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The predictive factors of gastric cancer recurrence after the completion of adjuvant chemotherapy in advanced gastric cancer

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ETHICAL STANDARDS
This study was approved by the Institutional Research Ethics Board of The Catholic University of Korea (VC17RESI0157) and adhered to the Declaration of Helsinki.

ABSTRACT
Objective: the administration of adjuvant chemotherapy after a curative resection is accepted as the standard treatment to improve the prognosis of advanced gastric cancer. Nevertheless, the prognosis of recurrence-related gastric cancer is still not clinically satisfactory. We aimed to assess the therapeutic yield of a radical gastrectomy with D2
lymphadenectomy (R0 resection) and the completion of adjuvant chemotherapy. The predictive risk factors for recurrence were also assessed.

**Methods:** A retrospective cohort study was designed with patients diagnosed with advanced gastric cancer. Patients with an R0 resection who had completed adjuvant chemotherapy were included in the study.

**Results:** Data from 130 patients who had undergone an R0 resection and had completed six cycles of adjuvant chemotherapy were analyzed. The chemotherapy compliance rate was 63.11% and the overall recurrence rate was 36.9%. The lymph node ratio (LNR), which was defined as the number of metastatic lymph nodes divided by the retrieved lymph nodes, was a significant risk factor in the lymph node-positive group (p < 0.01). This parameter had a relatively high sensitivity to predict recurrence compared with the 7th and 8th edition of the AJCC staging system, with an area under the curve of 0.735 (95% confidence interval: 0.639-0.832). Baseline CA19-9 level was a risk factor in the lymph node-negative group (p = 0.01).

**Conclusions:** LNR and baseline CA19-9 levels, as simple markers, had strong predictive values for the recurrence of advanced gastric cancer. With regard to recurrence, more potent adjuvant therapy should be considered in high-risk patients.

**Key words:** Stomach neoplasm. Chemotherapy. Adjuvant. Lymph nodes. CA19-9 antigen.

**INTRODUCTION**

Although the incidence and mortality rate of gastric cancer have been steadily declining, it is still the fourth most common cancer worldwide and more than 50% of cases occur in East Asia (1-3). Curative resection including systemic lymph node dissection is the main treatment method for advanced gastric cancer. The standard surgical procedure is a gastrectomy with radical D2 lymphadenectomy (4). After curative gastrectomy, the main cause of treatment failure for these patients is recurrence. The recurrence rate after a curative resection is reported as 22% to 45% (5,6). Recurrence occurs in several patterns such as loco-regional recurrence and hematogenous and peritoneal metastases, which adversely affect patient survival (7). More than half of advanced gastric cancer cases have lymph node metastasis, and lymph node involvement is the most important indicator for survival following a curative resection (R0). Improved survival was observed in node-
negative compared to node-positive gastric cancer cases (8,9).

Adjuvant chemotherapy after surgery has been accepted as the standard treatment to improve prognosis since the large-scale phase III studies were performed, such as the ACTS-GC and CLASSIC trials (10-12). Previous meta-analyses showed that adjuvant chemotherapy increased the survival rate and decreased mortality (13,14). Nevertheless, the prognosis of recurrence-related gastric cancer is still not clinically satisfactory. Although various prognostic factors have been reported, the ability to identify high-risk recurrence cases is still limited. Thus, it is difficult for clinicians to determine a prognosis. Therefore, predictive factors need to be identified to precisely predict recurrence and identify high recurrence risk cases in order to offer a multimodal therapy that may provide a modest survival advantage. This study aimed to assess the therapeutic yield of an R0 gastrectomy with adjuvant chemotherapy and to evaluate the predictive risk factors of overall recurrence according to nodal stage.

MATERIALS AND METHODS
Study population
A retrospective cohort study of patients diagnosed with advanced gastric cancer and treated with curative gastrectomy and systemic adjuvant chemotherapy was performed. All patients were treated at the St. Vincent’s Hospital, Suwon, The Catholic University of Korea, from January 2007 to January 2012. Patients were excluded if they had a history of another type of cancer, had undergone an endoscopic mucosal resection or neo-adjuvant chemotherapy, or were initially diagnosed with a metastatic lesion. Chest and abdomen/pelvis computed tomography (CT) and positron emission tomography (PET)-CT were performed before surgery to exclude distant metastasis. Blood tests to measure tumor markers carcinoembryonic antigen (CEA), cancer antigen 19-9 (CA19-9) and alpha-fetoprotein (AFP) were performed and iron levels were measured. Demographic findings including age, sex, body mass index and history of alcohol abuse and smoking were collected.

Surgical treatment
All patients who underwent distal or total gastrectomy with extended (D2) lymph node dissection according to the guidelines of the Japanese Gastric Cancer Association were
included in the analysis (15). Curative gastric resection was defined as the macroscopic removal of all visible tumors and metastatic lymph nodes, with a pathologically negative resection margin of 4-5 cm (R0 resection). D2 lymphadenectomy involves the removal of all lymph nodes in N1 and N2 stations. The extra-perigastric lymph nodes along the left gastric artery, common hepatic artery, celiac artery, splenic artery and splenic hilum were also dissected in the D2 resection.

Tumor staging and histological classification
Histopathologic features were recorded, such as tumor invasion depth, histology and lymph node status including the number of metastatic lymph nodes and resected lymph nodes found during surgery. Tumor size, tumor location, invasion depth and nodal status were based on the 6th and 7th edition of the AJCC Staging System (16). Patients diagnosed using the 6th edition staging system were reclassified using the 7th edition. In order to compare the prognostic value of the 7th edition, all patients were restaged using the 8th edition of the AJCC pathological staging system (16,17). The lymph node ratio (LNR) was defined as the number of metastatic lymph nodes divided by the number of retrieved lymph nodes (18).

Adjuvant chemotherapy
After surgery, the enrolled patients diagnosed with stage II or III cancer received postoperative adjuvant chemotherapy following the National Comprehensive Cancer Network (NCCN) guideline for gastric cancer, unless the patient disagreed or rejected the procedure. The adjuvant 5-fluorouracil and cisplatin (FP) chemotherapy was adapted and patients received cisplatin (60 mg/m²) as a two-hour intravenous infusion on day 1 with hydration and 5-fluorouracil (500 mg/ m²/day) as a continuous infusion on days 1-5 every four weeks. This regimen was repeated for six cycles.

Follow-up of patients
After the completion of all cycles of adjuvant chemotherapy, patients were followed up according to our standard protocol of every three months for two years, every six months for the next three years and then every 12 months at five years after surgery. Check-ups included a physical examination, tumor marker examination and a CT scan. Endoscopic
examination was performed regularly every six months for at least two years and every 12 months over the following years. Recurrence was confirmed radiographically and/or pathologically and described as either loco-regional or distant.

**Statistical analysis**
Continuous data are expressed as the mean ± standard deviation and were analyzed using an independent-sample t-test or the Kruskal-Wallis test. Categorical variables are expressed as quantities and were analyzed using the χ² test or Fisher’s exact test. Logistic regression analysis was used to identify the independent factors associated with recurrence. The diagnostic yield of the LNR for the prediction of recurrence was calculated using the area under the receiver operating characteristic (ROC) curve. All statistical analysis were two-sided and p < 0.05 was considered as statistically significant. The SPSS statistical package (version 19.0.1; SPSS Inc., Chicago, IL, USA) was used for all analyses.

**RESULTS**
Of the 890 patients identified, 456 underwent surgery with adjuvant systemic chemotherapy. Patients who died from a cause that was not related to cancer (n = 108) and those who underwent a non-curative resection (palliative or R2 resection, n = 54) or with a non-adenocarcinoma pathology (n = 1) were excluded. Stage I early gastric cancer (n = 87) were excluded in order to precisely evaluate the effect of adjuvant chemotherapy. A total of 206 patients with advanced gastric cancer were enrolled and patients lost to follow-up (n = 17) and those who did not complete the chemotherapy treatment (n = 59) were excluded. Finally, 130 patients who underwent an R0 resection and completed six cycles of adjuvant chemotherapy were analyzed (Fig. 1). The median follow-up duration after the initial treatment was nine (range, 7-11) years. The median age of patients was 59 (range: 27-81) years. The chemotherapy compliance rate was 63.11% (130/206) and the overall recurrence rate was 36.9% (48/130).

Univariate analysis showed that the number of metastatic lymph nodes was a statistically significant risk factor associated with recurrence. Patients were divided into two subgroups according to the presence of metastatic lymph nodes, as lymph node-positive and lymph node-negative groups. Approximately 83% (108/130) of patients with confirmed metastatic
lymph nodes were classified in the lymph node-positive group and 43 (39.8%) of patients had a recurrence, whereas 22.7% (5/22 cases) of cases suffered a recurrence in the lymph node-negative group. The difference in recurrence rate (39.8% vs 22.7%, p = 0.20) was not statistically significant. Although there were significant differences in cancer stage according to the 7th and 8th edition of the AJCC staging system. Specifically, the lymph node-negative group did not have a lower recurrence rate than the lymph node-positive group. Predictive factors of overall recurrence were analyzed according to the metastatic lymph node status. In the lymph node-positive group, the number of metastatic lymph nodes and retrieved lymph nodes were significant risk factors according to the multivariate analysis (Table 1). The LNR was a significant risk factor (p < 0.01) and had a predictive value for recurrence as shown by the ROC curve (Fig. 2). The optimal cutoff value of LNR was 0.19 owing to its best predictive value (area under the curve, 0.735; 95% confidence interval, 0.639-0.832) (p = 0.01) and recurrence was predicted with a sensitivity of 62.8% and specificity of 70.8%. In particular, the recurrence rate was 57.4% (27/47 cases) when the LNR was above 0.2.

According to the 7th and 8th AJCC staging system, recurrence episodes correlated with tumor stage. The rates according to the 7th AJCC stage were as follows: stage Ila: 16.0%; stage Iib: 21.4%; stage IIa: 28.6%; stage IIIb: 59.1%; and stage IIIC: 63.0%. The rates according to the 8th AJCC stage were as follows: stage Ila: 16.0%; stage Iib: 21.4%; stage IIa: 38.9%; stage IIb: 57.1%; and stage IIIC: 60.0%). LNR was shown to be a better marker for the prediction of recurrence compared with the previous staging system and was a unique independent risk factor of recurrence in the data evaluated using the 7th or 8th AJCC staging system (Table 2). In addition, 22.7% (5/22 cases) of the patients developed recurrence in the lymph node-negative group. Three of the 15 patients with T3 stage disease had a recurrence (20.0%) and two of the seven patients with T4a stage had a recurrence (28.5%). Of the five patients with a recurrence, four had local recurrences around the resection site (two anastomotic margin, one pancreas head and one transverse colon) and the remaining patient had a hematogenous metastasis. Only baseline CA19-9 level were associated with recurrence (p = 0.01) (Table 3).

DISCUSSION
The results of this study demonstrated that adjuvant chemotherapy in advanced gastric cancer has a survival benefit, as the loco-regional recurrence rate was reduced to 70% of the level of the control group (19). A large-scale prospective study showed that adjuvant chemotherapy improved prognosis with a prolonged effect on disease-free survival and should be considered as a treatment option (11). A meta-analysis revealed that adjuvant chemotherapy led to a 6% increase in the five-year overall survival rate compared with surgical treatment alone (14,20). Based on the previous results, adjuvant chemotherapy has been administered as a standard therapy according to the clinical practice guideline for gastric cancer in Korea. Even with a curative resection with adjuvant chemotherapy, a considerable number of patients with advanced gastric cancer experienced episodes of recurrent disease, resulting in a decreased survival. From this point of view, patients at high risk of recurrence should be distinguished for individualized treatment. Subsequently, different therapeutic strategies should be applied. Unfortunately, no definite markers for predicting recurrence existed at this time. Until now, the need to develop reliable markers to identify patients with increased recurrence risk has clearly been unsatisfied. Although the UICC/AJCC stage was the most commonly used staging system for gastric cancer, clinicians occasionally experience its limitations. Therefore, a new edition has been established and an effort has been made to develop a new staging system. However, these systems are complex and staging shifts are common during treatment. In the clinical practice, oncologists are consistently searching for simpler and more accurate markers.

In this study, the recurrence rate of the standard treatment for advanced gastric cancer (i.e., curative gastrectomy with completion of adjuvant chemotherapy) was 36.9%. Lymph node involvement was a strong predictive factor of recurrence in the lymph node-positive group and it was more common than in the lymph node-negative group. Generally, advanced gastric cancer without lymph node metastasis shows a relatively good prognosis. However, a statistically significant difference between groups is unlikely if the presence of metastatic lymph nodes is excluded from the analysis. Subgroup analysis according to lymph node involvement revealed that the LNR was a significant risk factor for recurrence. When the LNR was defined as the number of metastatic lymph nodes divided by the retrieved lymph nodes, it was a stronger predictive risk factor for recurrence than the 7th and 8th AJCC staging system. Several previous studies of the predictive value of LNR have reported that its use
was inconclusive (9,21-23). In contrast, other studies showed that LNR was as an independent prognostic factor in gastric cancer (16,17,24,25). As ambiguous results may be caused by heterogeneous enrollment, this study was designed with a clear inclusion criteria including an R0 resection with the completion of adjuvant chemotherapy. LNR is a very simple marker and has minimized the shifting effect of cancer stage during treatment. Furthermore, it is less influenced by the extent of lymphadenectomy, pathological diagnosis, or inter-observer variation (24-26). For example, in D1 and D2 lymph node dissection, this value has been proposed as a single strong prognostic factor.

We chose the strict inclusion criteria that enrolled patients who had completed adjuvant chemotherapy after a curative resection. Considering that a non-negligible number of recurrences was a major issue in the prognosis of advanced gastric cancer, it would be meaningful to analyze the risk factors of these patients. Our results revealed that recurrence could be predicted using LNR with a reliable sensitivity and specificity. The ROC curve for LNR showed an optimal cutoff value of 0.19 for the prediction of recurrence. However, there is no consensus with regard to the appropriate LNR cutoff value and further studies are needed to determine the reference value.

Although the presence of metastatic lymph nodes is a well-known predictor of a poor outcome, the absence of metastatic lymph nodes does not guarantee a good prognosis. Our results show there was significant number of patients with recurrence even in the lymph node-negative group. Most recurrences occurred around the surgical site and these local recurrences probably had an infiltrative growth pattern of gastric cancer. It was noteworthy that a deeper tumor invasion (T stage) correlated with more frequent recurrence in node-negative disease. Micrometastasis was closely related to advanced T stage and therefore, we believe that the prognostic value of T stage may be underestimated (27,28). When we considered the concept of micrometastasis in extension, the baseline CA19-9 level was an important risk factor for recurrence. The clinical usefulness of tumor markers has been studied in several previous studies. CEA and CA19-9 are prognostic factors in gastric cancer and have been widely used (29-31). Recent studies show that the preoperative CA72-4 level is related to a poor prognosis in gastric cancer, whereas AFP is useful for detecting and predicting hepatic metastasis (32-38). Several researchers insist that positive CEA or CA19-9 serum values correlate with a poor prognosis, although preoperative CA19-9 is a better
predictor (39,40). Even though the diagnostic significance of various tumor markers is limited in gastric cancer, its usefulness in postoperative prediction of recurrence may be promising. Our data show that CA19-9 could be a representative marker for predicting postoperative recurrence.

The strength of this study is that patients with stage I early gastric cancer, stage IV advanced gastric cancer and those who did not complete chemotherapy were excluded in order to precisely assess the effect of adjuvant chemotherapy. In addition, we analyzed the risk factors for recurrence according to nodal involvement. However, our study has several limitations. First, this was a retrospective study conducted at a single center, with a relatively small sample size. To overcome this issue, we evaluated patients for an extended follow-up period. Secondly, recent potent regimens of adjuvant chemotherapy such as a combination of capecitabine and oxaliplatin were not included in this study. In the mid-1990s, the FP regimen was adopted as a standard regimen in Korea. The main adjuvant chemotherapy regimen was FP chemotherapy before the approval of capecitabine. Thus, we believe that the recurrence rate varies little depending on the treatment regimens.

In conclusion, when patients have a high LNR or a high preoperative serum CA19-9 level, they should be classified as high-risk recurrence cases, despite the standard treatment of advanced gastric cancer. The therapeutic strategy should be individualized in these high-risk patients and therefore, more potent adjuvant chemo-regimens or immunotherapy should be considered.

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factor in gastric cancer after curative resection (R0) regardless of the examined number of lymph nodes. Am J Clin Oncol 2013;36:325-30. DOI: 10.1097/COC.0b013e318246b4e9


Table 1. Multivariate analysis of recurring gastric cancer after a curative resection with complete adjuvant chemotherapy in the lymph node positive group (n = 108)

<table>
<thead>
<tr>
<th></th>
<th>Sig.</th>
<th>Exp (B)</th>
<th>95.0% CI for Exp (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.12</td>
<td>0.95</td>
<td>0.91 - 1.01</td>
</tr>
<tr>
<td>Sex</td>
<td>0.90</td>
<td>0.92</td>
<td>0.27 - 3.14</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.50</td>
<td>1.06</td>
<td>0.89 - 1.26</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.11</td>
<td>3.25</td>
<td>0.77 - 13.64</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>0.19</td>
<td>0.40</td>
<td>0.11 - 1.56</td>
</tr>
<tr>
<td>CEA before operation</td>
<td>0.61</td>
<td>1.01</td>
<td>0.97 - 1.04</td>
</tr>
<tr>
<td>CA19-9 before operation</td>
<td>0.59</td>
<td>1.00</td>
<td>0.99 - 1.01</td>
</tr>
<tr>
<td>T stage by 7th AJCC (T3 and T4)</td>
<td>0.32</td>
<td>0.46</td>
<td>0.10 - 2.15</td>
</tr>
<tr>
<td>Pathologic result (poorly differentiated or SRC)</td>
<td>0.12</td>
<td>4.46</td>
<td>0.69 - 28.84</td>
</tr>
<tr>
<td>Number of dissected lymph node at operation</td>
<td>0.03*</td>
<td>0.94</td>
<td>0.89 - 0.99</td>
</tr>
<tr>
<td>Number of metastatic lymph node</td>
<td>&lt; 0.01*</td>
<td>1.20</td>
<td>1.06 - 1.36</td>
</tr>
<tr>
<td>Iron level before operation</td>
<td>0.19</td>
<td>1.01</td>
<td>0.99 - 1.02</td>
</tr>
</tbody>
</table>

*Statistically significant.
Table 2. Comparison of lymph node ratio (LNR) and TNM staging system (data setting with the 7th and 8th AJCC staging system) in the lymph node positive group (n = 108)

<table>
<thead>
<tr>
<th>Data analysis</th>
<th>Significance</th>
<th>95.0% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p-value</td>
<td>OR</td>
</tr>
<tr>
<td>(a) with 7th AJCC staging system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.06</td>
<td>0.35</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.06</td>
<td>1.00</td>
</tr>
<tr>
<td>p-stage by 7th AJCC</td>
<td>0.08</td>
<td>1.12</td>
</tr>
<tr>
<td>LNR</td>
<td>0.01*</td>
<td>65.26</td>
</tr>
<tr>
<td>(b) with 8th AJCC staging system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0.07</td>
<td>0.35</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.28</td>
<td>1.00</td>
</tr>
<tr>
<td>p-stage by 8th AJCC</td>
<td>0.14</td>
<td>1.12</td>
</tr>
<tr>
<td>LNR</td>
<td>0.01*</td>
<td>73.37</td>
</tr>
</tbody>
</table>

CA19-9: cancer antigen 19-9; AJCC: American Joint Committee on Cancer Classification;
LNR: lymph node ratio; p-stage: pathologic stage. *Statistically significant.
Table 3. Factors analyzed with regard to recurring gastric cancer after a curative resection with adjuvant chemotherapy in the lymph node negative group (n = 22)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.33</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.55</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.60</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.12</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>0.56</td>
</tr>
<tr>
<td>CEA</td>
<td>0.16</td>
</tr>
<tr>
<td>CA19-9</td>
<td>0.01*</td>
</tr>
<tr>
<td>Pathologic result (PD or SRC)</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of resected lymph node</td>
<td>0.40</td>
</tr>
<tr>
<td>Iron</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Fig. 1. Flow diagram of the study.
Fig. 2. Receiver operating characteristic curve (ROC) curve for the lymph node ratio (LNR) as a marker of recurrence.