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Positive lymph node ratio as a prognostic factor for gastric cancer patients

Is it going to supersede positive lymph node number in guidelines?

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Abstract

Gastric malignancies constitute the sixth most common cancer with regards to incidence and have the fifth most mortality rates. Extended lymph-node dissection is the surgical modality of choice while treating advanced stage gastric cancer. It is yet a topic of debate, whether or not the amount of positive lymph nodes after a pathological examination following the surgical intervention is of prognostic value. In this study, it is aimed to evaluate the prognostic significance of positive lymph nodes following the surgery. A total of 193 patients who underwent curative gastrectomy between January 2011 and December 2015 have been considered for a retrospective data collection. The cases with R1-R2 resections, palliative or emergent surgeries are excluded. Metastatic to total number of lymph nodes, corresponded a ratio which was analyzed in this survey and practiced as a predictive parameter of disease outcome. This survey includes 138 male (71.5%) and 55 female (28.5%) patients treated between 2011 and 2015 in our clinic. The survey follow-up duration of the cases range between 0, 2, and 72 months, corresponding an average of 23.24 ± 16.99 months. We calculated cutoff value of 0.09 with, sensitivity is 76.32% for positive to total number of lymph nodes ratio, whereas specivity applies for 64.10%, positive predictive value for 58% and negative predictive value for 80.6%. Positive lymph node ratio has a prognostic value in terms of predicting the prognosis of the patients with gastric adenocarcinoma following a curative gastrectomy. This might in long term contribute to the prognostic analysis of patients if integrated in the current staging system.

Abbreviations: BMI = body-mass-index, LNR = lymph node ratio, NCSS = Number Cruncher Statistical System.

Keywords: gastrectomy, gastric cancer, lymphadenectomy, positive lymph node ratio, prognosis

1. Introduction

Globacan 2020 data places the gastric cancer on the 6. most common and 5. most deadly malignancy among all cancers.[1] Despite the new efforts as well as the improvement in management of the disease, it still represents itself with an unpleasant course with a low prognostic expectation affecting more than 1 million people.[2] Particularly in cases which are being diagnosed in an advanced stage, the prognosis is remarkably low despite chemotherapy and targeted therapies.[3] There are studies claiming that the advanced staged tumors having lower rates of 5-year survival in comparison with T1 tumors which are limited to mucosa.[4] Early stage gastric cancer achieves a 5-year survival rate of more than 90%.[5,6] Nevertheless, there is an increasing amount of gastric cancer cases in early ages of life and the younger age is associated with increased mortality.[7,8]

Management of the cases with gastric carcinoma includes surgery, chemotherapy and radiotherapy. Extended lymph node dissection surgery is the mainstay treatment of local advanced gastric carcinoma.[9] Metastatic status of the lymph nodes, defined by D2-dissection, is an important prognostic factor not only in that it helps to evaluate the pathological staging and therefore help managing the systemic chemotherapy, but also in that it helps predicting the survival outcomes.[10] Surgically dissected lymph nodes contribute to gastric cancer staging.[11] On the other hand, the suboptimal dissection of lymph nodes or despite the efforts unsatisfactory numbers of lymph nodes to dissect following a neoadjuvant therapy might deteriorate the validity of this method to identify the actual stage of the cancer.[12] In order to optimize this process, studies focus on identifying the effective parameters to adequately stage the gastric cancer.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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There is an increase in the amount of studies concluding that the positive lymph node ratio (LNR) is a more plausible parameter when compared to TNM staging.[13–15] Nevertheless, positive lymph node ratio is recently being discussed as an independent risk factor in current literature.[16,17] This survey aims to evaluate the metastatic lymph node ratio in local advanced gastric tumors and to compare the prognostic significance of LNR with the number of lymph nodes.

2. Materials and methods

A total of 193 gastric cancer cases treated with curative gastrectomy between January 2011 and December 2015 have been recruited retrospectively into this survey. The data regarding the duration of life, body-mass-index (BMI), pathological stages, whether or not neoadjuvant therapy was applied, the localization of the tumor, as well as the postoperative complications were recorded. The studies involving human participants were reviewed and approved by Institutional Review Board of University of Health Sciences Turkey, Sisli Hamidiye Etfal Training and Research Hospital (Date: 25.05.2022/No:3268). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

2.1. Statistical analysis

For the statistical analysis NCSS (Number Cruncher Statistical System, 2007, Utah) was utilized. While evaluating the data, complementary statistical methods were used (mean, standard deviation, median, frequency, percentage, minimum and maximum). The Shapiro–Wilk test as well as the graphical assessments were used to evaluate the normality in frequentist statistics.

In order to compare the means of two independent groups with normal distribution the Independent Samples *t* Test and Mann–Whitney *U* test to compare two groups of quantitative parameters without normal distribution. Pearson chi-square test, Fisher's exact test, Fisher–Freeman–Halton exact test were used to compare qualitative data. cutoff values of the parameters were determined by using diagnostic tests (accuracy and precision, positive and negative predictive value) and ROC analysis. Statistical significance is defined by $P < .05$.

3. Results

This survey includes 138 male (71.5%) and 55 female (28.5%) patients treated between 2011 and 2015 in our clinic. The average age of the population was 63.41 ± 12.56, patients ranging between 27 and 91 years. The BMI measures of cases are ranging between 17.7 and 49.9, and the average BMI was 32.97 ± 6.68. Demographic features of the population are represented in Table 1.

The survey follow-up duration of the cases range between 0,2 and 72 months, corresponding an average of 23.24 ± 16.99 months. Seventy six patients (39.4%) died and 117 (60.6%) has been living.

Neoadjuvant therapy has been applied in 57 (29.5%) of the patients. One patient has undergone proximal gastrectomy (0.5%), 138 patients had total gastrectomy (71.5%) and 57 patients had distal subtotal gastrectomy (29.5%).

In terms of tumor localization, 41 of the cases (21.2%) were upper, 113 of them (58.5%) were middle and 21 of them (10.9%) were distal tumors.

Comorbid clinical conditions were accompanying the gastric cancer in 67 of the cases (34.7%). In thirty nine (20.2%) of the cases resection of another organ was necessarily performed. Spleen (33.3%), liver (12.8%), colon (15.4%), pancreas (17.9%), gallbladder (15.4%), and small intestines (5.2%) were resected as concomitant organs with gastrectomy (Table 2).

The staging of the cases found to be significantly different amongst the groups of different survey outcomes ($P = .005$; $P < .01$). Survey groups did not found to be statistically different in terms of sex, age, BMI measures, whether or not neoadjuvant was applied, the type of surgical intervention, localization of tumor and the presence of a leakage from the site of the anastomosis ($P > .05$) (Table 3). Comorbidities or resection of another organ was not found to have a significant impact on survey outcomes ($P > .05$) (Table 4).

Preoperative N staging differs significantly among survey outcomes ($P = .012$; $P < .05$). It was reported that preoperative N0 patients have higher survival rates than N2 patients. Postoperative N scoring was reported to have a significant impact on survey outcomes ($P = .001$; $P < .01$). Postoperative N0 cases have higher survival rates than N2 and N3 cases.

Preoperative T staging do not reveal a statistically significant impact on survey outcomes while postoperative T stage has significant impact on survey outcomes ($P > .05$) (Table 5). The number of positive lymph nodes in dead cases following the survey, was found to be significantly higher in comparison to the ones who were still alive ($P = .001$; $P < .01$) (Table 6).

Carcinoembryonic antigen measures of the cases who were Group 1 were found to be significantly higher than the Group 2 ($P = .013$; $P < .05$).

The total number of dissected lymph nodes, preoperative CA19-9 and preoperative Hemoglobin measures were not reported to have a significant impact on the survey outcomes ($P > .05$).

4. Discussion

Gastric cancers still possess very high mortality rates. The amount of particularly the newly diagnosed gastric cancer cases are higher in Asia and Southern America.[18] Gastric cancers deteriorate the quality of life and have high health care expenses, causing various morbidities and has a high rate of mortality.[19] Overall survival rate of gastric cancers in United States of America was reported to be 31%, whereas it is 25% worldwide.[20] One of the most important factors that affect the mortality is the stage at the diagnosis.[2] Gastric cancers are yet most

Table 1

Demographic features of the cases and their distributions.

		n (%)
Sex	Male	138 (71.5)
	Female	55 (28.5)
Age	Mean ± SD	63.41 ± 12.56
	Median (Min–Max)	65 (27-91)
BMI	Mean ± SD	32.97 ± 6.68
	Median (Min–Max)	32.4 (17.7–49.9)
Survey (mo)	Mean ± SD	23.24 ± 16.99
	Median (Min–Max)	24 (0.2–72)
Survey	Deceased	76 (39.4)
	Living	117 (60.6)
Neo adjuvant	No	136 (70.5)
	Yes	57 (29.5)
Surgical method	Proximal gastrectomy	1 (0.5)
	Total gastrectomy	138 (71.5)
	Distal gastrectomy	54 (28.0)
Tumor localisation	Upper	41 (21.2)
	Middle	113 (58.5)
	Distal	21 (10.9)
	Mixed	18 (9.4)
Anastomotic leakage	No	182 (94.3)
	Yes	11 (5.7)

BMI = body-mass-index.

commonly diagnosed in an advanced stage and therefore have a poor prognostic expectancy.[21] The management largely depend on the stage of the disease, the positivity of given biomarkers and the expert opinion of the clinicians. In order to contribute to the efforts of deciding for the right management strategies. There is an effort to define the most important prognostic parameters of gastric cancer. Current literature attributes prognostic value to various markers. Albumin to Fibrinogen Ratio, The hemoglobin, albumin, lymphocyte, and platelet score, multiple tumor markers, increased expression of Histone Deacetylase 5 appear to be useful parameters in predicting orignostic expectancy in gastric tumors.[22–25] In 2017, the American Joint Committee on Cancer made revisions on cTNM staging system in their 8th Edition.[11] The staging system of American Joint Committee on Cancer only takes the number of positive lymph nodes into consideration but not the positive to total lymph node ratio.[26,27] Solely considering the number of positive lymph nodes as a predictive parameter does not appear to be efficient to makes statements about prognostic expectance. This is particularly pronounced in case of an insufficient dissection of the lymph nodes, which in turn may lead to errorous staging and treatment.[12,28] A number of studies conclude that the increased number of lymph nodes indicates a better survival outcome, in that it refers to a more radical and extended surgery.[29,30] The improvements in surgical techniques and the increasing surgical experience in the field, the amount of dissected lymph nodes increase but the need of a better prognostic marker to address a more accurate staging still exist. Positive to total of dissected lymph nodes ratio is a useful, readily accessible and reproducible marker that might also be used to better define subgroups in a particular malignancy.[15] LNR is a measure of number of positive lymph nodes in the total of dissected lymph nodes.[31,32] LNR ratio is increasingly being experimented in thyroid cancers, colon and gastric cancers and other kinds of malignancy, showing a promising prognostic value.[15,33–35] Recent studies indicate the accuracy of LNR in staging is superior than the total amount of the dissected lymph nodes.[36,37] When divided into the groups with regards to the duration of life using the cutoff values of LNR, the lower LNR indicated a longer duration of life.[14] In our survey, it is stated that the positive lymph node ratio, as well as the number of positive lymph nodes are correlated with prognosis. Different results in various series might imply the diversity of the statistical methods used in the studies.

Table 2

Comorbidities and additional organ resections.

		n (%)
Comorbidities	No	126 (65.3)
	Yes	67 (34.7)
	DM	9 (13.4)
	HT	27 (40.4)
	CHF	21 (31.3)
	COPD	8 (11.9)
	CRF	2 (3.0)
Additional organ resection	No	154 (79.8)
	Yes	39 (20.2)
	Spleen	13 (33.3)
	Liver	5 (12.8)
	Colon	6 (15.4)
	Pancreas	7 (17.9)
	Gall bladder	6 (15.4)
	Small intestine	2 (5.2)

CHF = chronic heart failure, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, DM = diabetes mellitus, HT = hypertension.

4.1. ROC curve analysis of the survey outcomes

In this survey, it is concluded that the number of positive lymph nodes, as well as the positive to total number of lymph nodes ratio have been significantly and negatively correlated with the life expectancy. In other words, patients with high numbers of

Table 3

Demographic features according to survey outcomes.

		Survey		
		Dead (n = 76)	Alive (n = 117)	*P*
Sex	Male	53 (69.7)	85 (72.6)	.661†
	Female	23 (30.3)	32 (27.4)	
Age	Mean ± SD	65.58 ± 12.87	61.98 ± 12.21	.052‖
BMI	Mean ± SD	31.91 ± 6.75	33.67 ± 6.58	.404¶
Stage	I	9 (11.8)	26 (22.2)	.005**§
	II	12 (15.8)	41 (35.0)	
	III	47 (61.8)	48 (41.0)	
	IV	8 (10.5)	2 (1.7)	
Neo Adjuvant	No	51 (67.1)	85 (72.6)	.409†
	Yes	25 (32.9)	32 (27.4)	
Operation type	Proximal gastrectomy	0 (0)	1 (0.9)	.388§
	Total gastrectomy	59 (77.6)	79 (67.5)	
	Distal gastrectomy	17 (22.4)	37 (31.6)	
Tumor localization	Upper	20 (26.3)	21 (17.9)	.564†
	Middle	42 (55.3)	71 (60.7)	
	Distal	8 (10.5)	13 (11.1)	
	Mixed	6 (7.9)	12 (10.3)	
Anastomotic leakage	No	72 (94.7)	110 (94.1)	1.000‡
	Yes	4 (5.3)	7 (5.9)	

BMI = body-mass-index.

**$P < .01$.

†Pearson chi-square test.

‡Fisher exact test.

§Fisher Freeman Halton test.

‖Student *t* test.

¶Mann–Whitney *U* test.

Table 4

Comorbidities and additional organ resections according to survey outcomes.

	Survey		
	Dead (n = 76)	Alive (n = 117)	*P*
Comorbidity			
No	47 (61.8)	79 (67.5)	.418*
Yes	29 (38.2)	38 (32.5)	
DM	3 (33.3)	6 (66.7)	.721†
HT	13 (48.1)	14 (51.9)	.223*
CHF	9 (42.9)	12 (57.1)	.193*
COPD	2 (25.0)	6 (75.0)	.450†
CRF	2 (100)	0 (0)	.184†
Additional organ resection			
No	55 (72.4)	99 (84.6)	.172*
Yes	21 (27.6)	18 (15.4)	
Spleen	9 (69.2)	4 (30.8)	.702†
Liver	3 (60.0)	2 (40.0)	1.000†
Colon	3 (50.0)	3 (50.0)	.638†
Pancreas	3 (42.9)	4 (57.1)	.392†
Gallbladder	2 (33.3)	4 (66.7)	.198†
Small intestine	1 (50.0)	1 (50.0)	1.000†

CHF = chronic heart failure, COPD = chronic obstructive pulmonary disease, CRF = chronic renal failure, DM = diabetes mellitus, HT = hypertension.

*Pearson-chi square test.

†Fisher exact test.

Table 5

Preoperative and postoperative staging and survey outcomes.

		Survey		
		Dead (n = 76)	Alive (n = 117)	*P*
Clinical tumor stage	T1	2 (2.6)	13 (11.1)	.052†
	T2	8 (10.5)	21 (17.9)	
	T3	42 (55.3)	56 (47.9)	
	T4	24 (31.6)	27 (23.1)	
Pathological tumor stage	T1	3 (3.9)	17 (14.5)	.048*†
	T2	8 (10.5)	18 (15.4)	
	T3	33 (43.5)	47 (40.2)	
	T4	32 (42.1)	35 (29.9)	
Clinical lymph node stage	N0	13 (17.1)	31 (26.5)	.004*†
	N1	11 (14.5)	36 (30.8)	
	N2	27 (35.5)	29 (24.8)	
	N3	25 (32.9)	21 (17.9)	
Pathological lymph node stage	N0	13 (17.1)	47 (40.2)	<.001**†
	N1	8 (10.5)	28 (23.9)	
	N2	17 (22.4)	20 (17.1)	
	N3	38 (50.0)	22 (18.8)	
Clinical metastasis stage	M0	48 (63.2)	95 (81.2)	.005*†
	M1	28 (36.8)	22 (18.8)	
Pathological metastasis stage	M0	41 (53.9)	104 (88.8)	<.001**†
	M1	35 (46.1)	13 (11.2)	

*$P < .05$.

**$P < .01$.

†Pearson chi-square test.

positive lymph nodes or higher LNR tend to live shorter ($P = .001$; $P < .01$).

We calculated cutoff value of 0.09 with, sensitivity is 76.32% for positive to total number of lymph nodes ratio, whereas specivity applies for 64.10%, positive predictive value for 58% and negative predictive value for 80.6% (Table 7). The area under the ROC curve occupies 72.6%, whereas 3.7% was reported to be the standard deviation. In predicting the mortality, positive to total lymph node ratio (with the cutoff ratio of 0.09%) is found to be significantly correlated ($P = .001$; $P < .01$) (Fig. 1).

Table 6

Measures and ratios and their implications on survey outcomes.

		Survey		
		Dead (n = 76)	Alive (n = 117)	*P*
Total lymph node	Median (Min–Max)	24 (1–73)	24 (1–93)	.690†
Positive lymph node	Median (Min–Max)	7 (0–42)	1 (0–43)	.001**†
Positive lymph node/total lymph node	Median (Min–Max)	0.3 (0–1.1)	0 (0–0.9)	.001**†
Preoperative albumin	Median (Min–Max)	3.6 (2.3–4.8)	3.8 (2.3–4.9)	.022*.†
Preop HGB	Median (Min–Max)	10.8 (7–15.8)	11,4 (8.3–16.1)	.285†
CEA	Median (Min–Max)	3.1 (0.8–571.4)	2.1 (0.4–278)	.013*.†
Ca19.9	Median (Min–Max)	12.4 (0.6–390.9)	10.5 (0.6–7835)	.311†

CEA = carcinoembryonic antigen, HGB = hemoglobin.

*$P < 0.05$.

**$P < .01$.

†Mann–Whitney *U* test.

Aside from the number of the positive lymph nodes or the positive to total number of lymph nodes ratio, another predictive factor is the postoperative metastatic status of the patient, significantly being correlated to life expectancy. Postoperatively metastatic gastric cancer cases have significantly lower expectancy of life. Pre- or postoperative T staging does not appear to have a significant impact on this manner. Other parameters like comorbidities or dissection of the other involved organs were not reported to have a significant correlation to life expectancy. Tumor markers, as well as the preoperative albumin measures do not significantly affect the overall survival rates.

Various studies reported the positive lymph node ratio corresponding to an independent risk factor.[38–40] cutoff values vary among studies, according to the statistical method, the number of cases and the duration of the follow-up period. Optimally defining the cutoff value might serve to better predict the prognosis of the gastric cancer cases. In our survey, we utilized a cutoff value of 0.09 following statistical calculations. Liu et al used a cutoff value of 0.1 in their studies in which Seer database was utilized.[41]

Despite the high numbers of the studies focusing on the prognostic measures, there are limited studies which cutoff value was determined. A consensus on the cutoff value might contribute to a more accurate estimation of prognosis following a surgical treatment and thereby in decision making processes regarding the adjuvant therapy. A good example to this is the cutoff value determined by Yalkin et al[17] as 0.18 and therefore median duration of survival was reported as 22 months. With the help of prospective randomized studies focusing on this challenge, addressing a cutoff value, which the experts agree on, might help clinicians to plan more individualized and in some cases more aggressive management strategies.

Despite the statements and their applicable value, this study has some limitations. The number of cases included in this survey might be inadequate. The retrospective design of the survey is also a methodological limitation. The scarcity of the information regarding whether or not the patients concluded the whole course of adjuvant treatment or the kind of adjuvant treatment they were assigned to limits the study in that these parameters might possibly have an impact on the life expectancy. We speculate that these parameters on the other hand, might have a more prominent impact, if any, for the studies in which the long term survival rates are higher.

Table 7

Diagnostic tests and results of ROC curve for positive LN/total number of LN.

	Diagnostic scan					ROC curve		
	Cut off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Area	95% confidence interval	*P*
Positive Ln/Total LN	≥0.09	76.32	64.10	58.00	80.60	0.726	0.653–0.800	.001**

**$P < 0.01$.

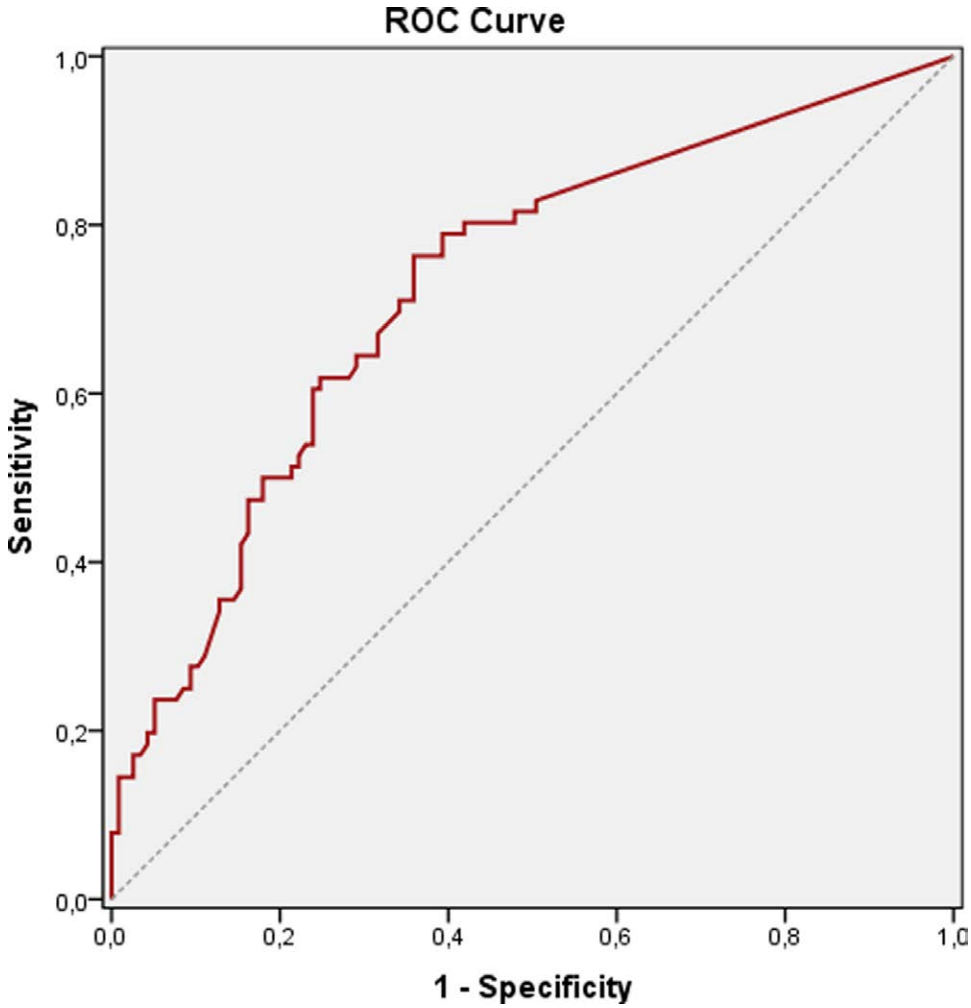

Figure 1. ROC curve analysis of the survey outcomes.

5. Conclusions

In this survey, it is concluded that the N ratio is a significant parameter in predicting the prognosis in cases with gastric adenocarcinoma, following a curative gastrectomy. In cases, where sufficient amount of lymph nodes were dissected, it is possible to determine a cutoff value. In order to obtain a consensus on a cutoff value, multicentered, prospective studies with a larger sample size, longer and follow-up duration are needed. NR might also be integrated into the current staging system and thereby contribute to a better estimation of the prognosis.

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