MEDDOCS Open Access Publisher

ISSN: 2637-4501

Annals of Gastroenterology and the Digestive System

Open Access | Research Article

Can the Metastatic Lymph Node Ratio Influence the Prognosis of Patients with Gastric Cancer? Preliminary Data of a Monocentric Study

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Received: Nov 09, 2020

Accepted: Dec 14, 2020

Published Online: Dec 17, 2020

Journal: Annals of Gastroenterology and the Digestive System

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Abstract

Gastric Cancer, is a frequent cancer in Italy, the mortality associated with it is still high. It is essential to detect more new prognostic factors that allow to identify patients at higher risk, to guide the new possibilities with adjuvant and neoadjuvant chemotherapies. Various prognostic factors have been identified; tumor diameter, degree and type of pathological differentiation, lymph node status, surgical resection, margins status. The number of metastatic lymph nodes could be one of the most important available data, according with the TNM staging system proposed by the American Joint Committee on Cancer (AJCC), where N stage determine its prognosis. This parameter is given by the total number of metastatic lymph nodes. For a correct staging of the tumor it is necessary to examine a minimum number of lymph nodes equal to 15. The accurate evaluation of the metastatic lymph nodes can lead to an appropriate staging and predict the patient's prognosis. On the contrary a number of analyzed lymph nodes <15 leads to an inaccurate prognosis due to an uncorrect estimation of the number of metastatic lymph nodes. Phenomenon known as "stage migration" present in the 15% of cases [1]. One of the reason of poor nodal collection is previous gastric surgery with the absence of some lymph nodal groups 3, 4, 5, 6, according with numbering and locations of lymph nodes in 16th stations as specified in the first edition of the General Rules of the JRSGC (Japanese Research Society for Gastric Cancer). The aim of the study, with our monocentric retrospective evaluation is to consider the prognostic value of the lymph-nodal ratio in patients with gastric cancer to understand if it could be a good indicator of survival and, to identify what could be the subclasses in which to stratify this parameter.

Cite this article: Rinnovati A, Barni L, Bichi A, Qirici E, Cianchi L. Can the Metastatic Lymph Node Ratio Influence the Prognosis of Patients with Gastric Cancer? Preliminary Data of a Monocentric Study. Ann Gastroenterol Dig Syst. 2020; 3(1): 1028.

Introduction

Epidemiology

Despite the constant decline in its incidence, gastric cancer accounts 4% of all tumors in Europe. It is placed in sixth place by incidence (13.7 cases/100,000 inhabitants) and in fourth place for mortality (10.3 deaths/100,000). It has an almost double frequency in the male population compared to the female one, representing the fifth cancer for men (19.5 cases/100,000) and the seventh for women (9.3 cases/100,000). The incidence varies according to age and reaches its maximum peak in the seventh decade. There is also a considerable geographical variability which allows to distinguish countries with higher incidence (Portugal, Estonia, Lithuania and Slovenia with 20 cases/100,000) and countries with lower incidence (United Kingdom, France, Norway and Sweden with 10 cases/100,000). Italy ranks among the countries with intermediate incidence. In Italy [2] during 2018 about 12,700 new cases of gastric cancer and about 10,000 deaths were expected. According to the data relating to the incidence in Europe, it represents 4% of all cancers and ranks fifth in incidence in men and sixth in women. With regards to mortality, it occupies the fifth place for both sexes [3]. Also in Italy we have witnessed a constant reduction over the years, both in the incidence and in the mortality from this disease in both sexes. Similarly to the rest of Europe we can distinguish geographical areas traditionally at high risk (like Appennino Tosco-Romagnolo-Marchigiano with 26 cases/100,000 in men and 13 cases/100,000 in women) and low incidence areas (southern regions with 16 cases/100,000 in men and 7 cases/100,000 in women). Mortality in the various geographical areas is consistent according with the incidence data. This difference is probably related to the dietary habits of the different regions [4]. The Casentino, a hilly valley area located at the border between Arezzo and Florence with about 35.000 inhabitants, in the 1970s presented an incidence of gastric cancer of around 120 cases/100.000 inhabitants, similar to that one of Japan [5]. The study of an area with such a high incidence of gastric cancer like the Casentino valley has made possible to obtain an excellent model for the identification of specific risk factors related to lifestyle dietary habits. The genetic substrate of the population and the pathogenetic mechanisms of the tumor itself could also become the object of study and analysis.

Risk factors

Gastric Cancer can be classified topographically into two macro categories: Cardias and Stomach tumors properly said. These are two completely different entities from an epidemiological, biological, genetic and clinical point of view, so that in the last decade there has been a progressive decrease in the incidence of distal tumors of the stomach and a simultaneous increase in those of cardias and gastro-esophageal junction, which currently represent about 40% of all gastric cancers [6,7]. The risk factors are also not the same in the two forms. Helicobacter Pylori (HP) represents the main risk factor especially for intestinal type carcinomas of the gastric antrum. In 1994 both the WHO (World Health Organization) and the IARC (International Agency for Research on Cancer) recognized it as a type I carcinogen [8,9]. The so-called "Correa hypothesis", from the name of the histopathologist who studied it, claims that a diet promoting Helicobacter Pylori infection and insufficient intake of vitamins lead to superficial gastritis and then to atrophic gastritis, a fundamental link in the karyokinetic process [10]. Gastric hyposecretion and bacterial proliferation, with the presence of nitrite and scarcity of vitamin C, determines the formation of nitrous compounds, which favors intestinal metaplasia up to dysplasia and finally carcinoma [11,12]. The atrophy of the gastric glandular epithelium, caused by the presence of the bacterium (HP), leads to a reduced secretion of hydrochloric acid and pepsin with a consequent increase in endoluminal p^H and growth of anaerobic bacteria, many of which have reduttasi capable of converting nitrates into nitrites, substances performing mutagenic action on DNA. The presence of HP induces an increase in the replicative activity of the gastric epithelium, which constitutes a risk factor for the development of dysplasia. Infected subjects have lower concentrations of ascorbic acid in the gastric juice than those of healthy subjects and this determines a reduced antioxidant capacity of the gastric microenvironment with greater possibility of oxidative damage to the DNA. The inflammatory infiltrate of the mucous membrane and gastric submucosa exposes the epithelial cells to the action of the products released by the disintegration of the polymorphonucleatous granulocytes, especially the hydroxyl radicals which have a significant mutagenic potential on actively proliferating cells [13,14]. Being able to intervene on metaplastic or dysplastic areas, these phenomena accentuate the possibility of further mutations and favor aggression and invasiveness to the already transformed cell. The eradication of HP infection is therefore a fundamental step for the primary prevention of gastric cancer. Other factors contributing to carcinogenesis are smoking habits, eating habits, especially the intake in large quantities of nitrates, smoked or salted foods and red meats [15,16]. On the other hand, a diet rich in fruit and vegetables is protective, which is why the southern regions of Italy are less subject to this type of pathology. By applying some precautions such as the eradication of HP and dietary rules, a reduction of distal stomach tumors has been seen over the years [17,18]. However, cardias and GE junction tumors are increased, which, as we have already mentioned, are a separate entity and present the Gastro Esophageal Reflux Disease (GERD) as the main risk factor, which causes chronic inflammation of the distal esophageal mucosa and cardias, promoting the onset of intestinal metaplasia (Barrett's esophagus). With the aid of digestive endoscopy, it is possible to identify and therefore monitor over time a series of morbid conditions that entail an increased risk of gastric cancer onset called "gastric precancerosis", which are divided into two groups: 1) Precancerous lesions: histological changes in which the carcinoma occurs more frequently than in the normal mucosa (mild, moderate and severe dysplasia). 2) Precancerous conditions: benign diseases of the stomach associated with a higher neoplastic risk compared to the healthy population (chronic atrophic gastritis and intestinal metaplasia, HP infection, peptic ulcer, polyps, gastric stump, Menetrier disease). In most cases, gastric carcinoma occurs sporadically. However, there are also hereditary forms (1-3% of the total) that can be associated with syndromes such as FAP (Family Adenomatous Polyposis), HNPCC, Li Fraumeni, Peutz Jeghers and HDGC (Hereditary Diffuse Gastric Cancer) characterized by the presence of gastric adenocarcinoma of the diffused type in I and II degree relatives and in women it is often associated with lobular breast cancer.

TNM

The pathological classification is based on clinical data integrated with data obtained during and after surgery and the analysis of the surgical finding. The one currently in use is the 8th edition [19].

T stage: It describes the thickness of the invasion of the gastric wall by the tumor. Is distinguished in T0: no tumor; Tis: carcinoma in situ without invasion of the lamina propria; T1a: the tumor invades the lamina propria or muscularis mucosae and T1b: the tumor invades the submucosa; T2: tumor invades-the muscolare propria; T3: the tumor invades the subserosal connective tissue, without however invading the visceral peritoneum or adjacent structures; T4a: the tumor penetrates the serous or visceral peritoneum and T4b: the tumor infiltrates the surrounding organs, in the latter case microscopic confirmation of the infiltration due to contiguity is required.

N stage: It is defined by the number of metastatic regional lymph nodes. Before 1997, N stage was determined by the anatomical position of the lymph nodes with respect to the primary tumor. Currently, however, what matters is the total number of metastatic lymph nodes regardless of their location. The most important thing is that at least 15 lymph nodes must be analyzed for adequate staging. Lymph node metastasis (N) are classified as follows, NX: regional lymph nodes cannot be assessed; N0: no regional lymph nodes metastasis; N1: metastasis in 1-2 regional lymph nodes; N2: metastasis in 3-6 regional lymph nodes; and N3: metastasis in 7 or more regional lymph nodes. Starting from the 7th edition of the TNM staging system N3 was divided into two subgroup: N3a, metastasis in 7-15 regional lymph nodes; N3b, metastasis in >15 regional lymph nodes.

M stage: It indicates the presence or absence of metastatic sites and this metastasis must be confirmed histologically. Metastatic diffusion occurs most often by blood and peritoneum. The liver is the most frequent site for hematogenous metastases, as gastric venous drainage is operated by the portal venous system. Lung, spleen, bone and CNS are affected less frequently. Coelomatic diffusion is more frequent in the cancer who emerging from the serous (T4), due to the fall and reimplantation of neoplastic cells on the peritoneal serous, thus leading to peritoneal carcinosis. Positive peritoneal cytology indicates the presence of metastatic disease.

Parameter R: It indicates the presence or absence of residual tumor after resection and therefore the adequacy of surgery. After surgical resection it is possible that there is residual disease at the primary site due to incomplete resection or due to the presence of advanced disease beyond the possibilities of surgical resection. R0: absence of residual tumor; R1: presence of microscopic residual tumor; R2: presence of macroscopic residual tumor. Only R0 corresponds to a curative resection, the prognosis is instead to be considered unfavorable for the other two categories.

Materials and methods

In our center we have identified 116 patients who underwent surgery for gastric pathology from January 2014 to June 2019. Of these, 29 were not suitable for our study as 11 patients did not have an adenocarcinoma but other pathology forms (GIST or Neuroendocrine Tumors); 2 patients were lost at follow-up, 6 patients died in the perioperative period (i.e. in the first 30 days after surgery) and 10 patients were excluded as they underwent palliative surgical procedure. In our sample there are 18 patients who resulted metastatic to the definitive pathologist examination, which we nevertheless considered eligible for the study, seen that the surgery procedure was done with all the criteria for curative purposes. This type of attitude state that radical surgery can be considered for metastatic patients for whom the procedure is technically feasible and biologically advantageous. There is a study by a Japanese group from 2016 [20,21] that precisely on this topic, identified 4 categories of metastatic adenocarcinoma. The first category, which includes patients without peritoneal carcinosis, with technically resectable metastases, such as para-aortic lymph nodal metastasis or single liver metastasis. The first category, which includes patients without peritoneal carcinosis, with technically resectable metastases, such as para-aortic lymph nodal metastasis or single liver metastasis <5 cm or positive peritoneal citology is suitable to radical treatment, especially after neoadjuvant chemotherapy [21,22]. In this retrospective study we therefore considered 87 patients who underwent curative gastrectomy for gastric cancer, between January 2014 and June 2019, at the General Surgery of the S. Donato Hospital of Arezzo and the General Surgery of the Casentino Hospital from the same team. Even if not all of them have yet completed the 5-year observation period, this condition affects the evaluation of the TNM parameter, N and of the rLN ratio in the same way. All patients had a definitive histological diagnosis of gastric adenocarcinoma on the biopsy performed during EGDS, were staged by chest and abdomen CT with contrast medium and assessed by the Multidisciplinary Oncological Group (GOM) before having an indication for surgical treatment. The criteria by which the patients were selected are the following: 1) Histologically identified adenocarcinoma, 2) Gastrectomy performed for curative purposes with D2 lymph-nodal dissection, 3) Postoperative survivors, then the first 30 days after surgery Resection of the tumor, lymphadenectomy and reconstruction were performed by the same surgical team, with the same technique, in all patients. Later on, the patients were divided into two groups. Group 1 consisting of 63 patients to whom 15 or more lymph nodes have been removed and Group 2 consisting of 25 patients to whom less than 15 lymph nodes have been removed.

Statistical plan

The variables that have been analyzed for each patient are sex, age, location and size of the lesion, parameters T, N and M, the histotype and degrees of differentiation, the type of growth, the post-surgical residue, the number of removed lymph-nodes, the lymph-nodal ratio and the current status of patients. Categorical variables were expressed as count and percentage of each category. In order to assess the association between survival data and each possible risk factor the Kaplan-Meier curve, log-rank test and Cox model, HR and the 95% confidence interval was calculated. To evaluate independent risk factors for survival multiple Cox Model, HR and the 95% confidence interval was calculate using backward selection method. The significant level was set to 5%. Data were analysed using the statistical software SAS version 9.2 (SAS Corporation, Cary, NC).

Results

Clinical and histopathology data

Among our 87 patients, 59 are male (67.82%) and 28 are female (32.18%). The average age is 74.96 years for men and 75.07 for women. 74 patients are 65 years of age or older (85.06%) and 13 patients are under 65 years of age (14.94%). With regards to the analysis of the characteristics of the tumor, we have seen that the antrum is the most involved site, in fact 55 patients (63.22%) have antral cancer, 14 patients (16.09%) presented cancer of the stump, 9 patients had a tumor of the gastric fundus (10.34%), 5 patients had a tumor of the gastric body (5.75%) and cardias (Siewert III) [13,31] is the least affected site with only 4 patients suffering from cancer in this location

(4.6 %). In most cases, i.e. in 50 patients, lesions up to a maximum diameter of 4 cm (58.82%) were identified, 21 patients had a lesion >4 cm and <= a 6 cm (24.71%), 8 patients had a lesion >6 cm and <= 8 cm (9.41%). There are also very advanced lesions, which also exceed 8 cm in diameter, identified in 6 patients (7.06%). Lauren's histotype was divided into intestinal type, by far the most frequent identified in 50 patients (57.47%), diffused type identified in 20 patients (22.99%), mixed type in 11 patients (12.64%) and classification "other type" was used to classify 4 patients with severe dysplasia and 2 not specified in the histological examination (6.90%). The degree of histological differentiation was divided into G1, G2, G3-4 respectively with groups of 10 patients (11.49%), 21 patients (24.14%) and 52 patients (59.77%) and "no degree of differentiation" which includes the 4 patients with severe dysplasia (4.6%) which can be considered equal to carcinoma in situ [23,24]. The type of growth was categorized as infiltrative, expansive, and indefinite for the cases where the form or predominance of one of the two forms was not specified on the histological examination. There was a clear prevalence of the infiltrative form identified in 55 patients (63.22%), while 20 patients had expansive growth (22.99%) and 12 patients had no definition of growth type on histological examination (13.79%). The T and N parameters were evaluated in accordance with the 7th edition of the TNM and with the 8th edition for those operated after the release of the new TNM. Regarding the T parameter, the T4 form or the advanced tumor, was the one most present in our sample with a number of 33 patients (37.93%), followed by 22 patients from the T3 group (25.29%) and 11 patients in the T2 group (12.64%). The early forms are also a good slice, 21 patients in fact belonged 25 to the T1 group (24.14%). The N parameter was stratified into N0 with 40 patients (45.98%), N1 with 9 patients (10.34%), N2 with 14 patients (16.09%) and N3 with 24 patients (27.59%). As already mentioned, in the literature there is no consensus in the definition of the subcategories for the Lymph Nodal Ratio (rLn) variable. Considering that TNM uses as a cut-off to divide patients into the different N groups a number equal to 0, 2 and 6 positive regional lymph nodes, we divided these values by the cut-off of good lymphectomy (15 LN). So we have chosen for the groups of rLn the values 0 given by the ratio 0/15, 0.13 given by the ratio 2/15 and 0.4 given by the ratio 6/15. These cut-offs groups are justified and in agreement with two Chinese studies by Chen et al. from 2012 [25,26] and Hou et al. from 2018 [26]. We were therefore able to classify as rLn0 the 40 patients (45.98%) who had a ratio between metastatic lymph nodes and examined lymph nodes equal to 0, rLn1 the 9 patients (10.34%) with a ratio >0 and <= 0.13, rLn2 the 20 patients (22.99%) with ratio >0.13 and <= 0.4 and rLn3 the 18 patients (20.69%) with ratio >0.4. With regards to the adequacy of lymphadenectomy, 62 patients (71.26%) had 15 or more lymph nodes removed with an average of 31 while 25 patients had less than 15 lymph nodes removed with an average of 7 lymph nodes removed. 10 of the patients in the group with less than 15 removed lymph nodes, were carcinomas of the stump, so these are patients who have already undergone gastric resection for peptic disease, where groups 3, 4, 5 and 6 had already been removed. Out of the 87 patients, 10 (11.49%) presented microscopic residue of disease (R1) on the circumferential margin at the definitive histological examination, therefore complete eradication appears impossible from the surgical point of view. On the other hand, 77 patients (88.51%) resulted R0 instead. Currently 36 patients (41.38%) died while 51 patients (58.62%) are still alive, but as we already specified many of these have not yet completed the 5-year observation period. However, this condition affects the evaluation of the TNM parameter N and of the rLN ratio in the same way.

Univariate and multivariate analysis of data.

All the variables considered and described so far have been included in the univariate analysis. They have therefore been tested individually in relation to survival to verify whether they were statistically associated in significant way with the latter. The results of the univariate analysis are shown in (Table 1). In this type of analysis Lauren, Grade, type of growth, T stage, N stage and Lymph Nodal Ratio are statistically significant variables in relation to survival; in particular N stage and rLn (p value <0,0001) which are the variables that describe the positivity of the lymph nodes. Observing the Cox model built for the lymph nodal ratio parameter. We see that the three categories of the variable present an estimate of the risk that grows as the ratio between the metastatic lymph nodes and the removed lymph nodes increases (HR: 2.040; 3.491; 8.130), in comparison to the control group (rLn0), with a p value of 0.2843 for rLn1, 0.013 for rLn2 and <0.0001 for rLn3 respectively. While the first interval probably fails to reach significance because of the small group of patients, the other groups are instead more numerous and therefore more powerful to show their significance. We can therefore say that although rLn1 has few patients and cannot express a significant value, the estimated risk (HR) increases as limph nodal ratio increases, so it is possible to assert that the parameter rLn can be a good parameter for the assessment of survival. Even the N parameter has an important significance to the univariate analysis, but by the observation of the Cox model, it is clear that the estimated risk (HR) does not really has a growing trend, indeed in paradox the N2 seems to have better prognosis than the N1, with a HR of 1.997 compared to a HR of 6.091 which is very close to the HR of the N that is equal to 6.310. it seems legitimate the thought that these N1 patients may have been subdued. In fact, going to look a tour sample, less than 15 lymph nodes were taken out in 44% of patients classified as N1.

The 10 variables analyzed with the univariate analysis were then re-evaluated in the Multivariate survival analysis showed in (Table 2), which confirms the significance of N stage, Lymph nodal ratio, histotype according to Lauren [28,29].

Also in this analysis the N category shows the same particularity found in the univariate analysis, i.e. a decreasing trend of the estimated risk between N1 and N2. N3 could not be estimated because there are too few events (deaths) in our sample to give a result from a statistical point of view. If we observe the lymph nodal ratio variable instead, we see how also in this case, the risk increases as the ratio increases, expressing the maximum significance when rLn is >0.4, while the other categories of rLn do not have enough power to appear always significant due to the lack of representativeness of the sample. This further confirms the validity of the lymph node ratio as a prognostic factor for survival and its superiority in comparison with N category of the TNM.

In the second part of the study we wanted to compare the variables N and rLn by repeating the Univariate analysis, stratifying our cohort according to the removal of a quantity of lymph nodes less (Table 3) or greater than or equal to 15 (Table 4).

In Group 1, observing only the Log-Rank just the variable N is significant; but evaluating also the Cox model we can observe how the two variables are actually very similar. The estimated

HR risk of the variable N presented the usual trend inversion fault. The variable rLn, on the other hand, does not highlight a change in risk between the various subcategories, in fact it has practically identical HR values.

In Group 2 instead, we see how both variables are very significant at the Log Rank; but going to evaluate HR, the lymph nodal ratio shows a growing HR trend with an increase in 30 the ratio between metastatic lymph nodes and removed lymph nodes. The same thing does not apply to the variable N, which has the same trend it had when less than 15 lymph nodes were removed, as if despite an adequate defined lymph node removal they may have been staged incorrectly. The rLn variable therefore could be a better descriptor of the correlation with survival than the parameter N.

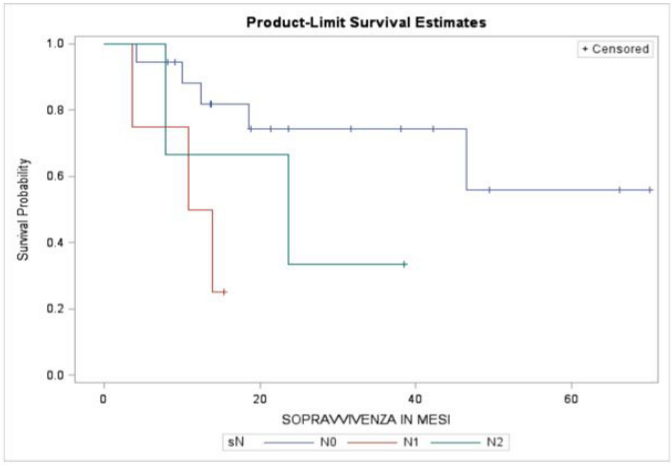

Figure 1: Group 1 stratified for N (p=0.04).

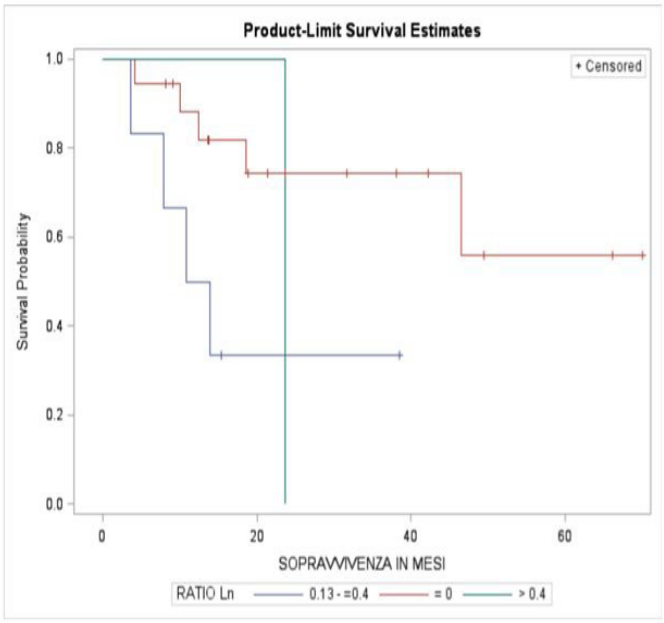

Figure 2: Group 1 stratified for rLn (p=0.07).

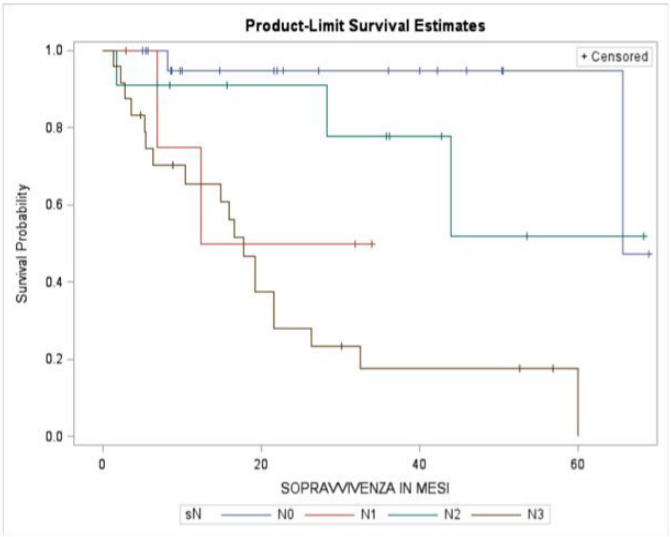

Figure 3: Group 2 stratified for N (p<0,001).

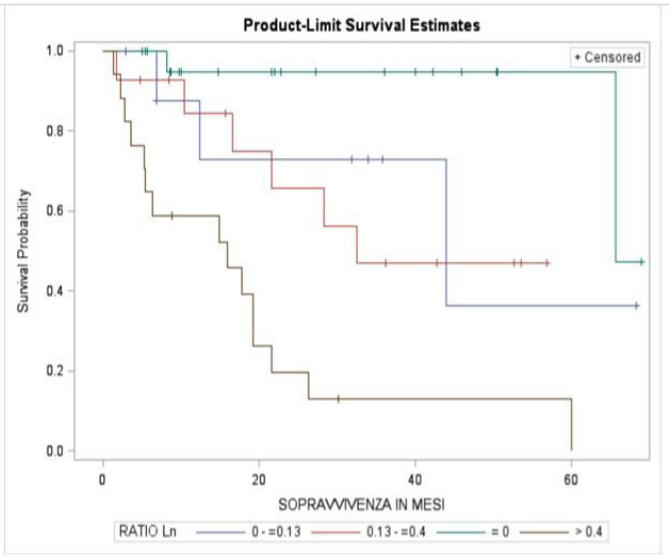

Figure 4: Group 2 stratified for rLn (p<0,001).

Table 1: Clinical and histopathology data of all 87 patients and Univariate analysis.

Variables	N (%)	p value Log Rank	3 yers OS	HR (IC 95%)	p Cox Model
SEX					
Male	59 (67.82%)				
Female	28 (31.18%)				
AGE					
>= 65	74 (85.06%)	0.2847	51%	1.645 (0.537-5.045)	0.3837
< 65	13 (14.94%)		77%	Ref.	
LOCATION					

Antrum	55 (63.22%)		57%	Ref.	
Body	5 (5.75%)		25%	1.739 (0.537-5.634)	0.356
Fundus	9 (10.34%)	0.9151	50%	1.339 (0.502-3.573)	0.5604
Cardias	4 (4.6%)		75%	0.891 (0.226-3.521)	0.8698
Stump	14 (16.09%)		52%	1.302 (0.491-3.453)	0.5962
DIAMETER					
<= 4 cm	50 (58.82%)		63%	Ref.	
>4 - <=6 cm	21 (24.71%)	0.4275	40%	1.844 (0.866-3.926)	0.1125
>6 - <=8 cm	8 (9.41%)		46%	1.616 (0.550-4.749)	0.3833
>8 cm	6 (7.06%)		45%	1.783 (0.605-5.252)	0.2939
LAUREN					
Intestinal	50 (57.47%)		65%	Ref.	
Diffused	20 (22.99%)	0.0191	45%	2.162 (0.975-4.797)	0.0579
Mixed	11 (12.64%)		26%	3.780 (1.530-9.338)	0.004
Other	6 (6.9%)		50%	3.049 (0.736-12.624)	0.1241
GRADE					
G1	10 (11.49%)		85%	0.246 (0.029-2.084)	0.1984
G2	21 (24.14%)	0.0086	77%	0.329 (0.050-2.151)	0.2461
G3-4	52 (59.77%)		40%	1.071 (0.194-5.923)	0.9373
No degree	4 (4.6%)		60%	Ref.	
GROWTH					
Infiltrative	55 (63.22%)		45%	0.968 (0.366-2.562)	0.9485
Espansive	20 (22.99%)	0.0146	87%	0.242 (0.067-0.878)	0.0309
Indefinite	12 (13.79%)		44%	Ref.	
T stage					
T1	21 (24.14%)		86%	Ref.	
T2	11 (12.64%)	0.0029	76%	2.312 (0.502-10.645)	0.282
T3	22 (25.29%)		50%	3.268 (0.917-11.651)	0.0679
T4	33 (37.93%)		36%	6.028 (1.839-19.754)	0.003
N stage					
N0	40 (45.98%)		83%	Ref.	
N1	9 (10.34%)	<0.0001	28%	6.091 (1.902-19.507)	0.0023
N2	14 (16.09%)		66%	1.997 (0.643-6.205)	0.2316
N3	24 (27.59%)		20%	6.310 (2.593-15.354)	<0.0001
RATIO LINFONODALE					
rLn0	40 (45.98%)		83%	Ref.	
rLn1	9 (10.34%)	<0.0001	69%	2.040 (0.553-7.527)	0.284
rLn2	20 (22.99%)		44%	3.491 (1.302-9.360)	0.013
rLn3	18 (20.69%)		11%	8.130 (3.253-20.322)	<0.0001
RESIDUE					
R0	77 (88.51%)	0.2467	57%	Ref.	
R1	10 (11.49%)		36%	1.713 (0.754-3.891)	0.1985
RETRIVED LN					
<15	25 (28.74%)				
>=15	62 (71.26%)				
STATUS					
Vivo	51 (58.62%)				
Deceduto	36 (41.38%)				

Table 2: Multivariate analysis of all variables using backward selection method.

Variables	p value	HR (CI 95%)
AGE		
< 65	Ref.	
>= 65	0.0183	5.208 (1.322-20.517)
LAUREN		
Intestinal	Ref.	
Diffused	0.2928	1.697 (0.634-4.546)
Mixed	0.1981	1.930 (0.709-5.256)
Other	0.0081	10.468 (1.843-59.469)
N stage		
N0	Ref.	
N1	0.029	5.056 (1.181-21.653)
N2	0.728	0.800 (0.228-2.810)
N3	.	.
RATIO LINFONODALE		
rLn0	Ref.	
rLn1	0.6769	1.473 (0.238-9.119)
rLn2	0.0632	3.460 (0.934-12.819)
rLn3	<0.0001	12.825 (4.033-40.784)

Table 3: Group 1: 25 patients with less than 15 removed lymph nodes. There are no N3 and rLn1 in this group.

Variables	p value Log-rank	3 years OS	HR (CI 95%)	p value Cox model
N stage				
N0	0.0458	71%	Ref.	
N1		14%	5.889 (1.184-29.292)	0.0303
N2		33%	3.162 (0.596-16.781)	0.1764
N3				
RATIO LINFONODALE				
rLn0	0.0755	71%	Ref.	
rLn1				
rLn2		27%	4.341 (1.036-18.184)	0.0446
rLn3		0%	4.241 (0.568-31.669)	0.159

Table 4: Group 2: 62 patients with 15 or more removed lymph nodes.

Variables	p value Log-rank	3 years OS	HR (CI 95%)	p value Cox model
N stage				
N0	<0.0001	93%	Ref.	
N1		42%	7.375 (1.126-48.303)	0.0372
N2		77%	2.478 (0.458-13.422)	0.2924
N3		20%	11.743 (2.795-49.336)	0.0008
RATIO LINFONODALE				
rLn0	<0.0001	93%	Ref.	
rLn1		69%	3.113 (0.576-16.835)	0.1873
rLn2		52%	4.791 (1.004-22.862)	0.0494
rLn3		12%	15.250 (3.596-64.673)	0.0002

Discussion

Stomach cancer, as said in the previous chapter, is one of the most frequent in Europe and in the world. In Italy it is in fifth place for mortality in both sexes, after lung, colorectal, and respectively breast and pancreas in women and prostate and liver in men [30,31]. In order to try to improve the currently poor prognosis of this pathology, it is necessary firstly a surgical intervention as radical as possible and secondly an accurate histological evaluation and staging of the disease, which can then guide the oncologist in prescribing the patient with the most suitable therapeutic scheme for their stage of illness.

The TNM staging system is the most used worldwide and we now know that the absolute number of metastatic locoregional lymph nodes (TNM-N category) is the most reliable prognostic indicator for patients with radically resected gastric cancer [32,33]. The UICC/AJCC classification, which is the most widely used for the staging of gastric cancer, suggests that at least 15 LN should be examined for a correct assessment of N category and this implies that D1 dissection, limited to the level I (1-6 group, perigastric LN), might not guarantee an accurate staging. On the other hand, sometimes a D2 lymph node dissection can be associated with major postoperative complications [34,35]. However, we know that if less than 15 lymph nodes are removed, becomes easier to run into the phenomenon called "stage migration", i.e. all those patients who have been classified as N0 or N1 with an inadequate lymphadenectomy (<15 Ln), could undergo an up staging of the disease if 15 or more lymph nodes were removed [36-39]. As proposed for other cancers such as breast or colorectal [40,41] various study groups have also thought of taking the lymph nodal ratio into consideration for the stomach, in order to reduce the phenomenon of stage migration [42,43]. With our study, we evaluated the prognostic value of the rLn parameter and in accordance with the literature we found that this parameter is statistically significant both in univariate and multivariate analysis. We can therefore say that the lymph nodal ratio is a simple, reliable and easily reproducible parameter to predict the prognosis of patients with stomach cancer and that could safely support and enhance the N parameter in the staging of patients. However, its use in clinical practice cannot be routine until universally valid cut-offs are agreed and shared by the scientific community. In our study we have tested various cut-offs that have been gradually proposed in the literature [44], but those that seemed to describe better the survival trend in our cohort of patients are those proposed in the work of Chen et al. [25], who considered the ratio between the cut-offs chosen by AJCC's TNM staging system and 15, i.e. the limit for a good lymph node dissection. The values 0 (0/15); 0.13 (2/15) and 0.4 (6/15) are therefore results. We were then able to categorize the patients into rLn0 (0), rLn1 (>0 - <= 0.13), rLn2 (>0.13 - <= 0.4) and rLn3 (>0.4). With this division, we noted how the lymph nodal ratio can even be more reliable than the N staging where N1, N2 and N3 have an HR compared to N0 respectively of 6.091, 1.997 and 6.310. For some reason this result seems to tell us that patients in group N1, therefore those with 1 or 2 metastatic lymph nodes, have a worse prognosis than N2, which have 3-6 metastatic lymph nodes. Why do we see this? Most likely, this result may be the manifestation of the effect of “stage migration”, as it is possible that if more than 15 lymph nodes would have been removed, these patients would not have been staged as N1 but as N2 or more. The same does not happen for the lymph node ratio parameter, which is not influenced by the total number of removed lymph nodes. The subcategories of the lymph node ratio rLn1, rLn2 and rLn3 indeed have an HR compared to rLn0 respectively of 2.040, 3.491 and 8.130. This rising risk trend therefore better describes the survival in gastric cancer patients. At this point, although we were not the first in doing it, we divided our patients into a group with inadequate lymphectomy, called Group 1 (<15 Ln) and a group with adequate lymphectomy, called Group 2 (>= 15 Ln) to see if rLn could be more reliable than N staging in both cases or even more so in Group 1 where N often presents a fault.

As can be seen from (Figures 1 & 2), in Group 1 only the parameter N is significant; it must be noted, however, that in this group there are a total of 25 patients and 10 events (death), which is a very small number divided into 4 variables that cannot give reliable results. In the stratification by variable N, we do not have patients in the N3 group and in the stratification by rLn we do not have patients in the rLn 1 group and in the rLn3 group there is only one patient. The only things we can notice are that N0 and rLn0 have a very similar trend. For parameter N, we can confirm the risk trend inversion for patients N1 and N2 (HR of 5.889 and 3.162 respectively). This confirms the hypothesis that in case of inadequate lymphectomy, patients may be sub staged. Unfortunately, however, we cannot confirm the validity of the rLn parameter in this case as it is not statistically significant.

(Figures 3 & 4) show instead how in Group 2 both variables are statistically significant with a p <0.001. This time the group is more numerous because it consists of 62 patients and the subcategories of the variables taken into consideration are all well represented. The subcategories at the extremes have a very similar trend, in the middle, they are not well distinct, but once again, the variable N shows an inversion of HR with the N1, which are worse than the N2, while rLn has an HR with a growing trend for all its sub-categories.

This means that by observing patients separately based on the adequacy of lymphadenectomy, the lymph nodal ratio is a better evaluation parameter than parameter N even when an appropriate number of lymph nodes are removed. Unfortunately, we were not able to demonstrate the same hypothesis in the inadequate lymphectomy group but we are convinced that increasing the number of patients observed could result in significant results even in that case.

The sample should be expanded to give more power to the variables and to the results of the analysis, which sometimes fail to be significant precisely because there are too few events (deaths). For an ideal statistical study, at least 10 events (death) would be needed for each variable. It would also be essential to complete the follow-up period for all patients so that it would be possible to evaluate the 5-years OS for all, without having censored patients.

The continuation of the study through the completion of the follow up and the wider enrollment, will allow to a more significant overall assessment.

Conclusions

Lymphadenectomy is the only prognostic factor for gastric cancer that can be influenced by the surgeon. One great advantage of extensive lymph node dissection (>15 LN) is that it allows improved staging of the disease and this is of utmost importance when survival rate is compared. Our study supports other study groups in demonstrating that the Lymph Nodal Ratio is a good parameter for assessing survival in patients who

underwent curative gastrectomy for Gastric Cancer, as it is less influenced by the total number of lymph nodes removed and by the individual dotation of lymphatic. For this reason, we think that this parameter could be added to parameter N in the staging of patients and therefore improve the selection of those who could benefit most from adjuvant therapies.

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