160). Many PNI lesions were difficult to recognize in H&E-stained slides (Figure 2, A), but they could be clearly displayed by single S-100 staining (Figure 2, B) or double immunohistochemical staining (Figure 2, C). Based on double immunohistochemical staining, PNI was determined in 104 cases (65.0%), and we found some PNI lesions were omitted when assessing PNI with H&E staining (Figure 3, A and single S-100 staining (Figure 3, B). In addition, nerves and cancer cells were in sharp contrast to the background in double-stained sections (Figure 3, C), and detecting PNI in these sections was easier and faster than in single S-100-stained or H&E-stained sections (1 minute versus 3–5 minutes, average time for PNI determination in each section).

Compared with the double-stained sections, there were 50 false-negative cases and 7 false-positive cases when reviewing H&E-stained sections, whereas 19 false-negative cases and 6 false-positive cases were found when surveying single S100–stained sections (Table 1). We found that PNI status determined in double-stained sections was significantly different from that based on H&E-stained sections (McNemar test \(P < .001, \kappa = .34\)). Single S100 staining was consistent with double staining in PNI determination (\(\kappa = .67\)), but we found all the 25 misdiagnosed cases (19 false-negative cases and 6 false-positive cases) in single S100 staining were diffuse gastric cancer, and in this gastric cancer type (our cohort contained 79 cases of diffuse gastric cancer), there was low consistency between single S100 staining and double staining (\(\kappa = .28\)).

To investigate factors attributing to misdiagnosis of PNI in H&E-stained and single S100–stained sections, these sections were reviewed in detail. In H&E-stained sections, we found 2 factors associated with missed diagnosis of PNI: (1) nerves were obscure, for example, nerves could be

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**Results**

The correlation between PNI positivity and other clinicopathologic variables was carried out using the \(\chi^2\) test and the Fisher exact test. The influence of PNI on overall survival rate was evaluated using the Kaplan-Meier method and the log-rank test. Cox proportional hazard regression analysis was used to assess the prognostic significance of PNI and other clinicopathologic variables, and hazard ratios (HRs) were calculated including 95% confidence intervals (CIs). To compare the results determined based on different staining methods, paired McNemar tests were performed, and \(\kappa\) values were calculated to reflect the agreement between 2 staining methods. Results were considered significant at \(P < .05\).

**RESULTS**

**Double Immunohistochemical Staining Was Superior to H&E Staining or Single S100 Staining in PNI Evaluation**

To evaluate the influence of staining methods on PNI determination, we detected PNI with 3 different staining methods, including H&E staining, single S-100 staining (to label nerves by immunohistochemistry), and double immunohistochemical staining (to label nerves and cancer cells by S-100 and AE1/AE3 antibody). Using H&E staining, we observed PNI in 61 cases (38.1%), and many PNI lesions could be easily identified with this staining method (Figure 1, A), as well as immunohistochemical staining (Figure 1, B and C). With single S-100 staining, we found that the positive rate of PNI was 56.9% (91 of 160). Many PNI lesions were difficult to recognize in H&E-stained slides (Figure 2, A), but they could be clearly displayed by single S-100 staining (Figure 2, B) or double immunohistochemical staining (Figure 2, C). Based on double immunohistochemical staining, PNI was determined in 104 cases (65.0%), and we found some PNI lesions were omitted when assessing PNI with H&E staining (Figure 3, A and single S-100 staining (Figure 3, B). In addition, nerves and cancer cells were in sharp contrast to the background in double-stained sections (Figure 3, C), and detecting PNI in these sections was easier and faster than in single S-100-stained or H&E-stained sections (1 minute versus 3–5 minutes, average time for PNI determination in each section).

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**Evaluation of PNI**

According to previous reports, PNI was determined as positive when cancer cells infiltrated into the perineurium or neural fasciculus intramurally. To investigate impacts of different staining methods on PNI evaluation, 3 pathologists evaluated PNI based on H&E-stained sections, single S100–stained sections, and double-stained sections (both nerves and cancer cells were labeled), respectively. During the process of evaluation, they were unaware of the results determined with other staining methods. To avoid variations among different observers, before review of the slides, 3 pathologists studied and discussed the criteria for PNI diagnosis, and they together reviewed typical slides that were PNI positive or PNI negative so that they reached agreement in PNI determination.

**Statistics**

The correlation between PNI positivity and other clinicopathologic variables was carried out using the \(\chi^2\) test and the Fisher exact test. The influence of PNI on overall survival rate was evaluated using the Kaplan-Meier method and the log-rank test. Cox proportional hazard regression analysis was used to assess the prognostic significance of PNI and other clinicopathologic variables, and hazard ratios (HRs) were calculated including 95% confidence intervals (CIs). To compare the results determined based on different staining methods, paired McNemar tests were performed, and \(\kappa\) values were calculated to reflect the agreement between 2 staining methods. Results were considered significant at \(P < .05\).
severely damaged by invading cancer cells, or they might be
concealed in mucus pools produced by cancer cells (Figure
2, A). This caused 31 false-negative cases: (2) In diffuse
gastric cancer, cancer cells were small and scattered, making
them difficult to recognize (Figure 3, A). In some
circumstances, small diffuse cancer cells had a high nucleus
to plasma ratio, resembling lymphocytes or plasma cells
morphologically. This caused 19 false-negative cases in
H&E-stained sections. When nerves were labeled in single
S100–stained sections, the first factor influencing PNI
determination was eliminated. However, the second factor
leading to misdiagnosis still existed, and we also found there
were 19 false-negative cases in single S100–stained sections.
In addition, there were 7 and 6 false-positive cases in H&E-
stained and single S100–stained sections, respectively. The
false-positive cases were all diffuse gastric cancer, and the
likeness between cancer cells and inflammatory cells
remained the leading cause of misdiagnosis; inflammatory
cells, especially plasma cells, were regarded as small cancer
cells in diffuse gastric cancer.

Correlation Between PNI and Clinicopathologic Variables

Clinicopathologic variables of 160 patients with gastric
cancer are listed in Table 2. In our cohort, 118 patients were
men and 42 patients were women. The median age was 61
years, with ages ranging from 20 to 81 years. According to
depth of tumor invasion, most cases (146 of 160) were
advanced gastric cancer (T2–T4 stage), and 14 cases were in
early stage (T1 stage). The majority of the patients (104 of
160) had lymph node metastasis; of these cases, 68 were
classified as pN1, 29 as pN2, and 7 as pN3. No patients had
distant metastasis. The median follow-up time was 43
months (range, 3–120 months).

In this study, we observed PNI in 104 cases (65.0%) with
double immunohistochemical staining. Perineural invasion
positivity was closely associated with tumor size, differen-
tiation, Lauren classification, depth of tumor invasion,
lymph node metastasis, clinical stage, and tumor recurrence.
In contrast, there was no significant relationship between
PNI positivity and sex, age, or tumor location. The incidence
of PNI was significantly increased in tumors with large size
( \( P = .03 \) ) or poorly differentiated histology ( \( P < .001 \) ). When
gastric cancer was divided into the intestinal type and the
diffuse type according to Lauren classification, we found
PNI ratio was higher in the diffuse type (61 of 79; 77.2%) than
in the intestinal type (43 of 81; 53.1%; \( P < .001 \)). Compared with PNI-negative tumors, PNI-positive tumors
exhibited deeper mural invasion ( \( P < .001 \) ), increased lymph
node metastasis ( \( P < .001 \) ), and worse clinical stage ( \( P < .001 \)). In addition, PNI was also markedly correlated with
tumor recurrence, which occurred in 61.5% (64 of 104) of
PNI-positive patients and in 39.3% (22 of 56) of PNI-
negative patients ( \( P = .01 \)).

Because PNI was defined as cancer cells infiltrated into the
perineurium or neural fasciculus intramurally, it could be
classified into 2 subgroups: extramural PNI group (cancer
cells infiltrated only into the perineurium; the neural
fasciculus was intact) and intramural PNI group (cancer
cells penetrated perineurium and neural fasciculus was
invaded). Of 104 PNI-positive cases in our study, 57 cases
were only extramural PNI and 47 cases contained intramural
PNI (31 were only intramural PNI, and 16 contained both

Figure 1. Determining perineural invasion (PNI) with hematoxylin-eosin (H&E) staining. A, In H&E-stained sections, a considerable proportion of
PNI lesions could be identified. B, With single S-100 staining, the nerve was labeled (brown), and PNI could be diagnosed easily. C, Based on double
immunochemical staining, both the nerve (dark blue) and cancer cells (red) were clearly displayed, and PNI was evident (original magnifications
×400).

Figure 2. Determining perineural invasion (PNI) with single S-100 staining. A, Some PNI lesions might be overlooked based on hematoxylin-eosin
staining, because the nerve was severely damaged by cancer cells. Moreover, this nerve was concealed in a mucus pool, and detecting PNI was quite
difficult. B, With single S-100 staining, the damaged nerve was shown clearly (brown) and PNI could be identified. C, Double immunohistochemical
staining labeled the damaged nerve (dark blue) and invaded cancer cells (red), confirming the existence of PNI (original magnifications ×400).
intramural PNI and extramural PNI). For each of the clinicopathologic variables (sex, age, tumor size, tumor location, differentiation, Lauren classification, depth of tumor invasion, lymph node metastasis, clinical stage, and tumor recurrence), there was no significant difference between the extramural PNI group and the intramural PNI group ($P > .05$ for all).

The Prognostic Value of PNI in Gastric Cancer

We then assessed the prognostic value of PNI based on double immunohistochemical staining. As is shown in Figure 4, median survival was better in PNI-negative patients ($n = 56$), PNI-positive patients ($n = 104$) exhibited a significantly worse overall survival (log-rank test, $P = .001$).

Table 1. Paired Comparison to Assess the Influence of Different Staining Methods on Perineural Invasion Determination

<table>
<thead>
<tr>
<th>Double Staining</th>
<th>H&amp;E Staining</th>
<th>Single S100 Staining</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>- P</td>
<td>+ P</td>
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<tr>
<td>+</td>
<td>$.001$</td>
<td>$.34^a$</td>
</tr>
<tr>
<td>-</td>
<td>$.001$</td>
<td>$.67^b$</td>
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Abbreviation: H&E, hematoxylin-eosin.

*a P values are based on McNemar test; $\kappa$ values reflect degree of agreement between 2 groups.
survival rate was 35.6%; for patients with PNI-negative tumor, 5-year overall survival rate was 62.5%, and median survival time was 72 months (censored). We further found the 2 subgroups of PNI-positive patients (extramural and intramural PNI) had no significant difference in overall survival ($P = .76$, log-rank test). In addition, when PNI was determined with H&E or S100 staining, we also found PNI-positive patients had a poorer outcome ($P = .04$ for results from H&E staining; $P < .001$ for results from S100 staining; log-rank test).

To compare the prognostic significance of PNI with that of traditional clinicopathologic variables, a Cox multiple regression model was used. Based on the results from reviewing doubly stained sections, we found that age ($P = .009$; HR, 1.039; 95% CI, 1.016–1.063), lymph node metastasis ($P = .03$; HR, 1.414; 95% CI, 1.027–1.948), clinical stage ($P = .01$; HR, 1.653; 95% CI, 1.111–2.460), and recurrence ($P < .001$; HR, 5.033; 95% CI, 2.749–9.217) were independent prognostic factors to overall survival. Perineural invasion had a tendency to be an independent factor, but this finding did not reach statistical significance ($P = .11$; HR, 1.063; 95% CI, 0.366–3.110). Additionally, when PNI was determined using H&E staining, we found it was not an independent prognostic factor ($P = .50$; HR, 1.171; 95% CI, 0.737–1.860). When assessed with S100 staining, PNI seemed to be a high risk factor, but this finding was not statistically significant ($P = .13$; HR, 1.469; 95% CI, 0.896–2.409).

## Table 2. Association of Perineural Invasion (PNI) Status and Clinicopathologic Variables

<table>
<thead>
<tr>
<th>Factors</th>
<th>PNI Positive, No. (%)</th>
<th>PNI Negative, No. (%)</th>
<th>$P$</th>
</tr>
</thead>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>77 (48.1)</td>
<td>41 (25.6)</td>
<td>.91</td>
</tr>
<tr>
<td>Female</td>
<td>27 (16.9)</td>
<td>15 (9.4)</td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$&lt; 60$ y</td>
<td>52 (32.5)</td>
<td>26 (16.3)</td>
<td>.67</td>
</tr>
<tr>
<td>$\geq 60$ y</td>
<td>52 (32.5)</td>
<td>30 (18.7)</td>
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</tr>
<tr>
<td>Location</td>
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<tr>
<td>Upper</td>
<td>33 (20.6)</td>
<td>25 (15.6)</td>
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<tr>
<td>Middle</td>
<td>15 (9.4)</td>
<td>8 (5.0)</td>
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<tr>
<td>Lower</td>
<td>38 (23.8)</td>
<td>17 (10.6)</td>
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<tr>
<td>Tumor size, cm</td>
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<td></td>
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<tr>
<td>$\leq 3$</td>
<td>32 (20.0)</td>
<td>28 (17.5)</td>
<td>.03</td>
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<tr>
<td>$&lt; 6$</td>
<td>46 (28.8)</td>
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<td>$\geq 6$</td>
<td>26 (16.2)</td>
<td>7 (4.4)</td>
<td></td>
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<tr>
<td>Tumor differentiation</td>
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<td></td>
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<tr>
<td>Well differentiated</td>
<td>7 (4.4)</td>
<td>23 (14.4)</td>
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<tr>
<td>Moderately differentiated</td>
<td>36 (22.5)</td>
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<tr>
<td>Poorly differentiated</td>
<td>61 (38.1)</td>
<td>18 (11.2)</td>
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<td>Histologic type</td>
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<tr>
<td>Intestinal</td>
<td>43 (26.9)</td>
<td>38 (23.8)</td>
<td>.001</td>
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<tr>
<td>Diffuse</td>
<td>61 (38.1)</td>
<td>18 (11.2)</td>
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<td>pT stage</td>
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<tr>
<td>T1</td>
<td>1 (0.6)</td>
<td>13 (8.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>T2</td>
<td>12 (7.5)</td>
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<td>T4</td>
<td>54 (33.8)</td>
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<tr>
<td>pN stage</td>
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<tr>
<td>N0</td>
<td>22 (13.7)</td>
<td>34 (21.2)</td>
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<td>23 (14.4)</td>
<td>6 (3.8)</td>
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<tr>
<td>N3</td>
<td>6 (3.8)</td>
<td>1 (0.6)</td>
<td></td>
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<tr>
<td>Clinical stage</td>
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</tr>
<tr>
<td>I</td>
<td>7 (4.4)</td>
<td>26 (16.3)</td>
<td>&lt;.001</td>
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<tr>
<td>II</td>
<td>36 (22.5)</td>
<td>14 (8.8)</td>
<td></td>
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<tr>
<td>III</td>
<td>57 (35.6)</td>
<td>15 (9.4)</td>
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<tr>
<td>IV</td>
<td>4 (2.5)</td>
<td>1 (0.6)</td>
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<tr>
<td>Recurrence</td>
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<tr>
<td>Presence</td>
<td>64 (40.0)</td>
<td>22 (13.8)</td>
<td>.007</td>
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<tr>
<td>Absence</td>
<td>40 (25.0)</td>
<td>34 (21.2)</td>
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## COMMENT

To our knowledge, most studies, if not all, have evaluated PNI based on H&E-stained or nerve-labeled sections (by immunohistochemical staining). In H&E-stained sections, PNI might be underestimated. This is attributable in part to obscure nerve fibers, because many factors could make nerves obscure and difficult to recognize; for example, nerves could be severely damaged by invading cancer cells (Figure 2, A), or they might be concealed in mucus pools produced by cancer cells. Labeling nerves by immunohistochemical staining aids the identification of PNI. It has been reported that in head and neck squamous cell carcinoma, PNI was detected in 82% of cases when stained for S100, whereas only 30% of cases were determined PNI positive when stained by H&E.19 However, to identify PNI, invading cancer cells also need to be recognized. When cancer cells are small and diffuse, distinguishing them from inflammatory cells is a tough challenge. Cancer cells in diffuse gastric cancer are usually small with a high nucleus to plasma ratio, closely resembling lymphocytes in morphology (Figure 3), and this would lead to misdiagnosis of PNI. Therefore, for accurate PNI detection, it is necessary to label both nerves and cancer cells simultaneously to enhance their visualization.

In this study, we applied double immunohistochemical staining to label nerve fibers and cancer cells to determine PNI status in gastric cancer, and we found that 65.0% (104 of 160) of cases were PNI positive. Compared with double staining, we found 50 false-negative and 7 false-positive cases based on H&E-stained slides, and there were 19 false-negative and 6 false-positive cases with S100-stained slides. Perineural invasion status determined by double immunohistochemical staining differed significantly in comparison with that determined by H&E staining ($\kappa = .34$). Despite high consistency between single S100 staining and double staining in PNI detection for all cases ($\kappa = .67$), in diffuse gastric cancer, double staining was superior to single S100 staining ($\kappa = .28$). In addition, we observed that cancer cells and nerves were in strong contrast with the background, and PNI could be identified easily and quickly. Therefore, staining methods had profound influence on PNI determination of gastric cancer, and to evaluate PNI correctly, double staining should be suggested, especially in diffuse gastric cancer.

In previous studies, PNI in gastric cancer was consistently defined as cancer cells infiltrating into the perineurium or neural fasciculus intramurally. Our study also applied this definition. Although the standard of determining PNI has been consistent, different studies have had different results. Based on H&E staining, Duraker et al14 found that in advanced gastric cancer, 59.6% of cases were PNI positive, whereas Hilici et al15 reported a higher incidence: PNI was determined in 49.1% of advanced gastric cancers, whereas Tianhang et al 11 reported that the PNI rate was 37.1% in a cohort containing 1632 gastric cancer patients. In this study, we found PNI...
positivity in gastric cancer was 65.0%, similar to the results reported by Duraker et al. In our opinions, except for discrepancy in patient selection in previous studies, difference in staining methods may be an important cause for difference in PNI positivity in gastric cancer.

Accumulating evidence suggests that PNI was a valuable clinicopathologic indicator that was closely correlated with progression of malignant tumors. In head and neck cancer and colorectal cancer, PNI has been proposed to be a useful prognostic factor that could predict tumor recurrence and poor outcome independently, and the College of American Pathologists has determined that PNI status should be reported in pathologic analysis for head and neck cancer. Pathologists has determined that PNI status should be reported in pathologic analysis for head and neck cancer. However, in gastric cancer, there have been conflicting viewpoints about the prognostic value of PNI in gastric cancer, despite significant association between PNI and tumor progression. Some reports have demonstrated that PNI could not provide more prognostic information than classical clinicopathologic variables, but recently it has been suggested that PNI could serve as an independent prognostic factor. In this study, we found PNI was significantly correlated with many traditional pathologic variables, such as tumor size, differentiation, histologic type, lymph node metastasis, depth of invasion, and tumor recurrence. Although PNI-positive tumors had a lower 5-year overall survival rate than PNI-negative tumors, multivariate analysis indicated PNI was not an independent prognostic factor from traditional clinicopathologic variables. Therefore, PNI status is probably not a necessary component of pathologic reports for gastric cancer. Because our study was limited in case volume, samples from more patients should be harvested in further research.

In conclusion, the results of our study indicate that double immunohistochemical staining could improve accuracy of PNI detection in gastric cancer, especially for the diffuse type. Furthermore, PNI is closely associated with progression of gastric cancer, but it is not an independent prognostic factor of gastric cancer.

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References


