Evaluation of prognostic value and stage migration effect using positive lymph node ratio in gastric cancer

S. Komatsu[*], D. Ichikawa, M. Nishimura, T. Kosuga, K. Okamoto,
H. Konishi, A. Shiozaki, H. Fujiwara, E. Otsuji

*Division of Digestive Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachihirokoji,
Kamigyo-ku, Kyoto, Japan*

Abstract

Aims: To detect the best cut-off value of the positive lymph node ratio (PLNR) for stratifying the prognosis and analyzing its value with regard to stage migration effect using PLNR in gastric cancer.

Methods: We retrospectively analyzed 1069 consecutive gastric cancer patients, who underwent curative gastrectomy with radical lymphadenectomy from 1997 through 2009.

Results: 1) The mean number of dissected lymph nodes was 42.6 in pStage I, 32.4 in pStage II and 37.1 in pStage III. The PLNR of 0.2 was proved to be the best cut-off value to stratify the prognosis of patients into two groups ($P < 0.0001$; PLNR <0.2 vs. PLNR ≥ 0.2), and patients were correctly classified into four groups: PLNR 0, PLNR $0-<0.2$, PLNR $0.2-<0.4$ and PLNR ≥ 0.4 by the Kaplan—Meier method. 2) Compared patients with the PLNR <0.2, those with the PLNR ≥ 0.2 had a significantly higher incidence of pT3 or greater, pN2 or greater, lymphatic invasion, vascular invasion and undifferentiated cancer. Multivariate analysis showed that the PLNR ≥ 0.2 was an independent prognostic factor [$P < 0.0001$, HR 2.77 (95% CI: 1.87—4.09)]. 2) The PLNR cut-off value of 0.2 could discriminate a stage migration effect in pN2—N3 and pStage II—III, which patients with PLNR ≥ 0.2 might be potentially diagnosed as a lower stage after gastrectomy.

Conclusion: The PLNR contributes to evaluating prognosis and stage migration effect even in a single institute and enable to identify those who need meticulous treatments and follow-up in patients with gastric cancer.

Introduction

Despite recent advances in diagnostic techniques which have increased the early detection of gastric cancer, less invasive treatment techniques, and perioperative management[1] patients with advanced stage disease have a high incidence of lymph node metastasis and still present a poor prognostic outcome. Nodal status is the strongest predictor of the prognosis of gastric cancer patients, and treatment strategy against metastatic lymph nodes is the most important clinical issue.[2]

Radical lymphadenectomy is recognized as the pivotal strategy for macroscopic tumor clearance for advanced gastric cancer. However, the enthusiasm for optimal lymphadenectomy is different between Eastern and Western countries because of the incidence of obese patients, for whom a surgical approach is difficult, and differences in the management strategy for resection and epidemiologic characteristics of gastric cancer.[3—5] Thereby, enthusiasm varies for lymphadenectomy have given rise to differences in the number of retrieved lymph node number between Eastern and Western countries, which may give rise to the stage migration phenomenon and the prognostic difference according to each stage. Therefore, to develop a better

* Corresponding author. Division of Digestive Surgery, Department of Surgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachihirokoji, Kamigyo-ku, Kyoto 602-8566, Japan. Fax: +81 75 2515522.

E-mail address: skomatsu@koto.kpu-m.ac.jp (S. Komatsu).

system of nodal staging, which enables a common evaluation for nodal progression in both countries, is needed.

In various cancers, the positive lymph node ratio (PLNR), which is obtained by dividing the metastatic lymph node counts by the retrieved lymph node counts, has been reported to be a promising prognostic indicator.[6–8] In this study, we hypothesized that the PLNR could be a prognostic factor and reflect the stage migration effect of gastric cancer at a single institution. The results of our study may provide evidence that the PLNR could be better system of nodal staging and a possible indicator of stage migration effects.

Methods

Patients and surgical procedures

Between 1997 and 2009, 1069 consecutive gastric cancer patients underwent curative gastrectomy with radical lymphadenectomy at the Department of Digestive Surgery, Kyoto Prefectural University of Medicine. Patients underwent preoperative assessments including gastric endoscopy, computed tomography (CT) scans, and laboratory tests. Based on the preoperative diagnosis, total or distal gastrectomy and appropriate lymphadenectomy was performed, mainly according to the Japanese guidelines for the treatment of gastric cancer.[9,10] Patients with clinical T1 and N0 tumors underwent D1 or D1+ lymphadenectomy whereas patients with clinical T2 or more advanced tumors and/or those with N1 or more advanced tumors underwent D2 or D2+ lymphadenectomy. In the D2 dissection, the perigastric lymph nodes and all second-tier lymph nodes were completely retrieved. Depending on the location of the tumor, lymphadenectomy was added along the distal side of the splenic artery (No. 11d) and at the splenic hilum (No. 10), together with splenectomy or splenectomy with distal pancreatectomy.[10]

Resected specimens were examined and evaluated by pathologists based on classifications of the 14th JCGC[11] and the 7th TNM staging manual.[12] As a result, 649 patients were staged as pStage I, 190 as pStage II and 230 as pStage III. All enrolled patients underwent pathologically or macroscopic curative resection (R0). Histological types were classified as differentiated (papillary adenocarcinoma, or moderately or well-differentiated adenocarcinoma) or undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous adenocarcinoma) based on the 14th JCGC.[11]

Assessment of clinical impact of positive lymph node ratio (PLNR)

To confirm the clinical feasibility of the PLNR, we firstly investigated whether the average number of retrieved lymph node was sufficient in all stages of our cohort (Supplementary Table S1). Secondly, the PLNR was calculated by the following formula: PLNR = total pathological metastatic lymph node numbers/total retrieved lymph node numbers. We calculated the PLNR and performed survival analysis using various cut-off values of the PLNR (Table 1 and Fig. 1). Thirdly, we investigated the prognostic difference and the related clinicopathological factors according to the cut-off value of the PLNR (Table 2) and multivariate analysis using Cox's proportional hazard model was performed (Table 3). Fourth, we examined whether the PLNR could detect the stage migration effect following gastrectomy in a single institute (Fig. 2). Finally, we evaluated the effect of the number of retrieved lymph nodes for use of the PLNR system (Table 4).

Statistical analysis

The χ^2 test and Fisher's exact probability test were performed for categorical variables, while the Student's t-test and Mann–Whitney *U*-test for unpaired data of continuous variables were performed to compare clinicopathological characteristics between the two groups. Survival curves were estimated using the Kaplan–Meier method, and statistical differences were examined using the log-rank test. Univariate and multivariate survival analyses were performed using the likelihood ratio test of the stratified Cox proportional hazards model, $P < 0.05$ was considered statistically significant.

Results

Average number of retrieved lymph node

Supplementary Table S1 shows the average number of retrieved lymph node. The mean number of retrieved lymph nodes was 42.6 in pStage I, 32.4 in pStage II and 37.1 in pStage III. The mean number of retrieved lymph nodes was sufficient in all stage of our cohort.

Cut-off value of the PLNR to stratify the prognosis

As shown in Table 1, we performed detailed survival analyses using various cut-off values and demonstrated that the cut-off value of 0.2 could most significantly stratify the prognosis of gastric cancer patients into two groups

Table 1
Survival analysis according to each cut-off value of PLNR.

PLNR cut-off value	*P* value (Log rank test)	
<0.1 vs. ≥0.1	1.5051×10^{-53}	<0.0001
<0.2 vs. ≥0.2	1.9249×10^{-66}	<0.0001
<0.3 vs. ≥0.3	7.0342×10^{-62}	<0.0001
<0.4 vs. ≥0.4	3.8147×10^{-61}	<0.0001
<0.5 vs. ≥0.5	4.7431×10^{-47}	<0.0001
<0.6 vs. ≥0.6	6.0821×10^{-33}	<0.0001