

Metastatic lymph node ratio versus number of metastatic lymph nodes as a prognostic factor in gastric cancer

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Abstract

Objective: Knowledge of prognostic factors in gastric cancer is essential to decide on single patient management. We aim to establish the value of lymph node ratio compared to lymph node involvement in the prediction of gastric cancer survival and treatment approach.

Methods: Charts of ninety-six consecutive patients undergoing gastrectomy for resectable gastric cancer were reviewed between January 1996 and December 2005. Receiver operating characteristic (ROC) curves were plotted to verify the accuracy of metastatic lymph node ratio (MLNR) and number of metastatic lymph node (NMLN) cut-off values for survival prediction. Patients were divided into two groups according to ROC curve cut-offs and accuracy in prognosis was reviewed.

Results: ROC curves showed that 5 metastatic nodes and a node ratio value of 20% had the best survival prognostic correlation. The median survival of patients with MLNR and NMLN were similar according to cut-off determinations ($\leq 5 / > 5$ metastatic nodes and $\leq 20 / > 20\%$ lymph node ratio). Five-year survival rates were 70.9% vs 17.1% and 72.4% vs 15.6%, respectively ($p < 0.001$). Positive correlation coefficient was found between the number of excised nodes and the number of metastatic nodes.

Conclusion: Number of metastatic lymph nodes showed greater accuracy than lymph node ratio for survival prediction in gastric cancer. © 2012 Elsevier Ltd. All rights reserved.

Keywords: Gastric cancer; Lymph node ratio; TNM staging; Postoperative survival

Introduction

One of the most important goals in gastric cancer has been greater accuracy in defining survival prognostic factors. Physicians and surgeons still pursue solid criteria to define worse patient prognosis, adjuvant therapy being the only effective option for those with poor outcome. Lymph node affection is probably the most important prognostic factor. Variability in lymphadenectomy extension is found between studies, however proper staging requires the harvest of at least 15 lymph nodes.^{1,2} Lately, many authors

have suggested that the metastatic lymph node ratio (MLNR) is a more precise prognostic factor than the number of metastatic nodes. These authors defend MLNR as the best classification system to predict patients' survival, avoiding stage migration factor,^{3–8} although it is still not used in comprehensive clinical guidelines. Furthermore, the number of harvested lymph nodes depends on several factors such as the extension of the lymph node dissection or the depth at which specimens are examined.⁹ It is well known that the number of affected lymph nodes is directly related to the number of lymph nodes excised, although this relationship has not yet been well established and varies greatly between series. The aim of this article was to discuss the relationship between both prediction factors and to highlight a critical cut-off value as the main prognostic factor. To achieve this purpose, we have compared the accuracy between MLNR and NMLN using receiver

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operating characteristic (ROC) curves to evaluate the predictive survival value.

Patients and methods

Patients

A total of 96 consecutive patients undergoing gastrectomy for resectable gastric carcinoma between January 1996 and December 2005 were reviewed and included in our study. All cases underwent a total or subtotal gastrectomy with an en-bloc D2 lymphadenectomy, R0 resection, no evidence of distant disease and the analysis of more than 15 lymph nodes. All patients with metastatic lymph nodes completed an additional chemotherapy schedule based on alkylating agents and Fluorouracil. All surgical resected specimens were analyzed according to a specific pathology schema. Additional histologic prognostic factors directly related with gastric cancer survival were analyzed: age, gender, histological type (diffuse, intestinal and mixed) and differentiation grade (G1 and G2–3). The median follow up was 72 months.

Method

The survival accuracy of each group was evaluated by using ROC curves, frequently used to evaluate diagnostic procedures, where sensitivity is plotted against 1-specificity. Two cut-off points for MLNR and NMLN related to survival prediction were obtained. Two sets of patients with different prognosis were created for each group. Our study's main endpoint was to analyze overall survival after 5 years follow up in both groups and the interaction between MLNR and NMLN for survival prediction. A linear correlation was used to evaluate the relationship between involved and isolated lymph nodes. In addition, logistic regression curves were plotted to measure the increasing mortality percentage for every additional affected lymph node. Radicalness of surgery was considered similar in both groups.

Statistical analyses

The prognostic significance of MLNR and NMLN was determined by univariate analysis; Chi-square test and *t*-student – *U* Mann–Whitney tests were used for testing differences between two case series, qualitative and quantitative variables respectively. Spearman's correlation coefficient was calculated to assess the correlation between involved and isolated lymph nodes, $p < 0.05$ was considered significant. ROC curves were plotted to define cut-off points in order to discriminate survival. Kaplan–Meier method was used to analyze survival and log-rank test to compare MLNR and NMLN groups.

The risk of mortality for an increasing number of affected nodes was analyzed by logistic regression method. Statistical analysis was performed with SPSS software (Version 10.0; SPSS, Chicago, IL).

Results

Clinical and pathological data

Patients were predominantly men and average age was over 60 years in both groups, the oldest in the best prognosis group. Histological differentiation grade showed statistical difference between well and moderate to bad differentiation in both groups (12.7% vs 0% in MLNR groups and 13.7% vs 0% in NMLN groups, $p < 0.05$). The same occurred with the histological type with a greater proportion of intestinal type in the better prognosis group, a higher number of mixed type in the second group, and no differences for the diffuse histological type (28.8% vs 30% in MLNR groups and 29.2% vs 39.5% in NMLN groups, $p < 0.05$), (Tables 1 and 2).

Correlation between involved and isolated lymph nodes

There was a positive correlation between the number of excised nodes and the number of metastatic nodes ($p < 0.001$), however an r_s of 0.445 suggested low clinical significance (Fig. 1).

Cut-off and 5 years overall survival prediction (ROC curves)

Throughout the ROC curves we found that 5 positive lymph nodes and 20% metastatic lymph node ratio defined better discriminative value between overall survivors and

Table 1
Baseline of clinical and histopathological records with univariate analysis for lymph node ratio <20% and \geq 20%.

Factor	Category	MLNR <20%	MLNR \geq 20%	<i>p</i> value
Total cases		55	41	–
Age (years)		67 (35–88)	61 (40–86)	0.018
Gender				
	Men	37	27	ns
	Women	18	14	
Histological grade ^a				
	G1	7	0	0.029
	G2–G3	48	40	
Histological type ^a				
	Diffuse	15	12	0.006
	Intestinal	29	11	
	Mixed	8	17	
Examined lymph nodes		23.7 (15–48)	30.1 (16–67)	ns
Accumulated 5 years overall survival		71.4%	16.1%	<0.001

MLNR group <20%; Metastatic lymph node ratio <20%, MLNR group \geq 20%; Metastatic lymph node ratio \geq 20%. Histological grade; G1 (well differentiation), G2–G3 (moderate to bad differentiation).

^a Data were not available in all cases. Rank expressed in parentheses. ns = not significant.

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