

Prognostic analysis of submucosa-invasive gastric cancer with lymph node metastasis

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Background. The aims of this study were to identify prognostic factors of patients with submucosa-invasive (T1b) gastric cancer and to verify the validity of adjuvant chemotherapy for this disease.

Methods. We retrospectively examined the cases of 1,236 consecutive patients in our prospectively maintained database with T1b gastric cancer who underwent gastrectomy in 1995–2012. We used 11 clinicopathologic characteristics to identify prognostic factors by univariate and multivariate analyses. We compared the survival of the 160 node-positive T1b gastric cancer patients with that of 133 patients in the same database who had node-positive muscularis propria-invasive (T2) gastric cancer and had undergone gastrectomy without adjuvant chemotherapy during the same period, as a reference cohort.

Results. The 5-year overall survival rate was 91.4% for all 1,236 patients. Advanced age (hazard ratio [HR] 4.51; 95% confidence interval [CI] 3.26–6.24; $P < .01$), male sex (HR 2.26; 95% CI 1.56–3.26; $P < .01$), and the presence of lymph node metastasis (HR 1.89; 95% CI 1.33–2.70; $P < .01$) were independent prognostic factors. The 5-year overall survival rates were 92.5% in node-negative patients, 84.5% in patients with 1 or 2 metastatic nodes, and 80.1% in patients with 3 or more metastatic nodes ($P < .01$). The 5-year overall survival rates of the node-positive T1b and T2 gastric cancer patients were 83.6% and 81.2%, respectively ($P = .73$).

Conclusion. The prognosis of node-positive T1b gastric cancer patients after curative gastrectomy was unsatisfactory. Adjuvant chemotherapy should be considered for these patients, especially those with 3 or more metastatic nodes. (Surgery 2015;157:716-22.)

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EARLY GASTRIC CANCER has been defined as a tumor that is confined to the mucosa (T1a) or submucosa (T1b), regardless of lymph node metastasis.¹ Because patients with early gastric cancer generally have an excellent prognosis after curative resection, those with T1 tumors were excluded from the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ie, ACTS-GC) trial in Japan, which showed a survival benefit of adjuvant chemotherapy with an

oral fluoropyrimidine, S-1, for advanced gastric cancer. Some patients with T1 gastric cancer, however, have a recurrence even after curative gastrectomy, at the rate of 1.4–2.8%.²⁻⁵ Some surgeons prescribe S-1 as adjuvant chemotherapy for patients with early gastric cancer who are at high risk of recurrence, especially for node-positive patients, at the surgeons' discretion. The aims of the present study were to identify prognostic factors of patients with T1b gastric cancer and to verify the validity of adjuvant chemotherapy for these patients.

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METHODS

Patients. The cases of 1,236 consecutive patients with gastric cancer invading the submucosa (T1b) who underwent curative (R0) gastrectomy at Niigata University Medical and Dental Hospital or Niigata Cancer Center Hospital between January

1995 and December 2012 were selected from the prospectively maintained database of each hospital. Cases were excluded if the patient met any of the following criteria: (1) having simultaneous cancer(s); (2) having cancer in the remnant stomach; (3) receiving preoperative or postoperative adjuvant chemotherapy. We excluded 8 patients who received preoperative chemotherapy and 32 patients who received postoperative chemotherapy to eliminate the possibility of downstaging and the influence of chemotherapy on survival.

We also examined the cases of 406 patients with gastric cancer invading the muscular propria (T2) with the same criteria who underwent R0 gastrectomy alone during the same period, as a reference cohort for a comparison of their survival with that of the patients with T1b gastric cancer. The institutional review board of each institution approved the use of prospectively collected data for this study, waiving patient consent.

Tumor characteristics. The primary tumor characteristics were described according to the Japanese Classification of Gastric Carcinoma.¹ The median tumor size was 30 mm (range, 2–170 mm). The depth of submucosal invasion was subclassified as SM1 (tumor invasion is within 0.5 mm of muscularis mucosae) or SM2 (0.5 mm or deeper into the muscularis mucosae).

Operative procedures. The type and extent of gastric resection were selected according to the Japanese Gastric Cancer Treatment Guidelines.⁶ In general, distal gastrectomy was performed in 914 patients with carcinoma of the middle or lower third of the stomach ($n = 914$), and total gastrectomy was performed in 183 patients with carcinoma of the upper third of the stomach ($n = 183$). Limited resection, including pylorus-preserving gastrectomy ($n = 26$) and proximal gastrectomy ($n = 113$), also was performed at the surgeon's discretion. The extent of lymphadenectomy was determined according to the type of gastrectomy,⁶ with D1 and D2 lymphadenectomy performed in 733 and 503 patients, respectively.

Survival and statistical analyses. We calculated the overall survival rate using the Kaplan-Meier method, from the date of operative resection to death from any cause or the last follow-up. Similarly, the relapse-free survival rate was calculated from the date of operative resection to relapse or death from any cause, whichever came first, or the last follow-up. The disease-specific survival rate was calculated from the date of operative resection to death from gastric cancer or the last follow-up. We assessed the differences between the survival curves using the log-rank test as a univariate analysis. Cox's proportional hazards regression model was used to identify

the independent prognostic factors: stepwise selection was used for variable selection, with entry and removal limits of $P < .10$ and $P > .15$, respectively.

For the continuous variables, we used the cut-off values of 66 years for age and 30 mm for tumor size for entry into the multivariate model. The stability of this model was confirmed using a step-backward and step-forward fitting procedure. Between patients with node-positive T1b gastric cancer and node-positive T2 disease, we compared the continuous variables by the Mann-Whitney U test and the categorical variables using the χ^2 test. Univariate and multivariate logistic regression analyses were used to identify the independent risk factors for lymph node metastasis. All statistical evaluations were performed using the SPSS 21.0J software package (SPSS Japan, Tokyo).

RESULTS

The median age was 66 years (range, 23–89 years), with 900 male and 336 female patients (73% and 27%, respectively). The median follow-up period after gastrectomy was 78 months (range, 1–219 months).

Prognostic factors for patients with T1b gastric cancer. The 5-year overall survival rate of the 1,236 patients with T1b gastric cancer after curative gastrectomy was 91.4%. The univariate analysis revealed that advanced age, male sex, a large tumor, and the presence of lymph node metastasis were significant prognostic factors (Table I). The multivariate analysis revealed that advanced age, male sex, and the presence of lymph node metastasis were significant independent prognostic factors for patients with T1b gastric cancer after curative gastrectomy (Table II). In contrast, the 5-year disease-specific survival rate of patients with node-positive T1b gastric cancer was 95.1%, and lymph node metastasis was identified as only independent prognostic factor of disease-specific survival.

Survival analysis according to nodal status. A total of 160 patients (12.9%) had metastatic nodes. The overall survival curves stratified according to nodal status are shown in Fig 1. The 5-year overall survival rates were 92.5% in the patients with N0 status, 84.5% in those with N1 (the number of metastatic nodes = 1 or 2), and 80.1% in those with N2 or N3 (the number of metastatic nodes = 3 or more) ($P < .01$). The relapse-free survival rates of these patient groups were 92.4%, 83.0%, and 76.8%, respectively ($P < .01$).

Comparison of patients with node-positive T1b and T2 gastric cancer. Of the 406 patients with T2 gastric cancer, 133 (33%) had metastatic nodes.

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