Clinical significance of the metastatic lymph-node ratio in patients with D2 gastrectomies for gastric cancer

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Abstract

The Union Internationale Contre le Cancer/Tumor, Node, Metastasis (UICC/TNM, 5th edition) Classification established the number of the lymph nodes with metastatic deposits as the determinant factor for nodal category (N category) in patients with gastric cancer. This may suggest that N category could be influenced by the degree to which specimens are pathologically examined and the extension of lymph node surgical dissection. To correct this problem, the Lymph node ratio (LNR), which is the number of positive nodes divided by total number harvested, has been proposed. This study aims to investigate whether the LNR is a better prognostic factor as compared with N category (5th edition) proposed by the UICC in patients with gastric cancer. A retrospective review of a prospectively collected database of 63 patients with gastric cancer who underwent curative D2 gastrectomy between 2003 and 2007 was performed to determine the effect of the LNR on disease-free survival (DFS) and overall survival (OS). Prognostic factors were identified by univariate and multivariate analyses. Survival curves were constructed using the Kaplan-Meier method. The LNR was divided into four categories using the hazard ratio (HR). LNR categories (LNR 0= 0%; LNR 1= 1%–9%; LNR 2= 10%–25%; LNR 3= >25%) were determined by the best cut-off approach. After a median follow-up of 25.1 months (range, 4–32 months), analyzing the survival time comparing the lymph node ratio categories against the N categories (5th edition) demonstrated that the ratio stands out as the best prognostic factor. The implementation of proposed LNR nodal categories led to the identification of groups of patients prognostically more homogeneous than those classified by the UICC proposed nodal categories. Overall survival data according to LNR proposed nodal categories showed a statistically significant decrease in overall survival and disease free survival with increasing scores, which was more statistically significant than that observed with UICC proposed nodal categories (N categories, 5th edition), the LNR also discriminates different prognostic categories among patients with N1 and N2 lymph node involvement. In conclusion, LNR is a simple and reproducible prognostic tool that can stratify patients with gastric cancer. LNR gave a more accurate prognostic information from nodal involvement than the current N category of the TNM (5th edition). These data may represent the rational for improving the prognostic power of current UICC TNM staging system and ultimately the selection of patients who may most benefit from adjuvant treatments.

Introduction:

Lymph node involvement is a well-established prognostic factor for gastric carcinoma.[1,2] The Union Internationale Contre le Cancer (UICC, TNM 4th Edition, 1987) established the distance from the metastatic lymph nodes to the primary tumor as a factor to determine prognostic value from nodal involvement.[3] The Japanese Classification of Gastric Carcinoma (JCGC, 12th Edition) places lymph nodes into three categories according to their anatomical distribution, irrespective of their number.[4] Both classifications used nodal localization, but the system of evaluation is different. This makes it very difficult to compare the survival rates between western and Japanese experiences. In 1997, the UICC (5th Edition) changed their criteria, to use the

number of lymph nodes with metastatic deposits obtained from lymphadenectomy. The new N category established different groups of lymph node involvement (N0: 0, N1: 1–6, N2: 7–15 and N3: >15).[5] This is a simple and reproducible method that allows a comparison with the JCGC and enhances the prognostic information, but it does not provide information about anatomical node situation and it needs the examination of at least 16 lymph-nodes to achieve accurate staging.[3,6,7] There may be a relationship with the total number of removed lymph nodes.[8,9] Moreover, there is the potential for stage migration depending on the degree to which specimens are examined and the extension of lymph node surgical dissection,[10-12] which is classically termed D1, D2 and D3.[13,14] It would thus be useful to establish a corrective method for the number of lymph node metastases based on the total number of resected lymph nodes. The lymph node ratio may give a more accurate prognostic information from nodal involvement than the current N category of the TNM.

According to the Japanese Research Society for Gastric Cancer (JRSGC) guidelines ,[13] the radicality of gastric resections was classified into R0, R1, and R2. R0 stands for surgery after which no residual tumor is left; these operations were accepted to be absolutely curative, R1 is for microscopic and R2 is for macroscopic residual tumor; these operations were accepted to be palliative. The extension of lymph node surgical dissection is classified into D1, D2 and D3. D2 lymphadenectomy is indicated when there is potentially curative gastric tumor without liver or peritoneal metastasis. D2 lymphadenectomy is considered the gold standard procedure as many studies shown that the level of radicality of this procedure is usually found to be R0 in the pathology reports, the morbidity and mortality of the procedure are within the accepted range, and the number of resected lymph nodes is usually >15 which allowed proper staging according to the UICC, TNM 5th Edition, 1997. [12-15]

In this study, we evaluated the validity of LNR, which is the number of positive nodes divided by total number harvested, to stratify patients efficiently into different groups with distinct homogenous prognostic outcomes. We also compared UICC proposed categories for nodal staging (5th edition) versus the proposed lymph node ratio categories as regards to the overall survival rates and disease free survival.

Patients and methods:

We retrospectively reviewed a cohort of sixty three consecutive patients with histologically proven gastric adenocarcinoma who underwent curative resection from May 2003 to October 2007 at Ain Shams University Hospitals. Patients were identified from a prospective database of all patients undergoing therapy for gastric adenocarcinoma. They included 44 males and 19 females; mean age, 56 years (range, 38–69).

Eligibility criteria included histologically confirmed R0 gastric resection (i.e., negative resection margins, en bloc resection of adherent organs, and en bloc resection of greater and lesser omentum), pathologic evaluation of the total number of resected lymph nodes as well as the number of metastatic lymph nodes, absence of distant disease, more than 15 lymph nodes removed and a minimum follow-up of 2 years. Exclusion criteria included patients with distant metastases (e.g., hepatic, lung, peritoneal dissemination) or extraregional lymph nodes (superior mesenteric artery, middle colic artery, and para-aortic lymph nodes), tumors of the gastric stump after gastric resection for benign disease), and cases of post-operative death. All patients with less than 16 lymph nodes were excluded as they may have been inadequately staged by the TNM classification criteria.

D2 gastrectomy was carried out according to Japanese Research Society for Gastric Cancer (JRSGC) guidelines.[13,14] Depending on the location of the primary tumor, total or distal gastrectomy was performed. For advanced cancers of the upper or middle portion of the stomach, and when direct invasion to the pancreas or obvious/ suspected metastasis to the lymph nodes along the splenic artery or the splenic hilum was seen, pancreatosplenectomy or splenectomy was performed with total gastrectomy. Billroth I reconstruction was performed in principle after distal gastrectomy with gastroduodenal

anastomosis by the Albert-Lembert 2-layer technique. Antecolic Roux-en-Y reconstruction was performed after total gastrectomy with esophagojejunal anastomosis using a circular stapler with a 25-mm circumference. In the case of total gastrectomy, an enteral feeding tube was placed distal to the final anastomosis. Two drains were left after gastrectomy, one at the anastomosis and one in the left subphrenic space. **Figures(1-6)** illustrate the technique.

Lymph nodes were recovered by routine mesenteric dissection by the pathologist. The node status was assessed by the same pathologist, who also reviewed the slides of all primary tumors. Lymph node involvement was classified according to the 1997 UICC/AJCC TNM classification (N0 = no metastasis, N1 = 1 to 6 metastatic lymph nodes, N2 = 7–15 metastatic lymph nodes, N3 = more than 15 metastatic lymph nodes).[7]

Figure (1): Roof top incision allowing good exposure of the stomach, lesser omentum, greater omentum and duodenum.

Figure (2): The hepatic flexure of the colon is mobilised and packed out of the way as the duodenum is 'Kocherised'.

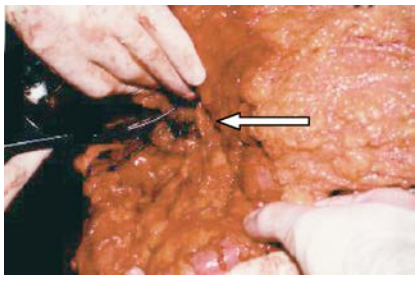

Figure (3): The right gastroepiploic artery is ligated (arrowed) having dissected the subpyloric lymph nodes with it.

Figure (4): Dissection of the lesser omentum.

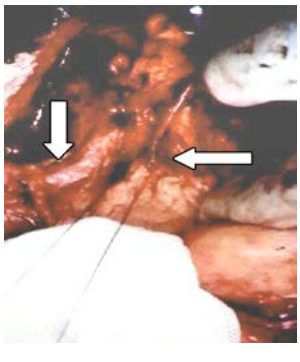

Figure (5): The left gastric vein is encountered and ligated (black arrowed), as dissection proceeds along the superior border of the pancreas. The skeletalised hepatic artery is visible with the gastroduodenal artery (white arrow).

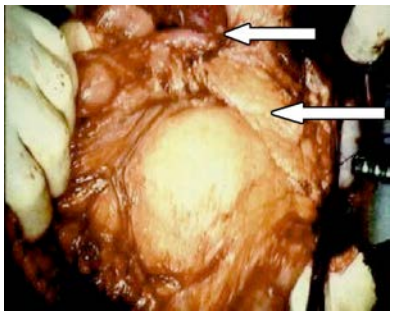

Figure (6): The stomach bed after completion of the lymphatic dissection. The duodenum has been transected and the capsule of the pancreas removed with the specimen. The skeletalised hepatic artery and the coeliac axis can be seen (white arrow), black arrow points to the pancreas.

All patients had follow-up controls at 6-month intervals; the final date of follow-up was October 2007. The median follow-up after surgery was 25.1 months (range, 4–32 months) for all patients (n = 63) and 28.7 months (range, 6–38 months) for survivors (n = 42).

LNR intervals were determined by using the best cutoff approach (a method aimed at minimizing the identification of rare classes of patients) and considering patients' survival (log-rank statistic) as the dependent variable. The functional form of the covariate under study was also evaluated by means of the martingale residual analysis.[16] Both analyses identified the following best-fit cutoff values: LNR 0= 0%; LNR 1= 1%–9%; LNR 2= 10%–25%; LNR 3 >25%. This stratification of LNR aims to evaluate the relative risk of their progressive increase as well as their prognostic significance.

Individual demographic and clinicopathologic data were collected including tumor stage, nodal stage according to the 1997 UICC/AJCC TNM classification, Lauren histological type, and tumor location. In addition, the number of examined lymph nodes, the number of metastatic lymph nodes, and the metastatic LNR (number of metastatic lymph nodes/number of examined lymph nodes) was determined for each patient. Tumors were staged according to the current Union Internationale Contre le Cancer (UICC, TNM 5th Edition, 1997)[5]. Adjuvant therapy was administered according to pathologic stage and physician recommendation.

The primary end points of the study were OS and DFS. OS was defined as the time from the date of primary treatment to the date of death. Perioperative deaths were excluded in the analysis of survival. DFS was defined as the time from primary treatment to the date of first recurrence. Recurrence, whether locoregional or distant, was confirmed histologically or clinically (palpable or radiographically identifiable tumor associated with clinical progression or increasing serum carcinoembryonic antigen level). Postoperative mortality was defined as death occurring during hospitalization or within 30 days of the primary surgery.

Data were collected into a spreadsheet program and then imported into statistical software packages (GraphPad Prism version 4.00 for Windows; GraphPad Software, San Diego, CA, SPSS version 11.5; SPSS Inc, Chicago, IL). Survival curves were plotted by the Kaplan-Meier method. Curves were analyzed by the log-rank method and hazard ratios were reported when applicable. Statistical significance was set at a P value of less than 0.05.

Results:

Patients' demographics showed a male/female ratio of 2.3:1, average age of 56±9.3 years (range 38–69). Predominant tumor localization was the distal third of the stomach with a higher frequency of intestinal forms at the histological examination. Most tumors were locally advanced (serosal involvement). The data of demographics, tumor characteristics, involved lymph nodes for N category (TNM 5th Edition, 1997) and metastatic lymph node ratio are listed in **Table(1)**.

A total of 1575 lymph nodes (mean, 24.7; range, 16–62) were removed and examined. A total of 693 lymph nodes (44.1%) were found to be metastatic (median, 11.5; range, 0–46).

Table (1): Patients demographics and tumor characteristics.

Factor	No. of Patients
All	63
Sex	
Female	19
Male	44
Site	
Lower	32
Middle	17
Upper	9
Cardias	2
Diffuse	3
Lauren histological type	
Intestinal	34
Diffuse	12
Unknown	17
UICC, TNM 5th Edition, 1997 stages	
Stage 1	4
Stage 2	24
Stage 3	26
Stage 4	9
T stage according to the 1997 UICC/AJCC classification	
T1	8
T2	15
T3	19
T4	20
Nodal stage according to the 1997 UICC/AJCC classification	
N0	1
N1	32
N2	21
N3	9
Nodal stage according to LNR	
LNR 0	1
LNR 1	23
LNR 2	28
LNR 3	11

The 2-year OS for the entire population was 62% **Figure(7A)**. The 2-year OS in stages I, II, III, and IV was 100%, 71%, 58%, and 33% respectively (Fig. 7B). OS at 2 years by LNR categories was 100% (LNR0), 87,8% (LNR1), 61.3% (LNR2), and 37% (LNR3).

DFS for the population at 2 years was 51% **Figure(8A)**. DFS at 2 years paralleled tumor stage: stage I 75%; stage II 71%; stage III 42%; and stage IV 11% **Figure(8B)**. DFS at 2 years by LNR categories was 100% (LNR0), 72% (LNR1), 26% (LNR2), and 9% (LNR3). Local and distant recurrence occurred in 19% (12 of 63) of patients at a median of 21±3.5 months; the predominant site of recurrence was the liver.

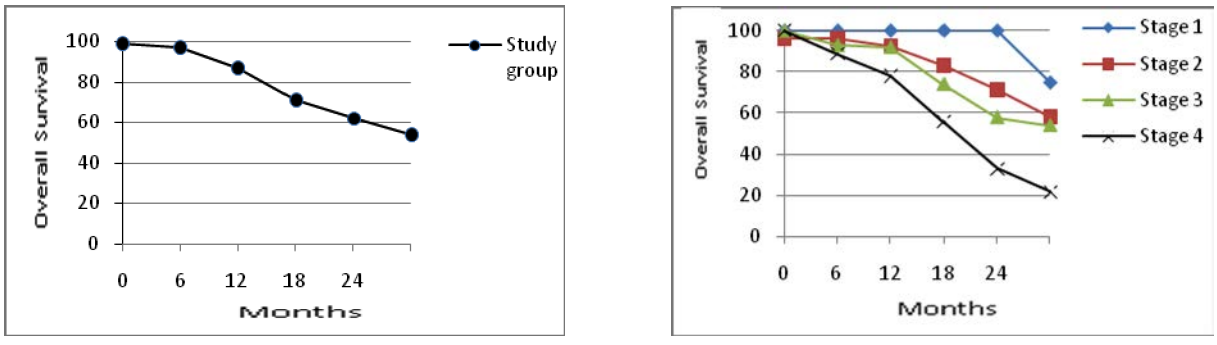

Figure (7): Two-year OS. Kaplan-Meier curves for the entire population (n = 63) show (A)2-year OS for the entire group (61%), and (B)stratified by stage: 100%, 71%, 58%, and 45% for stages I, II, III, and IV respectively.

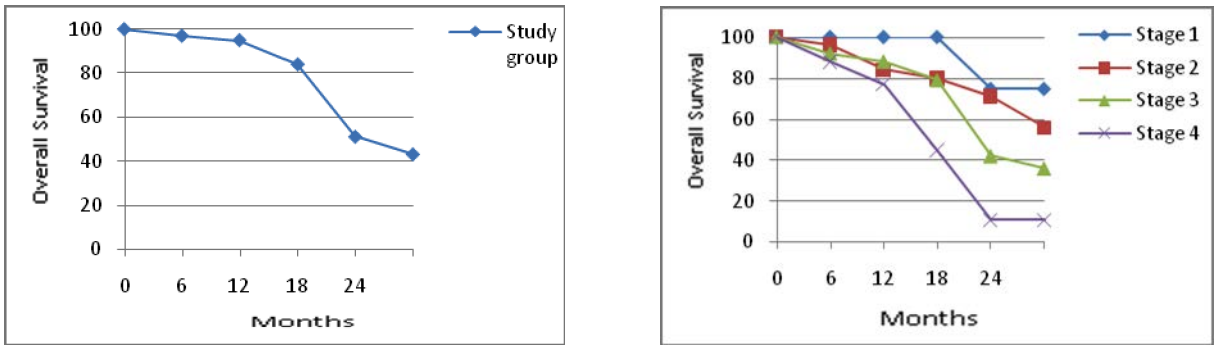

Figure (8): Two-year DFS. (A)DFS for all stages was 51% and (B)DFS by stage is shown: 75%, 71.9%, 42%, and 11% for stages I, II, III, and IV respectively.

LNR categories were determined by using the best cutoff approach and considering patients' survival (log-rank statistic) as the dependent variable. Both analyses identified the following best-fit cutoff categories: LNR 0= 0%; LNR1= 1%–9%; LNR2= 10%–25%; LNR3 >25%.

The distribution of LNR categories (1–3) across the N stage categories (N1, N2, and N3) was evaluated **Table(2)**. All 3 LNR categories were represented in N1 tumors (47.1% LNR1, 41.2% LNR2, and 11.7% LNR3); LNR2 and 3 (but not LNR1) were represented in N2 tumors (8% LNR2 and 62% LNR3); and only LNR3 was represented in N3 tumors **Table(2)**.

Table (3): Metastatic/examined nodes ratio distribution among TNM staging system categories.

	Metastatic/Examined Nodes (Lymph Nodes Ratio)				
	LNR 0 (0%)	LNR 1 (0%–9%)	LNR 2 (10%–25%)	LNR 3 (>25%)	
N0 (0)	1 (100%)				1 (100%)
N1 (1–6)		16 (47.1%)	14 (41.2%)	4 (11.7%)	34 (100%)
N2 (7–15)		0 (0%)	8 (38%)	13 (62%)	21 (100%)
N3 (>15)				9 (100%)	9 (100%)

We compared UICC proposed categories for nodal staging versus the proposed lymph node ratio categories as regards to the overall survival rates **Figure(10)** and disease free survival **Figure(11)**.

In **Figures(10&11)**, the similarity between the overall survival rates and disease free survival plotted according to UICC proposed nodal categories versus LNR proposed nodal categories was observed for N1 versus LNR1, but the others two curves change considerably.

The implementation of proposed LNR nodal categories led to the identification of groups of patients prognostically more homogeneous than those classified by the UICC proposed nodal categories. Overall survival data according to LNR proposed nodal categories showed a statistically significant decrease in survival with increasing scores. OS was significantly lower in the group of patients with a LNR3 in relation to LNR1 and LNR2 categories (P<0.001), this was more statistically significant than OS drop observed with UICC proposed nodal categories (P<0.05) **Figure(10)**. Similarly, when the data were analyzed for DFS, patients in the LNR3 category had a worse DFS (P< 0.001) in relation to LNR1 and LNR2 categories, which, again, was more statistically significant than that observed with UICC proposed nodal categories (P<0.05), **Figure(11)**.

The mean number of resected lymph nodes in each categories of the metastatic lymph node ratio curve was similar: LNR1=22.3±5.9, LNR 2=27.4±11.1 and LNR 3=26.2±13.1. These numbers show that the radicality of surgery was similar in each category.

Figure (10): Overall Survival according to the nodal involvement. (A) N categories (TNM, 5th Ed.). (B) Metastatic lymph node ratio categories.

Figure (11): Disease Free Survival according to the nodal involvement. (A) N categories (TNM, 5th Ed.). (B) Metastatic lymph node ratio categories.

As shown in **Figure(12)**, the use of LNR allowed us to identify subsets of patients with significantly different 2-year OS both within the N1 stage (three subsets identified; P-value <0.05) and within the N2 stage (two subsets identified; P < 0.001).

Figure (12): Overall survival curves for different LNR among N1 (A) and N2 (B) patients.

Discussion:

Staging systems are useful to define the patients with high risk and low risk. They are also useful for standardization of results and selection of prognostically homogenous groups for proper comparisons between different patient populations and for better assessment of different therapeutic strategies.[17] A staging system reduces all the clinical problems of including lots of variables to a simple number. With the help of this information, patients may be selected for adjuvant therapy protocols and some decisions such as intervals of follow-up can be made.

The presence or absence of lymph node metastases is an important predictor of survival in gastric cancer. The Union Internationale Contre le Cancer/Tumor Node Metastasis (UICC/TNM) 1997 Classification established the number of the positive lymph nodes as a factor to determine prognostic value from nodal involvement.[5] The new N category established different groups of lymph node involvement (N0: 0, N1: 1–6, N2: 7–15 and N3: >15).[5] This is a simple and reproducible method that allows a comparison with the JCGC and enhances the prognostic information, but it does not provide information about anatomical node situation and it needs the examination of at least 16 lymph-nodes to achieve accurate staging.[3,6,7] However, there is the potential for stage migration depending on the degree to which specimens are examined and the total number of lymph nodes harvested.[10-12] For this reason, the LNR, which is the number of positive nodes divided by total number harvested, has been proposed as a potentially more accurate prognostic indicator in gastric cancer[18-22] and other solid tumors.[23-25] Some of the additional advantages probably achieved with LNR are the quantification of the surgical clearance of the lymphatic system and the improvement of the prognostic information for cases with less than 15 dissected lymph nodes. This problem has been identified by Mullaney et al., who found that only 31% of surgically resected cases could be assessed accurately according to the TNM system suggesting the need of an improved nodal staging.[26]

This study included 63 patients who underwent R0 D2 gastric resections for histologically proven gastric cancer. In this cohort, it was showed that the LNR is a better predictive of OS and DFS than the nodal categories of the UICC/TNM 5th edition classification. The analysis of nodal involvement using the lymph node ratio have maintained the prognostic information proposed in the 5th edition but corrected for the number of dissected lymph nodes.

In this study, analyzing the survival time comparing the lymph node ratio categories against the number of involved lymph nodes (the N category, 5th edition) demonstrated that the ratio stands out as the best prognostic factor. The implementation of proposed LNR nodal categories led to the identification of groups of patients prognostically more homogeneous than those classified by the UICC proposed nodal categories. Overall survival data according to LNR proposed nodal categories showed a statistically significant decrease in overall survival and disease free survival with increasing scores, which was more statistically significant than that observed with UICC proposed nodal categories, the LNR also discriminates different prognostic categories among patients with N1 and N2 lymph node involvement.

Several authors have already suggested the role of the lymph node ratio as a prognostic factor proposing different levels of cutoff for its staging. Siewert et al., evaluated the results of the German Gastric Cancer Study in 1654 patients identifying the metastatic lymph node ratio (<20 and >20%) and the presence of residual tumor as the two best independent prognostic factors in patients with surgically removed gastric cancer.[27] Kodera et al., analyzed 656 patients with advanced gastric cancer that underwent a D2 lymphadenectomy and found significant prognostic differences in the metastatic lymph node ratio with levels of 0, 1–19, 20–60 and >60%.[21] Kwon et al., established different stages (1–15, 16–30, >30%) although they did not find differences between 16–30 and >30%.[22] Kim et al. found significant differences in survival for stages of 0, 1-10, 11-20, 21-50 and >50%.[28] Takagane et al., established stages of 0, 1–9, 10–24 and >25% with significant differences for each group.[29] Inoue et al., compared N of the

UICC/AJCC 1997 with a classification based on the metastatic lymph node ratio (0, 1-25, 26-50 and > 50%) in patients that underwent a R0 resection, using Cox's regression analysis and identified that the metastatic lymph node ratio is the most important prognostic factor.[18] The problems observed in the different proposed categories for LNR were also previously reported by Roder as regard the N categories (number of involved lymph-nodes).[3]

Using the log-rank test and the Martingale residual analysis,[16] which avoids the identification of rare classes of patients, we found that the best-fit cutoff values were 0%, 1% to 9%, 10% to 25%, and >25%. These cutoff values are similar to those reported by Nitti et al., who studied 277 gastric cancer patients after D2 lymphadenectomy.[19]

Taken together, these findings suggest that a ratio-based system for classifying gastric cancer is a simple method with powerful prognostic significance. The LNR may serve to decrease stage migration, which could occur when variable numbers of lymph nodes are harvested or if an inadequate number of nodes are examined.[30-32]

Conclusion:

The N category (5th Edition) has several limitations and should not be the only criteria to evaluate the prognostic value of nodal involvement. The information achieved from the lymph node ratio provides a more precise prognosis. An exhaustive evaluation of the lymph node ratio is needed to demonstrate its advantages.

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