

Association Between the Number of Harvested Lymph Nodes and Overall Survival After Gastrectomy for Gastric Cancer: A Retrospective Cohort Study

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Abstract- Gastric cancer remains one of the most prevalent and lethal malignancies globally. Continual advancements in staging modalities aim to optimize prognostic stratification and survival prediction. Among the highly useful approaches that have consistently garnered the attention of researchers is the examination of the lymph nodes of patients undergoing gastrectomy. Studies have shown a strong correlation between the number of involved lymph nodes and patient prognosis; however, other studies have reported insufficient sensitivity and specificity for these findings, which may be attributed to inadequate numbers of lymph nodes being removed during surgery. In this retrospective cohort study, patients diagnosed with gastric adenocarcinoma who were admitted to Sina Hospital between 2017 and 2023 and underwent gastrectomy were included. Demographic information, tumor pathology data, the number of excised lymph nodes, and the number of metastatic lymph nodes were collected. The survival status of the patients was assessed through telephone contact. A total of 118 patients were included in the study. The mean age was 62.59 years, and 78% of the patients were male. The most common tumor location was at the cardia and the gastroesophageal junction. The median tumor size was approximately 3 centimeters, with around 44% of the tumors being poorly differentiated. Approximately 70% of the patients had received neoadjuvant chemotherapy prior to surgery. The median number of resected lymph nodes was 14.0, which did not predict mortality in the analysis. However, the number of positive lymph nodes and the ratio of positive lymph nodes were significantly associated with mortality. Based on the results of this study, the number of positive lymph nodes and the ratio of positive lymph nodes to the total number of excised lymph nodes can be used to predict patient survival. The removal of a sufficient number of lymph nodes aids in accurately staging the disease and facilitates better treatment planning.

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Introduction

Gastric cancer remains a major global health problem. Worldwide estimates indicate that stomach cancer causes over one million new cases and on the order of 700 to 800 thousand deaths annually. Thus, it is ranked among the leading causes of cancer mortality. Contemporary GLOBOCAN analyses and global reviews emphasize the

substantial worldwide burden of gastric cancer and large geographic variation in incidence and outcomes (1,2).

Surgery with curative intent (subtotal or total gastrectomy with regional lymphadenectomy) is the cornerstone of treatment for resectable gastric adenocarcinoma (3). Nodal metastasis is one of the strongest prognostic determinants after gastrectomy. In this context, both the presence and the extent of lymph

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node involvement strongly influence stage, adjuvant treatment decisions, and long-term survival. Accurate nodal staging therefore depends not only on the pathologic status of the nodes removed but also on the adequacy of the lymph node harvest (4,5).

Guidelines and staging systems reflect this dependency. The American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM classification and contemporary guideline statements recommend examination of a minimum number of regional lymph nodes to reduce under-staging. While earlier recommendations used thresholds of at least 15-16 nodes, more recent analyses suggest that higher yields (≥ 20 -30 or more) provide improved staging accuracy and may be associated with better survival in some cohorts (6,7). Nevertheless, the optimal “minimum” number of nodes remains debated and appears to vary by tumor stage, geography, and extent of lymphadenectomy.

Total node count can be affected by surgical technique, the extent of lymphadenectomy, pathologic processing, and the use of neoadjuvant therapy. Hence, several alternative nodal metrics have been proposed to improve prognostic accuracy when node yield is low or variable. Among these, the lymph node ratio (LNR), the proportion of positive (metastatic) nodes among all nodes examined, has shown robust prognostic value in many studies and meta-analyses (8). Other approaches such as log odds of positive lymph nodes (LODDS) have also recently shown promise as potentially superior prognostic classifiers in some cohorts (9).

Despite substantial literature, there remains variability in the recommended minimum number of nodes for adequate staging and the relative prognostic value of total harvested nodes along metrics such as LNR. Local institutional series therefore remain important to characterize practice patterns. Accordingly, the Main focus of the present retrospective cohort study was to assess the association between the total number of lymph nodes harvested and overall survival following gastrectomy for gastric adenocarcinoma. Additionally, we sought to compare the prognostic value of total node count with the absolute number of positive nodes and the lymph node ratio (LNR).

Materials and Methods

Study design

This retrospective study, consecutively enrolled patients with gastric cancer who underwent gastrectomy. From April 2017 to May 2023, patients with gastric malignancy who met the following criteria were enrolled

in the study: 1) Histopathologic diagnosis of gastric adenocarcinoma, 2) Laparoscopic or open gastrectomy 3) survival more than 30 days after surgery, 4) complete clinicopathological data. The surgical operations were performed in Sina Hospital, affiliated with Tehran University of Medical Sciences. Ethical approval for this study was obtained from the ethics committee of Sina Hospital (IR.TUMS.SINAHOSPITAL.REC.1401.104).

Variable and outcome definition

The primary outcome was overall survival (OS), defined as the time from the date of surgery to death from any cause. Demographic variables included age and sex. Comorbidities and tobacco or substance use were also recorded. Tumor-related variables included primary tumor location, tumor size, and tumor differentiation. Pathological tumor stage (pT) was classified according to the 8th edition of AJCC TNM staging system. Lymphovascular invasion and perineural invasion were assessed histologically and coded as present or absent. The total number of lymph nodes resected was recorded for each patient. Nodal involvement was determined by histopathological examination, and both the absolute number of metastatic nodes and the lymph node ratio were calculated. The type of surgical procedure and margin status were determined from pathology and operative reports. Receipt of adjuvant therapy and pathological treatment response was recorded.

Data collection

Based on the electronic records, data regarding patient demographics, histopathologic features of the tumors, lymph node status, postoperative complications and application of neoadjuvant therapies were recorded. Lymph node ratio (LNR) was defined as the ratio of positive to total harvested lymph nodes harvested. The duration of follow-up was the period, in months, between the date of the surgery and date of death or last follow-up.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 22.0). Clinicopathological features were assessed by the Chi-square test. To determine significant associations between clinicopathological characteristics and patients' survival, univariate and multivariate analyses were performed using the Kaplan-Meier method and Cox proportional hazards analysis. Survival based on the number of positive nodes and lymph node ratio were determined using the area under a receiver operating characteristic

(ROC) curve. A two-sided $P < 0.05$ was considered statistically significant.

Results

Initially, 134 patients were identified who underwent gastrectomy for gastric cancer. After excluding 6 patients due to perioperative mortality and 10 patients due to incomplete medical records, 118 patients were ultimately included in the final cohort. The mean age was 62.59 ± 10.59 years, and 92 (78%) were male. Regarding tumor location, the most common site was cardia and gastroesophageal junction (23.9%). Median size of the tumors was 3 (2.5-5.0) cm. In terms of tumor differentiation, poorly differentiated tumors (44.3%) and moderately differentiated tumors (26.4%) comprised the vast majority. A total of 15 (12.7%) patients had an involved margin postoperatively. Considering perineural invasion, there were 44 (41.5%) patients in the positive group. Concerning lymphovascular invasion, there were 44 (38.9%) patients in the positive group. Distribution across overall TNM stages I, II, III, and IV was 28 (25.0%), 35 (31.3%), 34 (30.3%), and 12 (10.7%) patients, respectively. Neoadjuvant therapy had been applied in 79 (69.9%) of the patients. The surgical approach for 52 (49.52%) patients was total gastrectomy and for 23 (21.90%) was subtotal gastrectomy (Table 1).

The median number of harvested lymph nodes was 14.0 (8.0-19.0), with a range from 0 to 51. The median number of positive lymph nodes was 1.0 (0-5.25), with a range from 0 to 32. As demonstrated in figure 1. the

number of lymph nodes retrieved did not differ significantly between patients who were alive and those who had died during the follow-up period ($P = 0.139$). The number of positive lymph nodes and lymph node ratio (LNR) were significantly higher in patients who died during follow-up ($P < 0.001$).

Of the 118 gastric cancer patients, 58 died during the follow-up period. The mean and median survival times were 44.966 ± 3.466 months and 35.2 ± 7.258 months, respectively. Receiver Operating Characteristic (ROC) curve analysis revealed that the total number of harvested lymph nodes was not found to be a significant predictor of survival, yielding an Area Under the Curve (AUC) of 0.421 (Standard Error [SE] = 0.053; $P = 0.136$). This finding was supported by logistic regression, which showed no significant association between the number of harvested nodes and mortality ($P = 0.753$; 95% Confidence Interval [CI]: 0.966-1.025). In contrast, both the number of positive lymph nodes (AUC = 0.755; SE = 0.045; $P < 0.0001$) and the lymph node ratio (LNR) (AUC = 0.773; SE = 0.045; $P < 0.0001$) demonstrated significant predictive power for survival. Optimal cutoff values were determined to be 0.5 for the number of positive lymph nodes and 0.07 for the LNR. In the multivariate Cox regression model (Table 2), the association between both the number of positive lymph nodes and the LNR with overall survival remained significant after adjusting for the effects of other covariates, establishing them as independent prognostic factors (Figure 2).

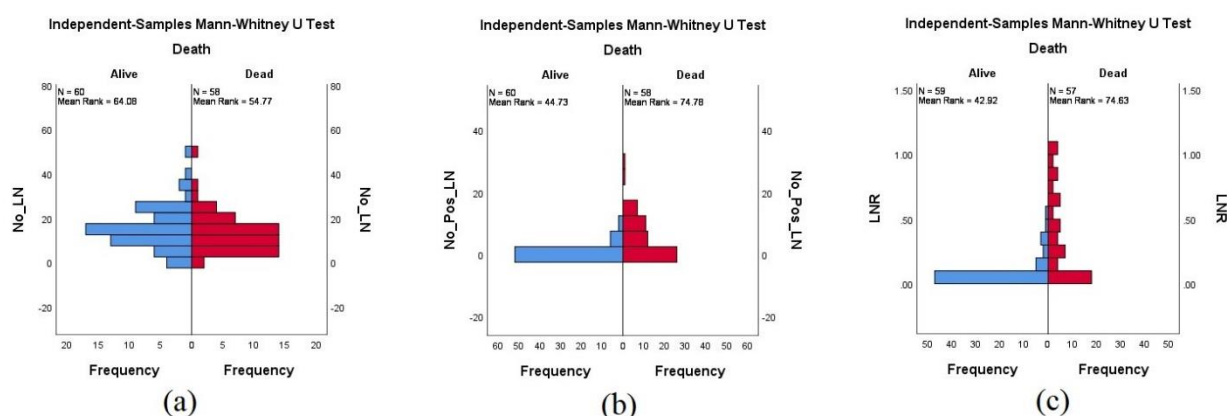


Figure 1. Comparison of (a) number of harvested lymph nodes, (b) number of positive lymph nodes, (c) lymph node ratio, between two groups of patients

Harvested lymph nodes and gastric cancer survival

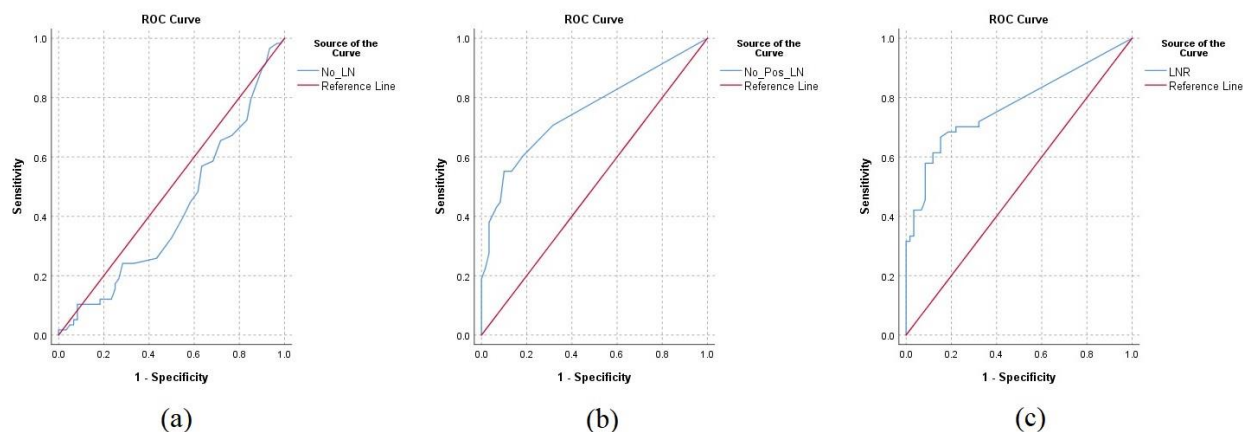


Figure 2. ROC analysis for (a) number of harvested lymph nodes, (b) number of positive lymph nodes, (c) lymph node ratio

Table 1. Baseline patient characteristics

Variable	Total n (%)	Alive n (%)	Dead n (%)
Sex			
Male	92 (78.0)	44 (47.8)	48 (52.2)
Female	26 (22.0)	16 (61.5)	10 (38.5)
Age (years)			
<60	40 (33.9)	19 (31.7)	21 (36.2)
≥60	78 (66.1)	41 (68.3)	37 (63.8)
Anatomical Site			
Cardia/GEJ	27 (23.9)	15 (55.6)	12 (44.4)
Fundus	3 (2.7)	1 (33.3)	2 (66.7)
Body	10 (8.8)	4 (40.0)	6 (60.0)
Antrum	21 (18.6)	13 (61.9)	8 (38.1)
Pylorus	11 (9.7)	2 (18.2)	9 (81.8)
Lesser curvature	21 (18.6)	15 (71.4)	6 (28.6)
Overlapping	20 (17.7)	6 (30.0)	14 (70.0)
Differentiation			
Well	31 (29.2)	18 (58.1)	13 (41.9)
Moderate	28 (26.4)	16 (57.1)	12 (42.9)
Poor	47 (44.3)	16 (34.0)	31 (66.0)
Signet Ring			
Present	19 (6.0)	6 (31.5)	13 (68.4)
pT stage			
T0	7 (5.9)	6 (85.7)	1 (14.3)
Tis	3 (2.5)	3 (100.0)	0 (0.0)
T1a	4 (3.4)	3 (75.0)	1 (25.0)
T1b	9 (7.6)	5 (55.6)	4 (44.4)
T2	22 (18.6)	13 (59.1)	9 (40.9)
T3	58 (49.2)	26 (44.8)	32 (55.2)
T4	17 (14.4)	3 (17.6)	14 (82.3)
N stage			
N0	58 (49.2)	41 (70.7)	17 (29.3)
N1	20 (16.9)	11 (55.0)	9 (45.0)
N2	16 (13.6)	6 (37.5)	10 (62.5)
N3a	12 (10.2)	6 (50.0)	6 (50.0)
N3b	4 (3.4)	0 (0.0)	4 (100.0)
Margin			
Free	103 (87.3)	59 (57.3)	44 (42.7)
Involved	15 (12.7)	1 (6.7)	14 (93.3)
Perineural Invasion			
Present	44 (41.5)	17 (38.6)	27 (61.4)
Absent	62 (58.5)	36 (58.1)	26 (41.9)
Lymphovascular Invasion			
Present	44(38.9)	15 (34.1)	29 (65.9)
Absent	69 (61.1)	40 (58)	29 (42)

Cont. table 1

Metastasis			
M0	91 (88.3)	52 (57.1)	39 (42.9)
M1	12 (11.7)	3 (25)	9 (75)
Neoadjuvant Chemotherapy			
Received	79 (69.9)	44 (55.7)	35 (44.3)
Not received	34 (28.8)	14 (41.2)	20 (58.8)
Stage pTNM			
0	3 (2.7)	3 (100)	0 (0)
IA	9 (8)	7 (77.8)	2 (22.2)
IB	19 (17)	13 (68.4)	6 (31.6)
IIA	19 (17)	12 (63.2)	7 (36.8)
IIB	16 (14.3)	9 (56.3)	7 (43.8)
IIIA	16 (14.3)	6 (37.5)	10 (62.5)
IIIB	16 (14.3)	2 (12.5)	14 (87.5)
IIIC	2 (1.7)	0 (0)	2 (100)
IV	12 (10.7)	3 (25)	9 (75)
Stage yTNM			
I	19 (26)	15 (78.9)	4 (21.1)
II	24 (32.9)	15 (38.5)	9 (37.5)
III	23 (31.5)	6 (26.1)	17 (73.9)
IV	7 (9.6)	3 (42.9)	4 (57.1)
Stage ypTNM			
Complete	6 (5.3)	5 (83.3)	1 (16.7)
Near complete	6 (5.3)	5 (83.3)	1 (16.7)
Partial	23 (20.4)	16 (69.6)	7 (30.4)
No Response	28 (23.7)	9 (32.1)	19 (67.9)
No Treatment	34 (30.1)	14 (41.2)	20 (58.8)
Unknown	16 (14.2)	9 (56.3)	7 (43.8)

Table 2. Multivariate Cox regression for number of positive lymph nodes

	HR (95% CI)	Sig.
Sex (male vs. female)	0.578 (0.262 - 1.275)	0.175
Hypertension	0.634 (0.336 - 1.197)	0.160
Habitual History	0.828 (0.468 - 1.465)	0.516
Positive Lymph Nodes	1.127 (1.082 - 1.175)	0.000

Table 3. Multivariate Cox regression for lymph node ratio

	HR (95% CI)	Sig.
Sex (male vs. female)	1.159 (0.530 - 2.537)	0.712
Hypertension	0.591 (0.314 - 1.114)	0.104
Habitual History	1.388 (0.783 - 2.460)	0.262
Lymph Node Ratio	11.531 (4.996 - 26.616)	0.000

Discussion

In this retrospective cohort of 118 patients who underwent gastrectomy for gastric adenocarcinoma at our center, the total number of harvested lymph nodes (median 14) was not associated with overall survival, whereas both the absolute number of positive lymph nodes and the lymph-node ratio (LNR) were independent predictors of mortality. These findings come from our multivariable Cox models and ROC analyses.

Our results are consistent with a substantial body of literature. Previous evidence shows that metrics which incorporate nodal positivity (absolute positive node count, LNR, and newer measures such as LODDS)

frequently outperform raw examined lymph node (ELN) count for prognostic discrimination. This is particularly prominent when ELN is limited. Meta-analyses and retrospective series have repeatedly demonstrated that a higher LNR is associated with worse overall survival in gastric cancer. Additionally, LNR remains prognostic across a range of ELN yields (8,10). Likewise, recent comparative studies have found that LNR and LODDS can offer improved risk stratification compared with pathological lymph node (pN) or ELN alone (9,11).

There are several, non-mutually exclusive explanations for why ELN (total nodes retrieved) was not prognostic in our cohort while positive node metrics were. First, insufficient median ELN (14 nodes in our

sample) lies below many guideline targets (AJCC recommends ≥ 16 and several groups advise aiming for ≥ 25 -30 when feasible) (7,12). Such lower yields reduce the ability of ELN to discriminate outcome because of stage migration and sampling variability. Second, the high rate of neoadjuvant therapy in our series can reduce node yield through treatment-related tumor regression and nodal fibrosis. Hence, it could lower ELN counts and complicate ELN's prognostic value. Prior studies have shown neoadjuvant chemotherapy is associated with fewer retrieved nodes in a substantial fraction of patients (13). Third, LNR and absolute positive node count directly capture tumor biology. Accordingly, they are less affected by total nodal sampling variability. This explains their stronger and consistent association with survival in our and others' analyses (8,14).

In addition, tumor location and surgical extent may have influenced lymph node yield and its prognostic performance in our cohort. A substantial proportion of tumors in our study were located at the cardia and gastroesophageal junction. In these sites, lymphatic drainage patterns differ from distal gastric cancers and may result in lower nodal retrieval, particularly when extended mediastinal dissection is not routinely performed. Previous studies have shown that proximal gastric and gastroesophageal junction tumors are often associated with fewer retrieved lymph nodes compared with distal tumors (15,16). Furthermore, nearly half of our patients underwent total gastrectomy, while a smaller proportion underwent subtotal gastrectomy. Prior evidence suggests that both tumor location and the extent of gastrectomy can influence the number of examined lymph nodes (15,17). These factors may limit the generalizability of absolute lymph node count thresholds across institutions with different case-mix and operative strategies. Our findings further support the use of lymph node-based metrics that incorporate nodal positivity, such as the lymph node ratio, which appear less sensitive to variations in tumor location and surgical extent.

The cutoff values we identified for positive node count and LNR reflect the distribution in this cohort and the relatively low ELN. Absolute thresholds should therefore be interpreted cautiously and validated externally. Nevertheless, the broad pattern that ELN nonpredictive while positive node metrics are predictive matches prior reports from lower-ELN series and supports use of LNR (or LODDS where available) to supplement TNM staging for prognostication when node harvest is suboptimal (5,18).

Clinical implications arise from these findings. First, when ELN is low (as in our cohort), clinicians and tumor

boards should consider LNR/positive node count when estimating prognosis and planning adjuvant therapy. This approach is supported by recent studies that proposed LNR as an adjunct prognostic index (11,19). Second, our data reinforce the need for institutional efforts to increase nodal yield where feasible through standardized surgical lymphadenectomy templates, surgeon training, and closer collaboration with pathology to optimize nodal retrieval techniques.

Limitations of this study must temper interpretation. The retrospective, single-center design and modest sample size limit generalizability and statistical power. Our cohort's relatively low median ELN and high rate of neoadjuvant therapy reflect local practice and case-mix and may not apply to centers performing routine D2 dissections with intensive pathology retrieval. Follow-up ascertainment by telephone and the lack of cause-specific survival may introduce outcome misclassification. Finally, the optimal LNR or positive-node cutoffs vary across cohorts. Hence, our cutoffs require external validation before clinical adoption.

Strengths of the study include consecutive case inclusion over a recent 6-year period, careful pathological review, and the comparison of several nodal metrics (ELN, positive node count, LNR) using both discrimination (ROC) and survival modeling approaches. Our findings therefore add contextually relevant evidence for centers with similar practice patterns.

In this single-center retrospective cohort of gastrectomy patients, the total number of harvested lymph nodes (median 14) did not predict overall survival. However, both the absolute number of positive lymph nodes and the LNR were independent and significant predictors of mortality. Given the relatively low lymph node yield and the high proportion of patients receiving neoadjuvant therapy in our cohort, LNR (and analogous measures such as LODDS) may provide more reliable prognostic information than ELN alone in similar settings. These findings support using positive-node metrics for risk stratification where node retrieval is limited. Moreover, our results encourage institutional efforts to increase and standardize lymph node harvest for improved staging. External validation and prospective evaluation of interventions to increase ELN are warranted.

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