Wall-invasion Pattern Correlates with Survival of Patients with Gallbladder Adenocarcinoma

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Abstract. Gallbladder carcinomas (GBC) frequently show vascular invasion and metastasis when the carcinoma cells invade the perimuscular connective tissue (pT2 according to the TNM classification) through the muscular layer. In this study, two intramural invasion patterns were defined as (i) infiltrative growth (IG) type, infiltrative growth in the muscle layer without destruction and (ii) destructive growth (DG) type, massive growth with destruction of the muscle layer. Sixty-six surgically resected gallbladder adenocarcinomas invading the perimuscular connective tissue (pT2) and beyond the gallbladder wall, including the visceral serosa, (pT3/pT4) were examined. The overall survival rate of the patients with the DG type was significantly lower than that of the patients with the IG type (p=0.018). Lymphatic invasion (37.5% of IG and 62.5% of DG, p=0.014), venous invasion (41.9%, 58.1%, p=0.089), nodal status (30.4%, 69.6%, p=0.015) and scirrhous growth (INFγ)(31.0%, 69.0%, p=0.0035) were more frequently detected in DG cases than in IG cases. In addition, median survival and survival rates were statistically analyzed. The patients with a high grade of lymphatic and venous invasion had lower survival rates (p<0.0001 and p<0.05, respectively). The patients with the DG type and scirrhous growth (INFγ) also had lower survival rates (p<0.05 and p<0.0001, respectively) than did patients with the IG type and expansive/intermediate growth (INFα,β). On multivariate analysis, neural invasion (odds ratio, 0.157; 95% confidence interval, 0.039-0.629) was an independent predictor of mortality. In conclusion, the DG invasion pattern is an indicator of high malignant potential and indirectly worsens the prognosis of patients with gallbladder adenocarcinoma.

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract and the fifth most common malignancy of the digestive system. The incidence of GBC varies in different parts of the world and also differs among different ethnic groups within the same country. Japan and several Latin American countries, such as Chile, Mexico and Bolivia, have the highest incidences of GBC in the world (1, 2). In Japan, GBC is responsible for 1.25% and 3.49% of cancer deaths in men and women, respectively. The number of surgically resected cases of GBC has recently increased because of advances in imaging diagnosis and operative procedures. However, wall-invasion patterns of GBC have not been defined.

The layers of the gallbladder wall include the surface epithelium, lamina propria, smooth muscle, perimuscular subserosal connective tissue and serosa, but a muscularis mucosa and submucosa are absent (3-7). The smooth muscle consists of loosely arranged bundles of circular, longitudinal, and oblique muscle fibers that do not form well-developed layers as they do in the luminal gut. In addition, fibrovascular connective tissue focally separates the muscle bundles. The perimuscular subserosal connective tissue contains collagen fibers, fibroblasts, elastic fibers, adipocytes, blood vessels, nerves and lymphatic vessels. Therefore, GBC easily invades the subserosal layer through the smooth muscle layers and frequently shows vascular permeation and perineural invasion, which means high malignant potential both histologically and clinically (8-14).

The aim of the present study was to identify indicators that could predict patients with advanced GBC at high risk of tumor recurrence, based on a new histological classification of gallbladder wall invasion.

Key Words: Gallbladder, adenocarcinoma, invasion pattern, vascular invasion, metastasis.
Patients and Methods

**Gallbladder tissue specimens.** All the tissue specimens were obtained at surgical resection of gallbladder adenocarcinomas at Tokai University Hospital. The subjects were 66 patients (30 men and 36 women; age range, 40-93 years; mean age, 64.1±10.1 years) with gallbladder tumors invading the perimuscular connective tissue (pT2) or tumors beyond the gallbladder, including the visceral serosa (pT3-4), without distant metastasis at surgery. The stages of GBC were based on the TNM classification. The median postoperative follow-up duration was 453.5 (228.0-1,269.3) days.

**Histological examination.** The gallbladder tissue specimens for histological analysis were rapidly fixed in 10% buffered formalin for 24 to 48 hours and routinely embedded in paraffin. Tumor invasion was examined with sections 4 μm-thick stained with hematoxylin and eosin. The degree of venous invasion was classified as: v0, no venous invasion; v1+, minimal venous invasion, *i.e.*, 1 or 2 foci of venous invasion in one histological section; v2+, moderate venous invasion, *i.e.*, 3 or 4 foci; and v3+, severe venous invasion with 5 or more foci. The degree of lymphatic invasion was classified as: ly0, no lymphatic invasion; ly1+, mild lymphatic invasion; ly2+, moderate lymphatic invasion; and ly3+, severe lymphatic invasion. The degree of perineural invasion was classified as: ne0, no perineural invasion; ne1+, mild perineural invasion; ne2+, moderate perineural invasion; and ne3+, severe perineural invasion. The subserosal invasion patterns were classified into three groups, according to the general rules for gastric cancer study of the Japanese Gastric Cancer Association (15-17), *i.e.*, INFα: cancer nests show expansive growth and present a clear borderline between perivesicular adipose tissue; INFβ: the growth fashion and invasive pattern are between those of INFα and INFγ; and INFγ: scirrhous growth, cancer nests show invasive growth and the borderline with perivesicular adipose tissue is unclear.

**Definition and histological identification of invasion pattern.** The following terminology was used to define and classify two patterns of invasion through the muscle layer. Infiltrative growth (IG) type: cancer cells show infiltrative growth in the muscle layer (through the intermuscular space) without muscle layer destruction (Figures 1A-1C). Destructive growth (DG) type: cancer cells show massive growth with destruction of the muscle layer (Figures 1D-1F). The cases that contained both DG and IG components were classified as the DG type because aggressive growth patterns were presented.

**Statistical analysis.** Descriptive statistics were employed to examine the demographic characteristics of the study population. Data are expressed as means ± SD and medians (25th and 75th percentiles). The baseline characteristics and disease and pathological variables were compared between surviving and nonsurviving patients and between patients with the IG and DG types by means of the Chi-square test for continuous and categorical variables. Univariate analyses (Chi-square test) were primarily used for selecting variables on the basis of a p-value <0.05. The significant variables and clinically effective factors were subjected to forward logistic regression analysis to determine the net effect for each predictor while controlling the effects of the other factors. Odds ratios (ORs) and their 95% confidence intervals (CIs) were used to assess the independent contributions of significant factors. A value of *p*<0.05 was considered to indicate statistical significance.

Survival times were measured from the date of surgery and death from all causes (without discrimination between deaths resulting from GBC or other causes) was taken as the outcome. Survival curves were traced with the Kaplan-Meier method and comparison of survival curves was based on the log-rank test. All the analyses were performed using the statistical software package SPSS II (version 11.0; SPSS, Tokyo, Japan).

**Results**

Thirty-five (53.0%) cases showed the IG type and 31 (47.0%) cases showed the DG type. Adenocarcinoma was the most frequent histological type (87.9% of cases). Other histological types, such as signet ring cell carcinoma, adenosquamous cell carcinoma, mucinous carcinoma, small cell carcinoma and undifferentiated carcinoma, were also observed. Fifty cases of primary tumors presented a well-to-moderate grade of differentiation and 16 cases presented a poor grade of histological differentiation or other histological types. The relationship between the invasion pattern through the muscle layer and the clinicopathological features is shown in Table I. Lymphatic invasion (*p*<0.05), nodal status (*p*<0.05), pattern of spread (*p*<0.01) and histological differentiation (*p*<0.01) were found at a significantly higher incidence in the DG type. In addition, cases of the DG type tended to show a higher incidence of venous invasion (*p*=0.089). Using the Kaplan-Meier method and the log-rank test, the relationship between the invasion pattern and the clinicopathological features was analyzed and the survival rates were compared (Table II). For most of the clinicopathological features, the survival rates were significantly correlated with the invasion pattern. Decreased postoperative survival was significantly associated with the invasion pattern (*p*<0.05), histological differentiation (*p*<0.001), lymphatic invasion (*p*<0.0001), venous invasion (*p*<0.05), nodal status (*p*<0.01), neural invasion (*p*<0.01) and the mode of subserosal infiltration (*p*<0.0001). The overall survival rate after curative resection was lower in the patients with the DG type than in the patients with the IG type (*p*<0.018, log-rank test) (Figure 2).

To determine whether the invasion pattern was an independent predictor of survival in the patients with GBC, univariate analysis was used for preliminary screening of the variables followed by stepwise logistic regression of the risk of mortality using the significant univariate predictors and clinically effective factors. Univariate analysis (Table III) identified four factors associated with increased mortality in patients with GBC. The degree of lymphatic invasion (OR, 0.196; 95% CI, 0.066-0.58), neural invasion (OR, 0.127; 95% CI, 0.039-0.41), the pattern of spread (OR, 0.199; 95% CI, 0.066-0.603) and the nodal status (OR, 0.294; 95% CI, 0.092-0.937) increased the risk of mortality. The invasion pattern itself did not significantly affect the survival of patients with GBC (OR, 0.386; 95% CI, 0.139-1.072).
Table IV illustrates the four factors that were retained in multivariate logistic regression analysis. Neural invasion (OR, 0.183; 95% CI, 0.050-0.670) remained a significant predictor of mortality even after control for the other variables. The lymphatic invasion (OR, 0.455; 95% CI, 0.116-1.788), the pattern of spread (OR, 0.564; 95% CI, 0.141-2.245) and the nodal status (OR, 0.483; 95% CI, 0.116-2.002) were not factors contributing to mortality after adjustment for the effects of the other factors.

**Discussion**

In the present study, two different cancer-invasion patterns, infiltrative growth (IG) and destructive growth (DG), through the muscle layer into the subserosal layer of the gallbladder wall were demonstrated. Forty-seven percent of the cases reviewed in this study were of the DG type and showed higher rates of lymphatic invasion and lymph node metastasis and a lower overall survival rate. To our
knowledge, this is the first report describing the relationship between wall-invasion patterns and the prognosis of patients with gallbladder adenocarcinoma.

Several investigators have reported the morphology and histogenesis of GBC including the adenoma-carcinoma sequence (18-22) and we previously demonstrated the morphological characteristics and histogenesis of early GBC (23). Most cases of early GBC exhibit metastatic phenotypes of tumor tissues, as well as that of their surrounding nonneoplastic mucosa. The metastatic changes are thought to play an important role in GBC histogenesis. Some recent studies have analyzed the subserosal invasion patterns and the lymph node spread in advanced cases of GBC (24, 25). GBC with serosal invasion showed frequent lymph node metastasis and frequent liver tumor infiltration. Lymph node metastasis is a significant clinicopathological indicator of prognosis (26, 27).

### Table I. Invasion pattern and clinicopathological features of human gallbladder cancer.

<table>
<thead>
<tr>
<th>Clinicopathological features</th>
<th>No. of patients</th>
<th>Invasion pattern</th>
<th>Rate of DG pattern (%)</th>
<th>p-Value (Chi-square test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at surgery (years)</td>
<td></td>
<td>IG   DG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>30</td>
<td>18   12</td>
<td>40.0</td>
<td>0.3000</td>
</tr>
<tr>
<td>≥65</td>
<td>36</td>
<td>17   19</td>
<td>52.8</td>
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<td>Gender</td>
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<td>Male</td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
<td>18   12</td>
<td>40.0</td>
<td>0.3000</td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>17   19</td>
<td>52.8</td>
<td></td>
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<td>Histological differentiation</td>
<td></td>
<td>Well, Mod.</td>
<td>Poor, Other</td>
<td></td>
</tr>
<tr>
<td>Well, Mod.</td>
<td>50</td>
<td>32   18</td>
<td>36.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Poor, Other</td>
<td>16</td>
<td>3    13</td>
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<td>Lymphatic invasion</td>
<td></td>
<td>ly0, 1</td>
<td>ly2, 3</td>
<td></td>
</tr>
<tr>
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<td>23   11</td>
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<td>v2, 3</td>
<td></td>
</tr>
<tr>
<td>v0, 1</td>
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<td>22   13</td>
<td>37.1</td>
<td>0.0890</td>
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<tr>
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<td>13   18</td>
<td>58.1</td>
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<td>pN0, 1</td>
<td>pN2</td>
<td></td>
</tr>
<tr>
<td>pN0, 1</td>
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<td>28   15</td>
<td>34.9</td>
<td>&lt;0.05</td>
</tr>
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<td>pN2</td>
<td>23</td>
<td>7    16</td>
<td>69.6</td>
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<td>INFα, β</td>
<td>INFγ</td>
<td></td>
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<td>26   11</td>
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<td>INFγ</td>
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<td>69.0</td>
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<td>pT4</td>
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<td>pT3</td>
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<td>pT4</td>
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<td>47.0</td>
<td></td>
</tr>
<tr>
<td>pM1</td>
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<td>0    0</td>
<td>0.0</td>
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<td>TNM stage</td>
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<td>II    III</td>
<td>IVA</td>
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</tr>
<tr>
<td>II</td>
<td>28</td>
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<td>0.6103</td>
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<tr>
<td>III</td>
<td>8</td>
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<tr>
<td>IVA</td>
<td>7</td>
<td>5    2</td>
<td>28.6</td>
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</tr>
<tr>
<td>IVB</td>
<td>23</td>
<td>7    16</td>
<td>69.6</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>66</td>
<td>35   31</td>
<td>47.0</td>
<td></td>
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</table>

IG: Infiltrative growth type; DG: destructive growth type; degree of lymphatic invasion (ly), venous invasion (v) and neural invasion (ne); INF α, β, γ: mode of subserosal infiltration, see Patients and Methods.

### Table II. Clinicopathological features and survival of gallbladder cancer patients.

<table>
<thead>
<tr>
<th>Clinicopathological features</th>
<th>No. of patients</th>
<th>Median (days)</th>
<th>1-year (%)</th>
<th>2-year (%)</th>
<th>p-Value</th>
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<tr>
<td>&lt;65</td>
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<td>550</td>
<td>76.7</td>
<td>46.2</td>
<td>0.773</td>
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<tr>
<td>≥65</td>
<td>36</td>
<td>461</td>
<td>63.8</td>
<td>48.6</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>30</td>
<td>832</td>
<td>72.3</td>
<td>53.8</td>
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<td>Female</td>
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<td>470</td>
<td>67.6</td>
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<td>281</td>
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<td>Stage II+III</td>
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<td>Invasion pattern</td>
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<td>IG type</td>
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<td>31</td>
<td>441</td>
<td>58.6</td>
<td>31.7</td>
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</table>

IG: Infiltrative growth type; DG: destructive growth type; degree of lymphatic invasion (ly), venous invasion (v) and neural invasion (ne); INF α, β, γ: mode of subserosal infiltration, see Patients and Methods.
poorly differentiated type in the gallbladder wall (from the muscle layer to the subserosal layer); therefore, advanced GBCs usually show invasive growth with desmoplastic reactions.

We previously analyzed the immunohistochemical expression of sialyl Le(a), mucin, carcinoembryonic antigen, and thrombospondin-1 in GBC (9-13) and found that mucin 1 (Muc1) was significantly correlated with prognosis. Muc1 is a

Figure 2. Wall-invasion pattern and cumulative survival of patients with GBC.

Table III. Univariate analysis: predictors of survival in gallbladder cancer patients.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Survivors (n=27)</th>
<th>Nonsurvivors (n=39)</th>
<th>p-Value</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>64.3±11.4</td>
<td>64.2±9.2</td>
<td>0.956</td>
<td>1.001</td>
<td>0.954-1.052</td>
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<tr>
<td>Male (n)</td>
<td>11</td>
<td>19</td>
<td>0.618</td>
<td>1.382</td>
<td>0.513-3.725</td>
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<td>Histological differentiation</td>
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<td></td>
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<td>Well, Mod. (n)</td>
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<td>27</td>
<td>0.137</td>
<td>0.391</td>
<td>0.110-1.380</td>
</tr>
<tr>
<td>Lymphatic invasion ly0, 1 (n)</td>
<td>20</td>
<td>14</td>
<td>0.002</td>
<td>0.196</td>
<td>0.066-0.58</td>
</tr>
<tr>
<td>Venous invasion v0, 1 (n)</td>
<td>18</td>
<td>17</td>
<td>0.065</td>
<td>0.386</td>
<td>0.139-1.070</td>
</tr>
<tr>
<td>Neural invasion ne0, 1 (n)</td>
<td>22</td>
<td>14</td>
<td>&lt;0.001</td>
<td>0.127</td>
<td>0.039-0.410</td>
</tr>
<tr>
<td>Spread pattern INFα, β (n)</td>
<td>21</td>
<td>16</td>
<td>0.003</td>
<td>0.199</td>
<td>0.066-0.603</td>
</tr>
<tr>
<td>Nodal status pN0, 1 (n)</td>
<td>22</td>
<td>22</td>
<td>0.034</td>
<td>0.294</td>
<td>0.092-0.937</td>
</tr>
<tr>
<td>Invasion pattern IG type (n)</td>
<td>18</td>
<td>17</td>
<td>0.065</td>
<td>0.386</td>
<td>0.139-1.072</td>
</tr>
</tbody>
</table>

IG: Infiltrative growth type; ly0, 1: mild or no lymphatic invasion; v0, 1: minimal or no venous invasion; ne0, 1: mild or no neural invasion; INF: mode of subserosal infiltration; n: Number of cases.
glycoprotein involved in cancer cell invasion. In the present study, pT2 and pT3-4 GBCs were classified into two groups, i.e. the IG type and the DG type, and the incidence of lymph node metastasis was significantly higher in the DG cases. Recently, other researchers have reported the expression of cell cycle-related molecules, (such as p53, retinoblastoma protein, cyclin D1, p27 and Ki-67) of GBC (28-31), which might be associated with cancer-cell invasiveness.

In conclusion, the DG type of GBC shows locally aggressive growth and is a useful indicator of lymph node status and prognosis.

References


Table IV. Multivariate analysis. Predictors of survival in gallbladder cancer patients.

<table>
<thead>
<tr>
<th>Factor</th>
<th>p-Value</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.731</td>
<td>1.010</td>
<td>0.953-1.071</td>
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<td>Lymphatic invasion</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ly0, 1</td>
<td>0.259</td>
<td>0.455</td>
<td>0.116-1.788</td>
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<tr>
<td>Neural invasion</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ne0, 1</td>
<td>0.010*</td>
<td>0.183</td>
<td>0.050-0.670</td>
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<tr>
<td>Spread pattern</td>
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<td></td>
<td></td>
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<tr>
<td>INF α, β</td>
<td>0.416</td>
<td>0.564</td>
<td>0.141-2.245</td>
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<tr>
<td>pN 0, 1</td>
<td>0.316</td>
<td>0.483</td>
<td>0.116-2.002</td>
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</tbody>
</table>

ly0, 1: Minimal or no lymphatic invasion; ne0, 1: mild or no neural invasion; INFα, β: subserosal infiltration of α and β type.

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