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Prognostic assessment of gastric cancer: retrospective analysis of two decades

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Summary. *Background*: Gastric cancer mortality rates have remained relatively unchanged over the past decades, in spite of progressive decrease in incidence. Nodal status represents a key factor for prognostic assessment, allowing a tailored-made adjuvant therapy for the patients. The aim of this study is to evaluate the prognostic influence of different nodal involvement indicators on the overall survival in a large series of patients submitted to gastrectomy at our Institution. *Methods*: we retrospectively collected data from 634 newly diagnosed patients with gastric cancer who underwent curative gastrectomy, with D1/D2 lymphadenectomy during the last 20 years. Prognostic values of age, histologic type, pN, nodal ratio (LNR) and log odds of positive lymph nodes (LODDS) of were analyzed. *Results:* The median overall survival was 40.2 +/-31 months. Multivariate analysis identified age at diagnosis, diffuse-type tumor, pN and LODDS as independent predictors of worse prognosis. Scatter plots of relationships between LODDS and LNR showed that LODDS seems to better assesses prognosis for patients at LNR stage 0 or 1. *Conclusions:* Nodal involvement confirmed to be a strong indicator of prognosis. LODDS demonstrated a theoretical advantage over pN and LNR system allowing more accurate patients stratification, but our results have to be confirmed by further trials. (www.actabiomedica.it)

Key words: gastric cancer, gastrectomy, survival, lymphadenectomy

Introduction

Gastric cancer represents the second leading cause of cancer-related death in the world (1). Although the incidence of gastric cancer has been substantially declining for several decades, it remains a major cause of cancer mortality because of its poor prognosis (2).

Adequate surgical resection is still the only curative therapeutic option for gastric cancer, even though recent progress in adjuvant therapies has led to improvement in overall survival (3). The lack of a reliable and non-invasive screening test has prevented any considerable improvement in early diagnosis, such as for colon cancer (4, 5), compromising an additional factor for prognosis amelioration (6). Therefore, it is crucial to identify reliable indicators of prognosis to set the therapeutic strategy. The prognosis of patients with gastric carcinoma is determined by a series of tumor and patient-related factors (7, 8); in particular, the evaluation of metastatic lymph nodes has always been considered a key factor for prognostic assessment (9-11). Not only does lymph node harvest represent a marker of tumour aggressiveness, but also a reliable indicator of surgical quality (3). The UICC/AJCC staging system classifies the nodal stage (pN) according to the number of metastatic nodes, but the N staging still presents some drawbacks, such as not considering the number of lymph nodes retrieved (12-14).

Ratio-based node staging (LNR) was introduced to minimize stage migration of pN, but its prognostic superiority to pN is still subject of debate (15-19).

Log odds of positive lymph nodes (LODDS) is another novel node staging system that has recently been proposed. LODDS is defined as the natural logarithm of the ratio of the probability of a lymph node being positive to the probability of a lymph node being negative, when a single lymph node is retrieved. Several studies have shown that LODDS suffers much less from stage migration and it is more reliable than the pN or LNR classifications in gastric cancer patients, when insufficient numbers of lymph nodes have been retrieved (16-19).

In light of these considerations, the aim of our study was to evaluate the prognostic influence of different nodal involvement indicators on the overall survival in a single Institution large series of patients submitted to curative (R0) gastrectomy during two decades.

Methods

Study Protocol and Data Collection

The medical records of patients diagnosed with primary gastric carcinoma and treated at the Parma City Hospital between 1991 and 2010 were retrospectively reviewed. Patients were identified by reviewing data from the Cancer Registry of our institution. A database of patients with a histological diagnosis of primary gastric adenocarcinoma was created. Exclusion criteria were: non-adenocarcinoma diagnosis, history of malignancy, gastric stump cancer, esophagogastric junction cancer (Siewert I and II), preoperative chemotherapy. Follow-up data were obtained from the Parma Tumor Registry and the patient clinical charts.

Demographic and clinical data (age, gender), surgical data (type of operation, perioperative morbidity and mortality), pathological data (tumor location; histotype according to the Lauren Classification (20); tumor grade; tumor, node, and metastasis (TNM) staging according to the American Joint Committee on Cancer (AJCC) (7th Edition) (12, 13); number of lymph nodes examined; number of lymph nodes positive; lymph nodes ratio;), and adjuvant chemotherapy and radiotherapy were collected. Tumor location was divided in proximal, defined as lesion of the corpus/fundus and distal, defined as lesion of the antrum.

Lymph node ratio (LNR) was calculated by dividing the total number of lymph nodes harboring metastases by the total number of examined nodes. The LNR ranged from 0 to 1 and was classified as follows: LNR0, 0; 0.01<LNR1<0.2; 0.21<LNR2<0.5; LNR3>0.51; in accordance to Sun et al (21, 22).

LODDS were calculated by Log (positive nodes + 0.5)/(total examined nodes − positive nodes + 0.5) [loge([pN + 0.5]/[nN + 0.5])], where 0.5 is added to both the numerator and the denominator to avoid an infinite number. Values of LODDS were classified as follows: LODDS0<−1; −1≤LODDS1<−0.5; −0.5≤LODDS2<0; 0≤LODDS3<0.5; LODDS4≥0.5, according to the classification published by Xu et al (23).

Statistical Analysis

Data were analyzed using the SPSS software (version 22.0; SPSS, Inc., Chicago, IL, USA). Survival analysis was performed using the Kaplan–Meyer method. Possible prognostic factors influencing survival were first evaluated by univariate analysis (log–rank test). Only parameters which showed significance by univariate analysis were further analyzed by multivariate analysis (Cox proportional hazards test, method forward-conditional). Statistical significance was defined as a p value of less than 0.05.

Results

Clinical and pathological findings

The records of 634 patients with primary gastric carcinoma were reviewed, of whom 388 were male (M:F=1.58). The mean age at diagnosis was 70.8 years (range: 25-93). Age-specific incidence rates rise sharply from around age 60-64, peak in the 85-89 age group and subsequently drop in those aged 90+. Incidence rates are higher for males than for females in all age categories. Figure 1 shows the trend for age at

diagnosis characterized by a progressive increase from 1991 to 2010 (r2 = 0.01657 IC95% 0.1144 - 0.4607, p = 0.0012). The results indicate an increase in this parameter with a male-specific prevalence (r2 = 0.03022 IC95% 0.1639 - 0.5937, p = 0.0006 – Fig. 2).

The majority of cancers was proximal (65.6%) with a slight prevalence of diffuse-type tumor according to Lauren classification (53.9%).

Patients most frequently had stage I disease (stage I, 65.2%; stage II, 21.1%; stage III, 13.7%). The TNM staging and pathological data are summarized in Table 1.

Presence of nodal involvement (N+) was reported in 377 patients (59.5%) and lymphadenectomy was considered adequate for 474 patients (74.7%).

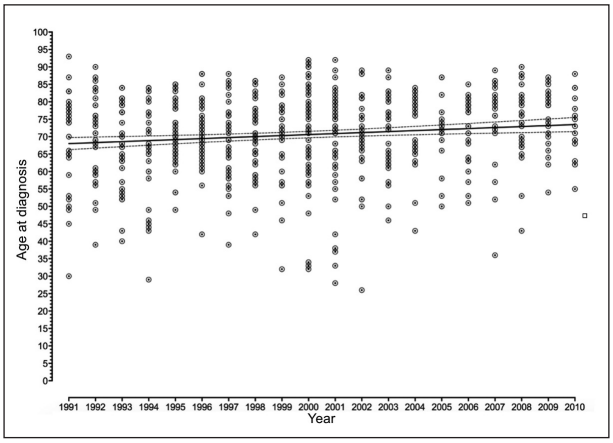

Figure 1. Trend for age at diagnosis

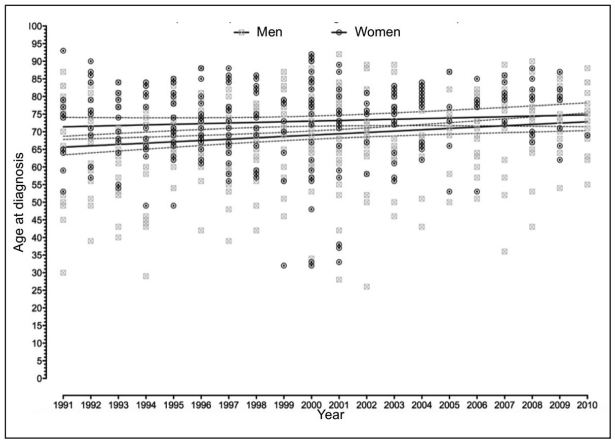

Figure 2. Trend for age at diagnosis by gender

Table 1. Clinical and pathological data

n=634		%	p value
Age (years)	70.8 (25-93)		0.004
< 50	38	6.0	
50-59	64	10.1	
60-69	166	26.2	
70-79	217	34.2	
≥ 80	149	23.5	
Gender			
Male	388	61.2	
Female	245	38.8	
Location			
Upper third	416	65.6	
Middle-lower third	218	34.4	
Surgical procedure			
Total gastrectomy	483	76.2	
Distal gastrectomy	151	23.8	
Histological Type			0.003
Intestinal	292	46.1	
Diffuse	342	53.9	
Tumor grading			
G1-G2	226	35.6	
G3-G4	408	64.4	
TNM stage			0.005
I	413	65.2	
II	134	21.1	
III	87	13.7	
Number of LNs retrieved			
<15	160	25.3	
>15	474	74.7	
pN			<0.0001
N0	257	40.5	
N+	377	59.5	

Survival analysis

Median follow-up was 35 months. The median overall survival was 40.2 +/-31 months. The overall actuarial survival at 3 and 5 years was 33 % and 21%, respectively.

At univariate analysis, age at diagnosis (p 0.004), histologic type (p 0.003), TNM stage (p 0.005) and lymph node involvement (p<0.0001) resulted as being

associated with significant decrease in overall survival (Table 1; Fig. 3-6). In particular, the curves demonstrate a different trend for stage I and II in early and middle-term observation, then their tendency becomes similar (Fig. 5). Regarding nodal involvement, pN, LNR and LODDS staging system demonstrated a significant association with prognosis ($p<0.0001$ for all).

Multivariate analysis identified age at diagnosis, diffuse-type tumor, pN and LODDS as independent predictors of worse prognosis (Table 2).

LODDS was positively correlated to pN and LNR (Fig. 7-8) with a similar patient distribution (except less than 10 positive nodes or LNR=0 or 1).

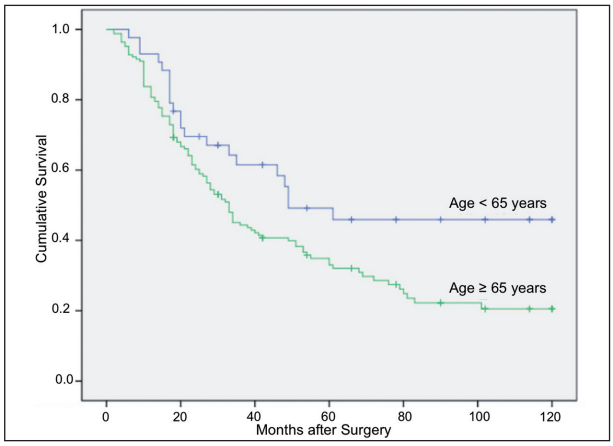

Figure 3. Kaplan-Meier overall survival depending on age at diagnosis

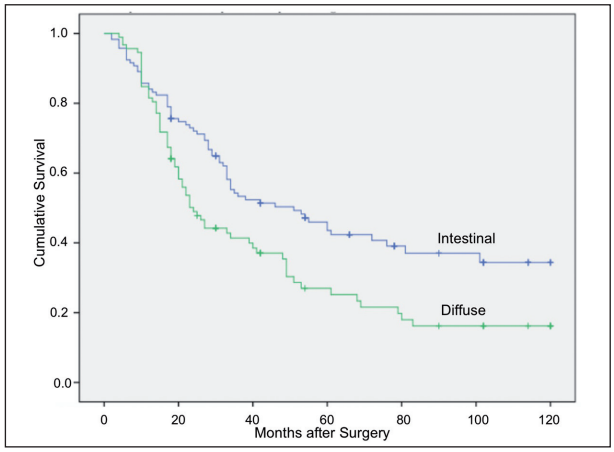

Figure 4. Kaplan-Meier overall survival depending on histotype

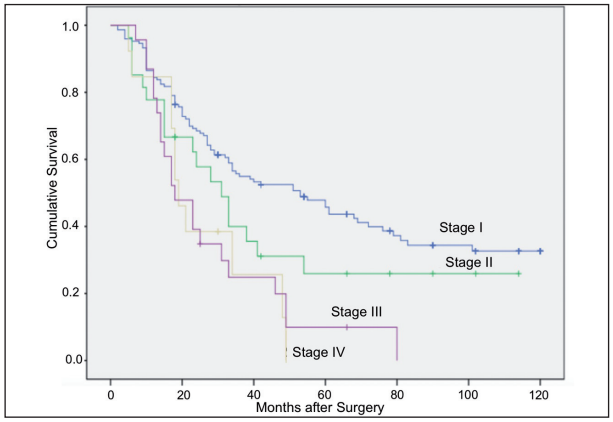

Figure 5. Kaplan-Meier overall survival depending on TNM stage

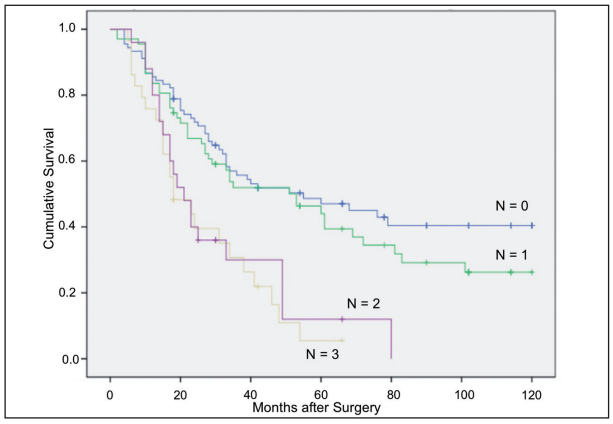

Figure 6. Kaplan-Meier overall survival depending on pN

Discussion

Gastric cancer is the fourth most common cancer worldwide and despite its decreasing incidence, it represents the third leading cause of cancer-related death (1-3). Although the survival rate for gastric cancer has steadily improved in countries such as Japan, substantial mortality associated with gastric cancer has remained stable despite technical advances in surgery and the use of new protocols of adjuvant therapy (24). In recent years the experience of bariatric surgery (25) contributed to developing minimally invasive approaches for gastric resections, allowing better postoperative recovery and a reduced incidence of ventral hernias (26). However, a complete loco-regional tumor removal with adequate margins of clearance (R0 re-

Table 2. Multivariate analysis

	HR	IC 95%		Sig.
		LI	LS	(p. value)
Age> 65	2,088	1,274	3,422	**0,004**
Gender				
Male (Ref)				
Female	0,916	0,632	1,325	0,640
Location				
Upper-middle third (Ref)				
Lower third	1,093	0,723	1,654	0,673
Histologic type				
Intestinal (Ref)				
Diffuse	1,62	1,116	2,341	**0,011**
TNM Stage				
I (Ref)	1,000	-	-	-
II	1,497	0,899	2,493	0,121
III	2,485	1,313	4,703	**0,005**
IV	2,545	1,567	4,133	**0,000**
T (T0 Ref)				
T 1	1,586	0,380	6,611	0,527
T 2	1,688	0,389	7,333	0,485
T 3	1,479	0,335	6,526	0,605
T 4	5,886	0,775	44,642	0,086
N				**<0.0001**
N0 (ref)	1,000	-	-	-
N1	1,227	0,801	1,880	0,347
N2	3,169	1,828	5,494	**<0,0001**
N3	2,373	1,333	4,225	**0,003**
LOODS				**<0.0001**
1 (Ref)	1,000	-	-	-
2	1,685	1,125	2,522	**0,011**
3	3,174	1,842	5,471	**0,000**
4	3,130	1,315	7,450	**0,010**

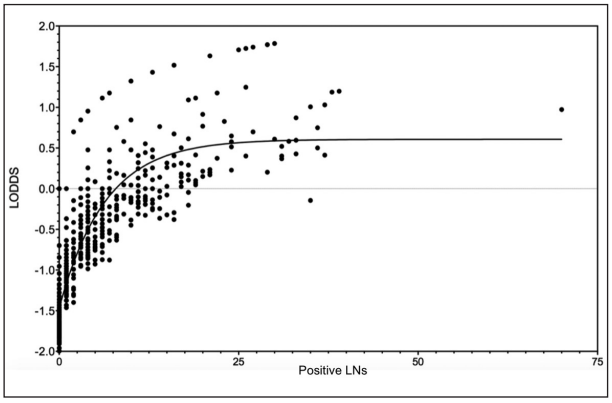

Figure 7. Scatter plot of relationship between LODDS and the number of lymph nodes involved

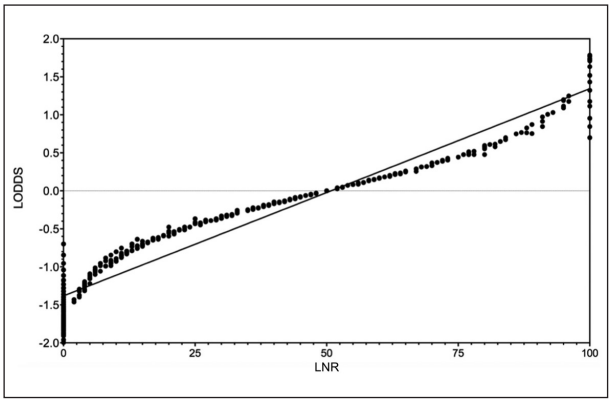

Figure 8. Scatter plot of relationship between LODDS and nodal ratio

section) is widely accepted as the major surgical factor for reduction of loco-regional tumor recurrences and improvement of survival (7,9).

Our study assessed a population of 634 patients submitted to curative gastrectomy for cancer. The large number of patients allowed a multivariate analysis to identify the frequently interrelated factors that independently influence survival, and permitted analysis of subgroups with different prognosis. Our results showed that age at diagnosis, histologic type, TNM stage, pN, LNR, and LODDS were strongly and significantly associated with overall survival. Information on lymph-node involvement in gastric cancer has a great clinical impact. Lymph node dissection of at least 15 lymph nodes is recommended for optimal staging of gastric cancer, according to the AJCC and NCCN guidelines (12, 27), in order to avoid staging migration, but the reasons for an insufficient number of tested lymph-nodes are related not only to the extent of lymphadenectomy but also to several biologic factors, reducing the prognostic predicting value of pN system (3). The LNR system, considering both the number of lymph-nodes involved and the total number of lymph-nodes retrieved, has the power to minimize the staging migration in case of insufficient number of tested lymph-nodes, therefore is considered superior by some authors (28). On the other hand, some authors assert that patients would not benefit from the ratio-based classification system, since the definition of the LNR0 classification was congruent with the pN0 classifica-

tion (22, 24, 29, 30). As expected, both the pN system and the LNR system were associated with overall survival, but LNR failed to predict the prognosis at multivariate analysis, demonstrating weaker association than the pN system. More recently, the LODDS system has been proposed for a more accurate definition of metastatic nodal involvement, in particular for breast, colon and gastric cancer (31, 32). The LODDS system is more complicated and difficult to interpret, since there is no standard categorization of LODDS values (33). Many studies compared the discriminatory capacity and the predictive accuracy of the three staging methods and assessed that LNR and LODDS are superior when an insufficient number of lymph nodes are analyzed (15-19, 22, 23). Comparing LODDS and number of metastatic nodes or LNR system, we found a close but not linear correlation. The value of LODDS increased as the number of nodal metastasis increased, indicating that there was close correlation between LODDS and pN. However, for patients with few lymph node metastasis (less than 10), it increased slower than LODDS, suggesting that the LODDS system might be better than the pN classification for discriminating patients with different prognosis, especially for those with less than 10 nodes with metastasis. Similarly, when the LNR was <0.15 the LNR curve increased at a slower rate vs. the LODDS, indicating that LODDS could be superior to LNR in predicting long-term survival. Moreover, when LNR was 0 or 1, the value of LODDS was still heterogeneous, suggesting that the LODDS system could discriminate different survival outcomes for patients with the same LNR category, especially for LNR score 0 or 1. This result has been confirmed by the multivariate analysis, showing the independent prognostic predicting value of LODDS system.

Our study presents a limitation due to the retrospective analysis of two decades because we cannot describe a homogenous surgical treatment and a standardized histopathologic analysis over the years.

In conclusion we confirmed the fundamental role of lymph node involvement as prognostic indicator. Furthermore, LODDS demonstrated a theoretical advantage over the pN and LNR systems, since it allows more accurate stratification of patients.

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