

Re-evaluating the prognostic validity of the negative to positive lymph node ratio in node-positive gastric cancer patients

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Background. Lymph node status is one of the most important clinical outcome determinants in gastric cancer patients. Categorization based on the metastatic node count alone, however, would presumably be influenced by the extent of lymphadenectomy and the stage migration phenomenon.

Methods. We statistically analyzed relevant clinicopathologic data of 351 gastric cancer patients with node metastasis who had undergone R0 surgery to compare the reliability of the negative to positive lymph nodes ratio to those of other classifications of lymph node metastasis for predicting outcomes.

Results. Survival analyses demonstrated the negative to positive lymph nodes ratio to be an independent predictor of overall survival in the 351 gastric cancer patients (hazard ratio = 0.414; $P < .001$) and revealed significant superiority ($P < .001$) for evaluating overall survival based on direct comparison with other categories of lymph node metastasis applying case-control matching. In addition, the negative to positive lymph nodes ratio was found to correlate significantly with the number of negative lymph nodes ($P < .001$), pN stage ($P < .001$), and the positive to dissected lymph nodes ratio ($P < .001$) by multinomial logistic regression analysis. Finally, the interplay effect analyses revealed the negative to positive lymph nodes ratio to yield information similar to that provided by the positive to dissected lymph nodes ratio ($R^2 = 1.000$), while providing more information on both the number of dissected lymph nodes and the number of negative lymph nodes than the positive to dissected lymph nodes ratio.

Conclusion. The negative to positive lymph nodes ratio, which reflects comprehensive information on dissected, positive, and negative node counts, appears to be a useful alternative for predicting the outcomes of node-positive gastric cancer patients. (Surgery 2016;■■:■■-■■.)

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LYMPH NODE status is one of the most important clinical outcome determinants in gastric cancer (GC) patients. Thus, accurate evaluation of lymph

node metastasis leads to appropriate staging and reliably predicts survival. Insufficient lymph node dissection, however, is associated with incorrect assessment of the metastatic node count and thus provides an inaccurate prognostic assessment.

J.D. and H.Y. contributed equally to this work and should be considered co-first authors.

The authors have no potential conflicts of interest to disclose.

Jingyu Deng, Hiroharu Yamashita, and Han Liang conceived and designed the project; Hiroharu Yamashita collected and assembled the data; Jingyu Deng analyzed and interpreted the data; Jingyu Deng and Hiroharu Yamashita wrote the manuscript; Yasuyuki Seto performed an initial review and revision of the manuscript; and all authors approved the final manuscript.

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Since 1987, lymph node metastasis has been categorized, according to the TNM classification system, by the number of metastatic nodes. Recently, the metastatic node count ranges were modified by applying the N stage of the newly established TNM classification for GC, as follows: pN1, 1 to 2; pN2, 3 to 6; pN3a, 7 to 15; and pN3b, 16 or more nodes with metastatic disease. The N stage of this TNM system was shown to be superior to the previous category in terms of accurately predicting the postoperative survival of GC patients,¹⁻³ though investigators have raised questions regarding its predictive ability.⁴⁻⁶ It is based solely on the number of positive lymph nodes, and its prognostic ability is lower in patients with fewer

retrieved nodes. Therefore, a parameter with high prognostic ability, regardless of the extent of lymphadenectomy, would be ideal and essential.

Another category reflecting lymph node status, the positive to dissected lymph nodes (R_{PD}) ratio, has also been advocated as a convenient, repeatable, and reliable variable for improving prognostic accuracy based on decreasing the stage migration phenomenon.⁷⁻¹⁰ No consensus has yet been reached as to whether R_{PD} is superior to other predictive factors, nor its exact value added to that of the TNM pN category.¹¹⁻¹⁴

The negative to positive lymph nodes ratio (R_{NP}), a novel category of nodal involvement proposed recently, initially showed promising superiority in terms of prognostic ability for GC in a Chinese population.^{15,16} This counterintuitive ratio is derived from R_{PD} , which is the ratio of the number of positive nodes to the sum of positive and negative nodes. R_{PD} is $1/(1+R_{NP})$, wherein both the numerator and the denominator are divided by the number of positive nodes. Therefore, R_{NP} and R_{PD} are somewhat reciprocal as well as being closely related.

The Chinese series consisted largely of patients with advanced stage cancer (stage I, 8.6%; stage II, 28.7%; stage III, 62.7%). In this study, we evaluated the validity of R_{NP} for predicting oncologic outcomes using a large scale GC cohort in Japan where systematic lymphadenectomy has long been routinely applied for gastric cancer, and more than half of patients are initially diagnosed in the early stage. Herein, we compared prognostic capabilities among the categories of nodal involvement in a node-positive population.

PATIENTS AND METHODS

Patients and operative management. Between January 2001 and May 2015, 1,525 patients with GC underwent operative resection in the University of Tokyo Hospital and were assessed for eligibility for inclusion in this study. Eligibility criteria included (1) histologically proven primary cancer of the stomach with positive node metastasis; (2) no history of gastrectomy or other malignancy; (3) no evidence of hepatic, peritoneal, or distant metastasis; (4) absence of positive peritoneal cytology, (5) no esophagogastric junction tumor; (6) pathologically negative resection margins (R0 resection); and (7) remaining alive during the initial hospital stay and during the first postoperative month.

The data from 351 patients in total, who had none of these exclusion criteria, were studied. All patients underwent curative gastrectomy with

systematic lymphadenectomy. The operative procedures were based mainly on the Japanese Gastric Cancer Treatment Guidelines.¹⁷ The seventh edition of the TNM classification for GC was adopted for staging of all enrolled patients. Follow-up of all patients included in this study was completed in October 2015. This retrospective study was approved by the local ethics committee of the faculty of medicine at the University of Tokyo.

Statistical analysis. Cut-point survival analysis was the method adopted to determine the most appropriate cutoff values for R_{PD} and R_{NP} .^{11,18} Clinicopathologic characteristics significantly related to survival were evaluated with reference to statistics obtained by the Kaplan-Meier method for calculating overall survival (OS), and the Cox proportional hazards model was used for the multivariate survival analysis. The Akaike information criterion and the Bayesian information criterion values within a Cox proportional hazard regression model were calculated for each category to measure its discriminatory ability. A smaller Akaike information criterion or Bayesian information criterion value indicated a better model for predicting outcome.^{19,20}

The χ^2 test was used for the univariate correlation analysis and logistic regression for the multivariate correlation analysis incorporating various clinicopathologic characteristics. The general line model was adopted for demonstrating the interplay effects between pairs of characteristics showing significant correlations. A higher R^2 value indicated a stronger interplay effect between 2 characteristics. Case-control matched logistic regression was used to directly compare the prognostic abilities of R_{PD} and R_{NP} . All statistical analyses were performed using PASW 19.0 software (IBM Corporation, Armonk, NY).

RESULTS

Data from our GC patients with node metastasis were analyzed, and the clinicopathologic characteristics of all 351 patients are shown in [Table I](#). The median follow-up time for the entire cohort was 38 (range, 2–173) months. A total of 78 (22.2%) patients had died at the completion of follow-up. The average age of all patients was 64.74 ± 11.12 years (range, 28–90 years). The median OS of all patients after surgery was 51.58 months, and the 5-year survival rate (5-YSR) was 72.7%.

According to univariate analysis, the following 10 clinicopathologic characteristics were significantly associated with OS after curative operation in the 351 patients: tumor location, tumor size, lymphatic invasion, venous invasion, type of gastrectomy, depth

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