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Original Article

A Novel Approach for Gastric Cancer Staging in Elderly Patients Based on the Lymph Node Ratio

Joonseon Park, Chul Hyo Jeon, So Jung Kim, Ho Seok Seo, Kyo Young Song, Han Hong Lee

Division of Gastrointestinal Surgery, Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Correspondence to
Han Hong Lee
Division of Gastrointestinal Surgery, Department of Surgery, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea.
E-mail: painkiller9@catholic.ac.kr

ORCID iDs
Kyo Young Song
https://orcid.org/0000-0002-5840-1638
Han Hong Lee
https://orcid.org/0000-0002-7541-8490

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Conceptualization: L.H.H.; Data curation: P.J., L.H.H.; Formal analysis: P.J., L.H.H.; Funding acquisition: L.H.H.; Investigation: P.J., S.H.S., L.H.H.; Methodology: P.J., J.C.H., K.S.J.,

ABSTRACT

Purpose: To date, no studies have been performed on staging based on the lymph node ratio (LNR) in elderly patients with gastric cancer who may require limited lymph node (LN) dissection due to morbidity and tissue fragility. We aimed to develop a new N staging system using the LNR in elderly patients with gastric cancer.
Materials and Methods: The present study included patients aged over 75 years who underwent curative gastrectomy between January 1989 and December 2018. Clinicopathological data including the number of retrieved and metastatic LNs were collected and the LNR values were obtained (LNR = the number of metastatic LNs/the number of retrieved LNs). Eleven LNR groups with intervals of 0.1 were divided into four stages based on the inflection points at which the hazard ratio (HR) increased. Survival analysis was performed to evaluate the prognostic value of the LNR.
Results: The four LNR stages included LNR0 (n=364), LNR1 (n=128), LNR2 (n=103), and LNR3 (n=10). In the multivariate analysis, both N staging and LNR staging exhibited significant prognostic values for predicting survival outcomes. However, the incremental change in the hazard ratio (HR) between consecutive stages was greater for the LNR staging than for the N staging (HRs: 1.607, 2.758, and 3.675 for N staging; 1.583, 3.514, and 10.261 for LNR staging).
Conclusions: LNR staging is more useful than N staging in predicting the prognosis in elderly patients with gastric cancer and may be used as a complement or alternative to N staging.

Keywords: Age; Lymph node ratio; Prognosis; Stomach neoplasms

INTRODUCTION

Due to improvements in the nutritional status and healthcare support systems, life expectancy has increased in recent years. However, the number of elderly patients with malignant diseases has also increased [1]. In Korea, the prevalence of gastric cancer is high and the number of elderly patients diagnosed with gastric cancer is increasing due to cancer screening through regular endoscopies [2]. The treatment principle in elderly patients is not different from that in non-elderly patients. However, there might be great concerns regarding the treatment approach and the extent of treatment due to the morbidity and fragility in

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

elderly individuals. Therefore, finding an optimal way for the management and evaluation of elderly patients has currently become a major concern and a point of interest.

Since elderly patients are more likely to have underlying diseases and unknown medical histories compared to younger patients, risk factors such as diabetes and hypertension may complicate surgeries in these patients with cancer [3]. Therefore, more delicate preoperative examination and postoperative patient care are necessary. In addition, extensive surgery may damage the fragile tissues of the elderly patients, causing severe complications [4]. Limited lymph node (LN) dissection due to concerns about postoperative morbidity and fragility can underestimate the practical LN status with conventional N staging.

The lymph node ratio (LNR) is the ratio of metastatic LNs to dissected LNs [5,6]. Several studies have shown that the LNR concept is more sophisticated than N staging for evaluating the prognosis in patients with advanced gastric cancer. In previous studies, the LNR was found to be a useful indicator and an independent negative prognostic factor in patients who had undergone curative gastric resection [6-12]. Moreover, studies have shown that the LNR is also useful in evaluating the indications for postoperative treatment such as adjuvant chemotherapy and in selecting the regimen [6,13].

The purpose of the present study was to develop a new N staging system using the LNR to evaluate the usefulness of LNR staging in elderly patients, and to compare it with the current N staging.

MATERIALS AND METHODS

Database and patient selection

Patients aged over 75 years who had undergone curative gastrectomy at Seoul St. Mary's Hospital between January 1989 and December 2018 were included in this study. Specialized gastric cancer surgeons performed all operations based on the Korean Guideline of Gastric Cancer and a team of specialized gastrointestinal pathologists performed the histological examinations [14]. Clinicopathological data were collected, which included demographic information, operative data, tumor stage, and survival status. Patients diagnosed with other malignant diseases were excluded. The pathological stage was classified according to the American Joint Committee on Cancer (AJCC) (8th edition) TNM criteria. Altogether, 605 patients were included in the study.

Regular follow-ups were conducted according to our standard protocol (every 3 and 6 months for advanced and early gastric cancer, respectively for the first 3 years and every 12 months thereafter). They included determination of tumor marker levels, abdominal computed tomography scans, and endoscopic examination. The observation period was the interval from the date of surgery to the time of death or loss to follow-up, whichever occurred first. Overall survival (OS) was calculated from the date of primary gastrectomy to the date of death due to any cause or the date of the last follow-up. The mean follow-up duration was 39 months (range: 1–256 months).

The study protocol was approved by the Institutional Review Board of the College of Medicine, Catholic University of Korea (KC20RASI1025). Patient records were anonymized and de-identified before the analysis.

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Statistical analysis

Linear regression analysis was used to detect the presence of a linear relationship between the LNR and the number of dissected LNs. Survival analysis was performed using the Kaplan–Meier method and the results were compared using the log-rank test. Multivariate analysis of survival was performed using a Cox proportional hazards model with the backward logistic regression method. All statistical analyses were performed using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA) and P-values <0.05 were considered statistically significant.

RESULTS

Relationship between the LNR and the number of dissected LNs

The scatter plot showed that there was no correlation (R^2<0.001) between the LNR and the number of dissected LNs (**Fig. 1A**). However, there was a linear relationship (R^2=0.769) between the LNR and the number of metastatic LNs. The LNR increased with an increase in the number of metastatic LNs (**Fig. 1B**).

Clinicopathological characteristics of elderly patients with gastric cancer

Among the enrolled patients, 393 (65%) were men and 212 (35%) were women. The mean age and mean body mass index were 78.4 years and 23.1 kg/m^2, respectively. The open approach (64.8%) was more frequent than the laparoscopic approach (35.2%) and distal gastrectomy was the most common surgical extent (480 patients, 79.3%). When classified according to LN dissection, 278 (45.95%) patients underwent D0 or D1 dissection, while 327 (54.05%) patients underwent D2 dissection or above.

Based on pTNM staging, 353 patients (58.4%) had stage I tumors, 123 (20.4%) had stage II tumors, and 129 (21.3%) had stage III tumors. The mean tumor size was 4.7 cm and the average number of retrieved LNs was 38.2 (**Table 1**).

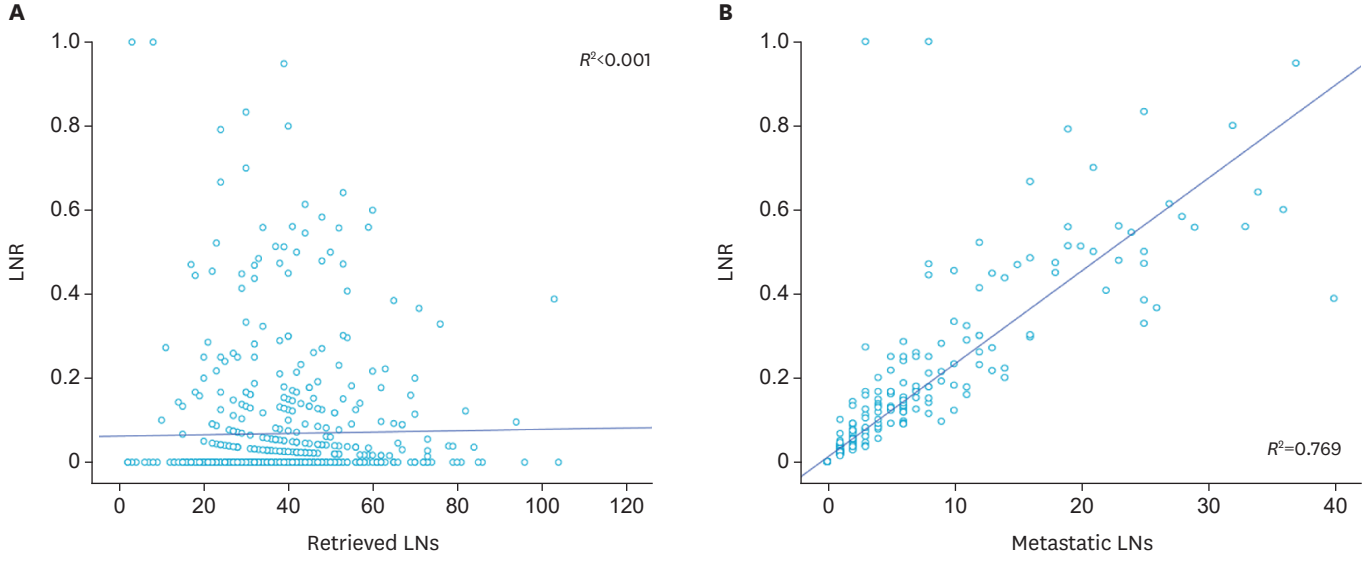

Fig. 1. Distribution of the LNR and its linear relationship with the number of LNs.
(A) Correlation between the LNR and the number of retrieved LNs (R^2<0.001). (B) Correlation between the LNR and the number of metastatic LNs (R^2=0.769).
LNR = lymph node ratio; LN = lymph node.

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Table 1. Clinicopathological characteristics of elderly patients with gastric cancer

Variables	Number (n=605)
Age (yr)	78.4±3.4 (75–92)
Sex	
Male	393 (65.0)
Female	212 (35.0)
BMI (kg/m^2)	23.1±3.2 (14.4–35.1)
ECOG status	
0	141 (23.3)
1	338 (55.9)
2	115 (19.0)
3	11 (1.8)
Approach	
Laparoscopic	213 (35.2)
Open	392 (64.8)
Extent of resection	
Total gastrectomy	124 (20.5)
Distal gastrectomy	480 (79.3)
Proximal gastrectomy	1 (0.2)
LN dissection	
Less than D2	278 (46.0)
D2 and above	327 (54.0)
Estimated blood loss (mL)	126.4±122 (0–1,300)
Operative time (min)	174.8±49.0 (85.0–540.0)
Tumor size (cm)	4.7±3.2 (0–34)
No. of retrieved lymph nodes	38.2±15.7 (2–104)
pT stage*	
T1	320 (52.9)
T2	81 (13.4)
T3	94 (15.5)
T4	110 (18.2)
pN stage*	
N0	364 (60.2)
N1	108 (17.9)
N2	59 (9.8)
N3	74 (12.2)
pTNM stage*	
I	353 (58.4)
II	123 (20.4)
III	129 (21.3)
Curability	
Curative resection	589 (97.4)
Palliative resection	16 (2.6)

Values are presented as mean±standard deviation (range) or number (%).
BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; LN = lymph node.
*Pathological stage classified according to the American Joint Committee on Cancer (8th edition) TNM criteria.

Grouping by the LNR and LNR-based staging

For survival analysis based on the LNR, we initially divided the LNRs into 11 groups using intervals of 0.1. We analyzed the 3-year and 5-year OS rates within each group and divided the 11 groups into four LNR-based stages according to the inflection points at which the hazard ratio (HR) increased.

LNR stage 0 (LNR0) corresponded to an LNR of 0 and was used as the reference level. LNR stage 1 (LNR1) included LNR values between 0 and 0.1. Stage 2 (LNR2) included LNR values from 0.1 to 0.6, for which the HR was 4.420. Stage 3 (LNR3) included LNR values above 0.6, the point at which the HR suddenly increased to 18.465. Among the included patients, 364 were classified into LNR0, 128 into LNR1, 103 into LNR2, and 10 into LNR3 (**Table 2**).

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Table 2. The 3-year and 5-year OS rates for each LNR group

LNR stage	LNR group	No. of patients	3-year OS	5-year OS	HR	95% CI
0	LNR = 0	364	89.3%	80.6%	Ref.	
1	0 < LNR ≤ 0.1	128	71.4%	63.0%	1.816	1.309–2.519
2		103				
	0.1 < LNR ≤ 0.2	49	49.2%	28.7%	4.420	3.005–6.502
	0.2 < LNR ≤ 0.3	22	25.5%	12.7%	6.641	4.005–11.014
	0.3 < LNR ≤ 0.4	7	41.7%	0%	8.866	3.216–24.441
	0.4 < LNR ≤ 0.5	15	35.7%	19.0%	5.252	2.875–9.595
	0.5 < LNR ≤ 0.6	10	40.5%	20.3%	6.307	2.735–14.546
3		10				
	0.6 < LNR ≤ 0.7	4	0%	0%	18.465	6.673–51.097
	0.7 < LNR ≤ 0.8	2	0%	0%	21.250	5.112–88.335
	0.8 < LNR ≤ 0.9	1	0%	0%	17.324	2.379–126.155
	0.9 < LNR ≤ 1.0	3	0%	0%	33.186	10.194–108.037

LNR = lymph node ratio; OS = overall survival; HR = hazard ratio; CI = confidence interval.

Table 3. Composition of LNR staging with the conventional N staging

LNR stage		No. of patients	N stage	No. of patients
0	LNR = 0	364	N0	364
1	0 < LNR ≤ 0.1	128	N1	106
			N2	21
			N3	1
2	0.1 < LNR ≤ 0.6	103	N1	2
			N2	37
			N3	64
3	0.6 < LNR ≤ 1.0	10	N2	1
			N3	9

LNR = lymph node ratio.

The number of patients classified into each LNR stage and the corresponding N stages are presented in **Table 3**.

Survival analysis

Fig. 2 depicts the Kaplan-Meier survival curves for each group. The OS decreased significantly with an increase in the N stage as well as in the LNR stage. However, the incremental change

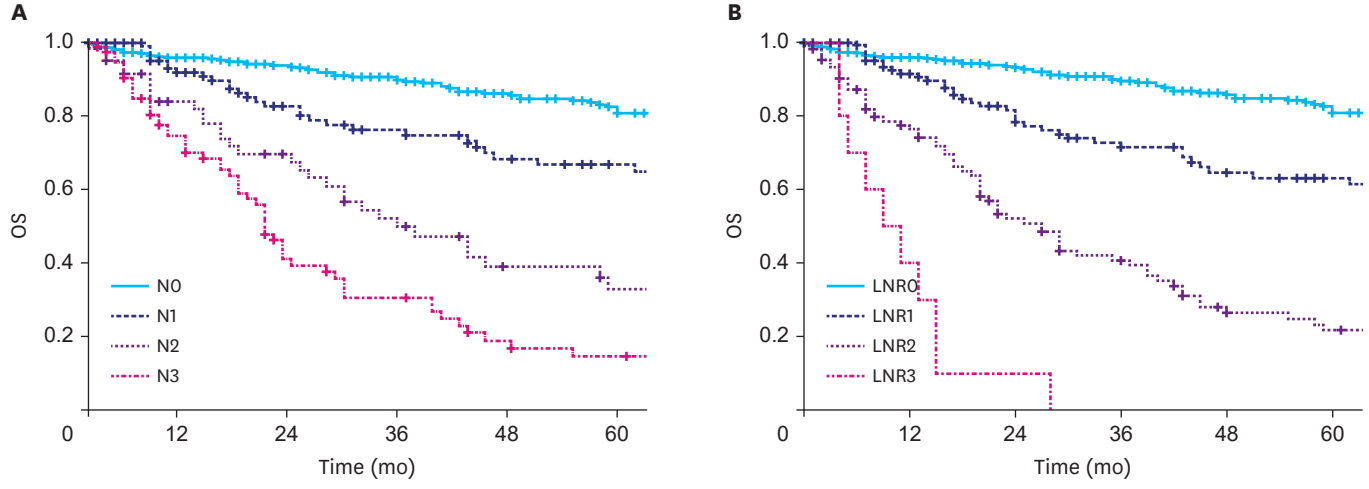

Fig. 2. Kaplan-Meier curves of OS in elderly patients with gastric cancer stratified according to the N stage and the LNR stage.
(A) OS by the N stage (P<0.001). (B) OS by the LNR stage (P<0.001).
OS = overall survival; LNR = lymph node ratio.

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Table 4. Results of multivariate analysis of OS

Variables	HR	95% CI	P-value
Sex	1.056	0.808–1.381	0.689
T stage			
T1	Ref.		<0.001
T2	1.568	1.054–2.332	0.026
T3	1.258	0.864–1.831	0.232
T4	2.642	1.785–3.910	<0.001
N stage			
N0	Ref.		<0.001
N1	1.607	1.124–2.297	0.009
N2	2.758	1.804–4.219	<0.001
N3	3.675	2.429–5.560	<0.001
LNR stage			
LNR0	Ref.		<0.001
LNR1	1.583	1.119–2.241	0.009
LNR2	3.514	2.425–5.094	<0.001
LNR3	10.261	4.867–21.633	<0.001

OS = overall survival; LNR = lymph node ratio; HR = hazard ratio; CI = confidence interval.

in the survival rate between the stages was greater for LNR staging than for the conventional N staging.

Table 4 shows the results of the multivariate analysis of OS using Cox regression. The Eastern Cooperative Oncology Group performance status, LN dissection, and surgical extent were not significant factors in the univariate analysis and were excluded from the multivariate analysis (data not shown). In conventional T staging, the T2 and T4 stages were significant predictors of OS (HR for T2, 1.568; 95% confidence interval [CI], 1.054–2.332; P=0.026 and HR for T4, 2.642; 95% CI, 1.785–3.910; P<0.001, respectively). The N stage and LNR stage were significant prognostic factors for survival outcomes in the multivariate analysis. However, the change in HR between stages was greater for LNR staging than for N staging (HRs for N staging: 1.607, 2.758, and 3.675; HRs for LNR staging: 1.583, 3.514, and 10.261, respectively) (**Table 4**).

DISCUSSION

In the present study, we classified 605 elderly gastric cancer patients using the newly defined LNR stages and analyzed their OS by stage (**Fig. 2**). Significant differences in OS were identified among the different N and LNR stages. To eliminate the effects of potential confounding factors that may influence the survival rate, we conducted a multivariate analysis, which showed that the N stage and LNR stage were significant predictors of prognosis. However, the change in the HR between the LNR stages was much greater than that between the respective N stages, indicating that the LNR stage is a more effective indicator of LN status and prognosis in elderly patients than the N stage. To the best of our knowledge, this is the first analysis of LNR staging in elderly patients with gastric cancer who may require limited LN dissection.

TNM staging is the most commonly used staging system for predicting the prognosis of gastric cancer and the most recent version was published in the 8th edition of the AJCC guidelines. The N stage represents the nodal status and the most advanced stage (N3b) requires the evaluation of at least 16 LNs [15]. Since the LNR is not affected by the number of retrieved LNs, it is advantageous when extensive LN dissection is harmful, especially in

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patients with preoperative morbidity. D2 LN dissection is the standard treatment for advanced gastric cancer. However, we previously reported that D2 or higher level of dissection did not improve survival, but increased the risk of complications in elderly patients [4]. Usually, extensive LN dissection requires a significantly longer operation than limited LN dissection, posing a risk of significantly greater blood loss. In addition, lengthier operations increase the risk of complications resulting from general anesthesia. Therefore, extensive LN dissection is likely to pose a higher risk to patients with cardiovascular or respiratory diseases and to elderly patients who are more vulnerable to postoperative bleeding and complications of anesthesia [4,16]. Limited LN dissection rather than extensive LN dissection is recommended for such patients. Our LNR staging may be more useful in cases requiring limited LN dissection when compared with traditional TNM staging, which requires at least 16 LNs. The LNR may exhibit a greater positive predictive value in elderly patients who can undergo limited surgery due to their fragility. This may support the official establishment and implementation of the LNR staging concept. Patients with high American Society of Anesthesiologists physical status scores (≥3) should be evaluated using LNR staging. Further studies including larger patient populations who require limited LN dissection may help establish the utility of LNR staging in clinical practice. If LNR staging is observed to be more effective than conventional N staging across all age groups, it may be used as an alternative to N staging.

To date, most of the studies involving the LNR have used a single cut-off value to divide patients into only two LNR groups. However, different studies have suggested different cut-off values and no official numerical standard has been put forth to replace the N stages. For example, various studies have proposed cut-off values of 0.1, 0.25, 0.4, and 0.75 for LNR staging [5,7,17]. Such two-stage systems are inappropriate for use in clinical practice. One of the strengths of the present study is LNR grouping and subsequent staging using three specific cut-off values: 0, 0.1, and 0.6. These values are easy to apply in clinical practice, as they follow a structure similar to conventional N staging. We initially selected a cut-off value of 0 and divided all patients into the LNR = 0 and the LNR >0 groups. Subsequently, we created 10 groups using increments of 0.1 and established the cut-off values of 0, 0.1, and 0.6 based on significant changes in the HR. This process resulted in four LNR stages: LNR0, LNR1, LNR2, and LNR3, the same number as that in the N staging system. The LNR staging concept can be applied in clinical practice in a manner similar to N staging while compensating for its deficiencies.

One of the advantages of the present study was the number of patients included in the study. Although we included only elderly gastric cancer patients (aged >75 years), the study population was sufficiently large to conduct a robust analysis. Hence, although our method of calculating the cut-off values was based only on the HRs, our results are expected to be reliable. We recruited a large number of patients from a limited age group and implemented practical and specific standards in a simple way. The results of this study suggest that LNR staging may be an effective new method for evaluating the prognosis in elderly patients with gastric cancer.

This study has several limitations. It was a retrospective single-center study. Therefore, there is a potential for selection bias. We divided the stages based on the HRs from the Cox proportional hazards model and did not employ more precise statistical methods such as a receiver operating characteristic curve. However, we included a relatively large number of patients and generated sufficient data to acquire cut-off values to demarcate the four groups, similar to the current N staging system.

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This is the first study to evaluate the usefulness of LNR staging in elderly patients with gastric cancer. Based on the results of this study, we propose a new LNR staging system, which is similar to conventional N staging. We found that LNR staging is more useful than N staging in predicting the prognosis in elderly patients with gastric cancer who may need limited LN dissection. Therefore, LNR staging can be used to complement or replace conventional N staging in elderly patients with gastric cancer.

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