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Original Research

Comparison of three lymph node classifications for survival prediction in distant metastatic gastric cancer

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HIGHLIGHTS

- LODDS is an independent prognostic factor in DMGC patients.
- LODDS would not be affected by nodal category migration.
- LODDS has superior prognostic prediction value over AJCC N category in DMGC patients.
- LODDS could serve as a referential indicator for postoperative radiotherapy.

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ABSTRACT

Background: The optimal lymph node (LN) classification system for prognostic assessment in distant metastatic gastric cancer (DMGC) patients who undergo LN dissection remains unclear. Therefore, we compared the prognostic performance of positive LN (PLN), LN ratio (LNR), and log odds of positive LNs (LODDS) in DMGC patients.
Methods: A total of 1999 DMGC patients who underwent lymphadenectomy recorded in the Surveillance Epidemiology and End Results database from 2004 to 2012 were reviewed.
Results: Univariate analyses showed that the PLN, LNR and LODDS systems were all significantly correlated with cancer-specific survival (CSS). However, only the LODDS classification remained an independent prognostic factor through the multivariate analysis. Furthermore, this classification could efficiently discriminate survival outcomes in patients within the same positive PLN category, as well as in patients with no positive node involvement. Both the LODDS and LNR classifications had better discriminatory ability, monotonicity, and homogeneity of prognostic stratification, as well as more accurate 1 or 2-year CSS prediction, than the PLN classification. The performances of the LNR and LODDS classifications were similar. Additionally, we found that inclusion of PORT carried a survival benefit across all LODDS intervals except the "LODDS ≤ -1.0" subgroup.
Conclusion: Our findings indicate that the LODDS classification is the most optimal system for prognostic assessment in DMGC patients. Incorporating LODDS into the staging system of DMGC patients will enable clinicians to more accurately predict prognosis and guide regional therapy regimen decisions in DMGC patients.

1. Introduction

Lymph node (LN) metastasis is one of the most authentic outcome measures in gastric cancer (GC) [1]. However, in distant metastatic GC (DMGC) patients (GC patients with an M1 diagnosis according to the seventh edition [2] of the American Joint Committee on Cancer [AJCC] staging guidelines), the regional LN burden does not change the overall pathological tumor-node-metastasis (pTNM) stage determination. In our previous study, we have demonstrated that the survival of DMGC patients who underwent LN dissection varied considerably according to their LN metastasis status [3].The survival of DMGC patients with N0 and N1 stages was significantly better than of patients with other stages. Besides, the LN metastasis was also revealed to be an important indicator

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affecting treatment decision, which could discriminate DMGC patients likely to benefit from postoperative radiotherapy (PORT). Therefore, accurate identification of LN metastatic status in DMGC patients is essential.

In order to describe LN status accurately, several nodal classification systems have been proposed to stratify GC patients with M0 disease. Among them, the N category of the AJCC TNM staging system is determined by the number of incremental tumor-infiltrated positive lymph nodes (PLNs) [2]. Separately, lymph node ratio (LNR), which refers to the ratio of the PLN count to the total number of examined lymph nodes (ELNs) [4–8], has also been investigated as a prognostic factor in M0 GC patients. Multiple reports have suggested that the classification system based on LNR is superior to that based on PLN with respect to determining M0 GC patient prognosis. Similarly, we also demonstrated that LNR was a more suitable independent prognostic indicator in DMGC patients than classification by PLN [3]. However, such issue remain fiercely debated. Interestingly, another novel prognostic indicator, log odds of positive lymph nodes (LODDS), has also been introduced in recent years [9–14]. LODDS is defined as the log of the quotient of the PLN number and the negative LN number. To date, however, its prognostic value in DMGC patients has not been investigated, nor has a comparison between PLN, LNR, and LODDS classifications in such patients been performed.

Therefore, we aimed to determine whether LODDS could be used as a prognostic indicator based on information derived from the Surveillance Epidemiology and End Results (SEER) database. We also compared PLN, LNR, and LODDS to determine the most suitable classification system for the prognostic assessment of DMGC patients who underwent lymphadenectomy.

2. Methods

2.1. Settings and patients

This was a retrospective study of histologically-confirmed DMGC patients who underwent LN dissection between 2004 and 2012, as recorded in the 2015 release of the public-use SEER database. All patients' demographic and clinicopathological data were retrieved from the SEER database to identify variables that predict survival. Detailed patient inclusion and exclusion criteria are shown in Supplementary Fig. S1. Briefly, eligibility criteria for inclusion in this study were as follows: 1) primary gastric adenocarcinoma confirmed microscopically; 2) diagnosed as M1 disease between 2004 and 2012; 3) palliative operation and lymphadenectomy had been performed with retrieval of at least one node; 4) The type of follow-up expected was limited to 'active follow-up' and 5) patients with the histologic subtypes listed in Supplementary Fig. S1. The National Cancer Institute's SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software, www.seer.cancer.gov/seerstat; Version 8.1.5) was used to access the database. The informed consent and institutional review board approval were not obtained, as this study was a retrospective analysis of a public database.

2.2. Outcome measures

The LNR value was calculated as the PLN count divided by the total number of ELNs [3,6], while the LODDS value was defined as $\log_{10}([PLN + 0.5]/[negative\ LN + 0.5])$ [13]. The classification intervals of the LNR and LODDS values were specified by respectively comparing the cancer-specific survival (CSS) rates determined by these two variables within an initial interval, and then combining the adjacent intervals according to which patient prognosis exhibited no statistically significant difference (Supplementary Tables S1–S2), as recommended by Qiu et al. [15]. The final subgroup definitions of LN-based variables are shown in Supplementary Table S3.

The primary endpoint of this study was gastric CSS, defined as the time period from diagnosis to death due to GC. Data of patients who died of other causes or alive on the date of their last follow-up were censored.

2.3. Statistical analyses

Spearman's correlation coefficient was used to investigate the relationships between the number of ELNs, PLN count, LNR value and LODDS value. The Kaplan-Meier method [16] with log-rank test [17] was used for univariate comparisons of survival. Multivariate analyses were performed using the Cox regression model [18] with the enter method to identify the independent prognostic factors. Factors found to be significant ($P < 0.05$) on univariate analysis were analyzed as covariates in multivariate analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, with an HR of <1.0 indicating a survival benefit.

The suggested criteria for assessing the prognostic performances of the different LN classifications were established by comparing homogeneity, discriminatory ability, and monotonicity [19]. Homogeneity within subgroups refers to small differences in survival among patients within the same LN category. Discriminatory ability is determined by the differences among various LN categories, and monotonicity of gradients is measured by the correlations between categories and survival rates. The likelihood ratio chi-square tests, linear trend chi-square tests, and Akaike information criterion (AIC) analyses were used to compare performances among different LN classification schemes based on homogeneity, discriminatory ability, and monotonicity across categories [19,20]. A higher likelihood ratio chi-square score and a linear trend chi-square score together with a smaller AIC value indicated a more desirable model for outcome prediction. Moreover, the comparison of prediction accuracy for the time point mortality between the LODDS, LNR and PLN was performed using receiver operating characteristics curves (ROCs) with the area under the ROC curve (AUC) values. All statistical analyses were performed using SPSS ver.19.0 (SPSS Inc., Chicago, IL) and MedCalc ver.15.10.0. A value of $P < 0.05$ indicated statistical significance.

3. Results

3.1. Patient selection and characteristics of the entire cohort

The patient selection schema is shown in Supplementary Fig. S1 1999 patients were ultimately included in this study. Detailed patient characteristics are listed in Supplementary Table S4. The median age at diagnosis was 65.0 years; the median survival was 12.0 months, and the 2-year survival rate was 28.4%. Throughout the follow-up period, 1664 deaths occurred of which 1320 were attributable to GC.

3.2. Correlations between the number of ELNs, the PLN count, the LNR value and the LODDS value

The results of Spearman's correlation analyses are shown in Table 1. We found that the PLN count significantly correlated with the number of ELNs ($r = 0.659$). However, no significant correlations between ELN count and either the LNR or LODDS values were observed. A bilateral comparison indicated significant and positive correlations between the LNR value and PLN count ($r = 0.618$), LODDS value and PLN count ($r = 0.706$), and LODDS and LNR values ($r = 0.977$).