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Number of Lymph Nodes Assessed in Iranian Gastric Cancer patients

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ABSTRACT

Background: We studied the number of lymph nodes (LN) assessed in gastric cancer, and evaluated the association between different factors and a lower number of LN assessed.

Methods: We conducted a retrospective study in three hospitals in Tehran city, I.R. Of Iran. We used patient medical and pathological reports to obtaine personal and clinical information. We studied the association of being on the N3 stage with the number of assessed lymph nodes (NALN), gender, tumor size, T stage, hospital, tumor site, histopathological diagnosis, tumor grade and age at diagnosis. In addition, we estimated the association between NALN and different clinical variables. A logistic regression model estimated the crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI).

Results: The average number of NALN was 10.48 (±6.9). We found that the probability of being diagnosed as stage N3 was significantly lower in patients who had less than 15 LN assessed in their pathology reports compared to those who had more than 15 LN assessed (OR=0.2; 95% CI 0.1-0.4). The hospital and tumor size were significantly associated with NALN.

Conclusion: Lower NALN led to stage migration and underestimation of the real tumor stage in GC patients. The LN assessments were lower than those recommended by the American Joint Cancer Clinician Association in all the three hospitals included in this study. Developing national guidelines, training surgeons and pathologists, conducting regular monitoring and evaluating the data are necessary to increase NALN and thus improve the staging of GC patients.

Keywords: Number of Assessed lymph nodes, gastric cancer, Iran, gastrectomy, staging

INTRODUCTION:

Gastric cancer (GC) is the third leading cause of cancer death worldwide[1]. GC patients are usually diagnosed in an advanced stage, and the prognosis is usually poor with five-year survival around 25-30%[2]. Surgery remains the only curative treatment for GC patients. Lymph node metastasis and, most importantly the number of involved lymph nodes (N stage), is the most important prognostic factors for operable GC patients[3,4]. It has been shown that the N stage is associated with the number of assessed lymph nodes (NALN) during the pathologic examination of the tumor specimen and the extension of the tumor and the adjacent tissue removed during the operation[4,5]. Inadequate NALN may lead to an underestimation of the N stage, a phenomenon known as "stage migration", influencing the patient's treatment protocol and survival estimation[6-8]. According to the literature, the tumor size[9], hospital volume, the skill of the surgical team and pathologists[10,11], the surgical method including total or sub-total gastrectomy, and lymphadenectomy level (D1-D2) are the most important factors that influence NALN[6,12]. Although different suggestions have been considered as the appropriate threshold for NALN, including 10, 15, and 25 lymph nodes[13-15], there is no doubt that a NALN lower than 10-15 will lead to stage migration[9]. According to the 7th revision of the American Joint Cancer Clinician Association and International Union for Cancer Control (AJCC/UICC) manual, at least 16 lymph nodes should be assessed for the appropriate staging of GC[16]. However, the NALN in routine clinical practice is usually less than the standard recommended. Based on an extensive study on 3,000 patients in 2005, the median NALN was 10 in the USA, and 9% of the patients had no LN assessment[5,10,17]. In addition, studies in Germany, France, and Italy showed a very low NALN in GC patients[4,9,12,13,18,19]. The situation was better in Asian countries where the NALN was higher than 15-30 in China, Japan and Korea[7,20,21] as surgeons prefer more extensive lymphadenectomy (D2 surgery) for GC. We conducted a cross-sectional study and evaluated NALN, N staging and related factors in I.R. Of Iran, where the GC is the most common cancer among men, and the prognosis of this disease is poor[18,22,23].

METHODS:

We conducted a retrospective study through collecting medical and pathological reports from three hospitals, including the Cancer Institute of Iran (2006-2011), as well as Baghiatallah (2010) and Milad (2010-2011) hospitals in Tehran, I.R. of Iran. Inoperable patients and those who had palliative surgery were excluded. We used the criteria from the 7th edition of American Joint Committee on Cancer TNM staging to determine the tumor stage[16].

Cancer Institute of Iran is a national excellence center for Cancer treatment where surgeries are mostly performed by oncology surgeons while Milad and Baghiatallah are General hospitals where general surgeons perform operations.

According to the 5th and 6th UICC/AJCC staging manual, assessment of 15 lymph nodes is recommended for accurate staging of gastric tumors[16], but in the last edition of the manual published in 2010, assessment of 16 lymph nodes was recommended. Because we reviewed pathology reports and obtained data from the patients operated on before 2010, the 15 lymph node count was used as the cut-off point to stratify patients into the low (NALN<15) and high (NALN>=15) lymph node count. The patients were categorized into two groups according to lymph node involvement. The patients who had more than seven involved lymph nodes were classified as stage N3, and the other patients were considered as the reference group for comparison.

Tumor size was defined according to the most signifi-

cant diameter of the tumor reported in the pathology reports. We stratified the patients into two groups, i.e., less than or equal to 4 cm and more than 4 cm. In addition, based on endoscopic findings, surgery notes and pathology reports, the patients stratified to cardia and non-cardia GC.

Statistical analyses:

We studied the association between N3 stage status and different demographic and clinical variables, including the NALN, gender, tumor size, T stage, hospital, tumor subsite, histopathology, tumor grade and age at diagnosis. Furthermore, we estimated the association between the NALN and different variables, including gender, tumor size, T stage, hospital, tumor subsite, histopathology of the tumor, grade and age. We used logistic and multiple regression models to estimate crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (95% CI). STATA statistical software (version 11.0, StataCorp LP, Texas, USA) was used for statistical analysis. This study was approved by the research ethics committee of Tehran University of Medical Sciences.

RESULTS:

Overall, we analyzed the data of 422 patients from the three hospitals (**Table 1**). We decided to keep the name of the hospitals confidential in our analyses and reports. The terms hospital A, B, and C were used to report the hospital-specific results. The average patient age was 61.5 years (SD±0.6), and the majority of patients were male (76%). The prevalence of T1, T2, T3, and T4 were 2%, 24%, 40% and 17%, respectively, and the prevalence of N0, N1, N2, and N3 were 29%, 16%, 22% and 26%, respectively. More than 50% of the patients were diagnosed with stage III. We could not perform staging in 87 (18%) patients.

The median NALN was about 10 (**Table 1**). NALN was lower than 5 in 13% of patients and more than 15 in only 22.5% of the patients. The average of NALN was 10.48 (±6.9) overall. However, it was higher in hospitals C (12.6, SD±9.6) and A (12.07, SD±7.7) than that in hospital B (9.16, SD±5.01).

Given the NALN as the dependent variable, found that the hospital and tumor size were significantly associated with the NALN. The probability of low NALN was higher in hospital B compared to hospital A (OR=3. 4; 95% CI 1.7-6.8). In addition, patients with small tumors had a significantly higher probability of having a report with a low NALN compared to patients with larger tumors (OR=3.0; 95% CI 95% 1.1-8.4). There were no associations between other variables, including age, gender, tumor site, grade, histopathology of tumors, and T stage with low NALN (**Table 2**).

Almost 26% of the patients were categorized as stage N3. It was found that the probability of being diagnosed as stage N3 was significantly lower in patients who had a NALN less than 15 compared to patients in whom the NALN was higher than 15 (OR=0.2; 95% CI 0.1-0.4). Likewise, the chance of diagnosis at stage N3 was significantly lower among patients who had a tumor size of less than 4 cm compared to those who had a large tumor (OR=0. 3; 95% CI 0.1-0.9). Patients with a higher T stage had a higher probability of being diagnosed in stage N3, and a statistically significant positive trend was found between T stage and N stage (P-value 0.035). The chance of being diagnosed in stage N3 increased for every unit of increase in T stage (OR=1.36, 95% CI 1.02-1.8). Although patients in hospital C had a 50% higher probability of diagnosis in stage N3 compared to those in hospital A (OR=1.5, 95%CI 1.0-2.4), the association was not significant in the multivariate model with adjustment for NALN (OR=3.6, 95% CI 0.7-18.0). There was no significant association between N stage and other variables, including gender, age, histopathology, tumor grade and tumor site (**Table 3**).

Table 1. Demographic and clinical information of gastric cancer patients in three referral hospitals in Tehran, I.R. of Iran All figures are numbers and (percentages), if otherwise stated.

Variables		Hospital A	Hospital B	Hospital C	Total
No. of patients		197 (100)	178 (100)	47 (100)	422 (100)
Age (year):	<50	30 (13)	39 (21)	4 (8)	73 (16)
	50-60	41 (18)	40 (22)	11 (23)	92 (20)
	60-70	70 (31)	51 (28)	12 (25)	133 (29)
	≥70	54 (24)	48 (26)	16 (32)	118 (26)
Gender:	Male	48 (21)	42 (23)	11 (23)	101 (22)
	Female	150 (79)	126 (77)	36 (77)	322 (78)
T stage:	T1	5 (2)	18 (10)	0 (0)	23 (5)
	T2	53 (24)	51 (28)	19 (40)	123 (27)
	T3	89 (40)	84 (47)	16 (34)	189 (42)
	T4	39 (17)	23 (12)	0 (0)	62 (13)
	Missing	33 (15)	2 (1)	12 (6)	47 (10)
N stage:	N0	55 (25)	68 (38)	8 (17)	131 (29)
	N1	35 (15)	35 (19)	5 (10)	75 (16)
	N2	54 (24)	39 (21)	7 (14)	100 (22)
	N3	54 (24)	36 (20)	27 (57)	117 (26)
	Missing	21 (9)	0 (0)	0 (0)	21 (4)
TNM Stag:	Stage1	21 (9)	40 (22)	4 (8)	65 (14)
	Stage2	51 (28)	49 (27)	10 (12)	110 (24)
	Stage3	105 (47)	65 (36)	21 (44)	191 (43)
	Stage4	0	0	0 (0)	0
	Missing	42 (19)	24 (13)	21 (44)	87 (18)
Tumor Size:	≤4 cm	39 (17)	78 (43)	7 (14)	124 (27)
	>4 cm	118 (53)	90 (50)	18 (38)	226 (50)
	Missing	62 (28)	10 (5)	22 (46)	94 (21)
Tumor site:	Cardia GC*	19 (8)	42 (23)	8 (17)	69 (15)
	Non Cardia GC	137 (62)	136 (76)	26 (55)	300 (67)
	Missing	63 (28)	0	13 (27)	75 (16)
NALN:**	<15	134 (68)	158 (88.8)	18 (42.7)	312 (73.9)
	≤5	21 (10.7)	29 (16.3)	7 (15)	57 (13.5)
	5-10	68 (34.5)	72 (40.5)	6 (17)	148 (35.0)
	10-15	45 (22.8)	57 (32.0)	5 (10.7)	107 (25.4)
	≥15	63 (32.0)	20 (11.2)	12 (25.5)	95 (22.5)
	Missing	0 (0)	0 (0)	15 (31.9	15(3.
NALN Mean (+/- SD)		12.07 (7,71)	9.16 (5.01)	12.65 (9.6)	10.84 (6.9)
NALN Median		10	9	10	9

*GC: gastric Cancer; **NALN: Number of Assessed Lymph Node

Table 2. Odds ratios and 95% confidence intervals to study the association between different variables and a low number of assessed lymph nodes (NALN<15) in gastric cancer (GC) patients.

Variables		Odds Ratio (95% CI)	
		Crude	Adjusted*
Gender:	Female	Reference	Reference
	Male	1.3 (0.8-2.2)	1.2 (0.5-2.5)
Hospital:	Hospital A	Reference	Reference
	Hospital B	3.7 (2.1-6.4)	3.4 (1.7-6.8)
	Hospital C	0.8 (0.4-1.7)	0.5 (0.2-2.1)
Tumor Site:	Cardia Gastric Cancer	Reference	Reference
	Non-Cardia Gastric Cancer	0.9 (0.5-1.7)	1.3 (0.6-2.9)
Tumor Size:	≥4 cm	Reference	Reference
	<4 cm	4.7 (2.0-11.3)	3.0 (1.1-8.4)
	P value for trend	0.02	0.022
T stage:	T1	Reference	Reference
	T2	0.3 (0.0-1.2)	1.2 (0.2-6.9)
	T3	0.3 (0.1-1.3)	1.1 (0.2-6.5)
	T4	0.5 (0.1-2.5)	2.1 (0.3-14.4)
	P Value for Trend	0.7	0.54
Histopathology:	Adenocarcinoma	Reference	Reference
	Signet ring cell	1.8 (0.9-3.3)	2.3 (0.8-6.0)
	Other	------	--------
Grade:	Grade I	Reference	Reference
	Grade II	0.9 (0.4-2.0)	1.9 (0.7-5.0)
	Grade III	1.0 (0.5-2.2)	1.4 (0.5-3.6)
	P Value for Trend	0.8	0.73
Age (year):	≤50	Reference	Reference
	50-60	0.5 (0.3-1.2)	0.3 (0.1-0.9)
	60-70	0.6 (0.3-1.3)	0.7 (0.2-2.0)
	≥70	0.8 (0.4-1.6)	0.6 (0.8-6.0)
	P Value for Trend	0.62	0.87

*All the variables were included in the multivariable model.

Table 3. Odds ratios and 95% confidence intervals to study the association between different variables and N3 stage in gastric cancer (GC) patients in I.R. Iran.

Variables		Odds Ratio (95% CI)	
		Crude	Adjusted*
Number of counted lymph node:	LN≥15	Reference	Reference
	LN<15	0.15 (0.1-0.2)	1.2 (0.5-2.5)
	P value for trend	0.0001	0.0001
Gender:	Female	Reference	Reference
	Male	0.9 (0.6-1.5)	0.9 (0.5-2.0)
Hospital:	Hospital A	Reference	Reference
	Hospital B	0.7 (0.4-1.08)	1.5 (0.7-3.0)
	Hospital C	1.5 (1.0-2.4)	3.6 (0.7-18.0)
Tumor site:	Cardia GC	Reference	Reference
	Non Cardia GC	1.1 (0.6-2.0)	0.6 (0.3-1.3)
T stage:	T1	Reference	Reference
	T2	7.1 (0.9-54.1)	2.8 (0.3-26.4)
	T3	8.4 (1.1-64.6)	3.1 (0.3-29.0)
	T4	9.7 (1.2-77.1)	5.6 (0.6-56.4)
	P Value for Trend	0.03	0.07
Histopathology:	Adenocarcinoma	Reference	Reference
	Signet ring cell	0.5 (0.3-1.0)	0.6 (0.2-1.4)
	Other	0.3 (0.1-2.0)	0.9 (0.1-8.9)
Grade:	Grade I	Reference	Reference
	Grade II	1.0 (0.5-2.0)	1.6 (0.6-4.4)
	Grade III	0.7 (0.4-1.5)	1.0 (0.4-2.7)
	P Value for Trend	0.7	0.6
Age (year):	≤50	Reference	Reference
	50-60	1.5 (0.7-3.0)	1.0 (0.4-2.8)
	60-70	1.2 (0.6-2.3)	0.8(0.3-2.1)
	≥70	1.1 (0.6-2.2)	0.9(0.1-8.9)
	P Value for Trend	0.4	0.64

*All the variables were included in the multivariable model.

DISCUSSION:

We performed a cross-sectional study and evaluated pathology reports from three referral hospitals in the I.R. Iran. The results showed that NALN was quite low in Iranian GC patients and that the diagnosis of GC patients in stage N3 was associated with the NALN and tumor size. In addition, the NALN was significantly linked to the tumor size and the treating hospital.

The probability of classifying patients in stage N3 was significantly lower for patients with NALN <15 rather than those with NALN ≥15. A significant positive association has been reported between the N stage and the NALN in different studies[4,10,24,25]. Bouvier et al. Studied 749 GC patients and reported a positive correlation between stage N3 and NALN. The risk of misclassification was about 47.1% when the number of LN assessed was fewer than 10, and proportion in stage N3 was significantly lower among these patients compared to those who had a NALN >15[9]. Smith et al. Demonstrated that one additional positive LN will be detected for every five additional LN assessed in GC patients[10]. These data suggest that insufficient NALN will lead to stage migration and under-staging of GC patients.

In line with this report, previous studies have reported a positive association between advanced N stage and large tumor size[10,26,27]. Hong et al. studied 430 gastric cancer patients and reported a significant progressive relationship between N stage and tumor size[21]. Huang et al. reported an increasing trend in LN metastases with an increase in T stage[21,28]. Likewise, Giuliani et al. reported a significant association between the depth of wall invasion and the number of involved lymph nodes[27]. Therefore, it can be expected that bigger tumors are associated with more lymph node metastases. Several studies have reported a significant positive association between NALN and tumor size[19,25,27] although Barbour et al., in a study on 366 patients, could not find such an association. The latter study was restricted to gastroesophageal junction tumors[29]. More invasive or extensive lymphadenectomy with larger tumors may explain this association[6,17]. Although there is evidence about the relationship between tumor size, T stage and N stage, there is no recommendation for lower NALN with smaller tumors. Both the pathology and surgery teams are encouraged to resect and examine an appropriate number of lymph nodes.

The chance of NALN <15 was significantly higher in one of the three hospitals that collaborated in this study. Previous studies have also found a significant difference between hospitals. Variations in hospital volume and caseload, surgery methods, the skill of the surgeons and pathologists and the methods used to evaluate the specimen by the pathologist could explain the difference between hospitals[10,17,27]. We did not collect such data in this survey, and the name of hospitals was kept confidential because of ethical considerations. Therefore, we cannot explain the reasons for the observed differences between hospitals.

According to the results, the median number of NALN was about ten lymph nodes, which is considerably lower than the recommended amount. According to previous reports, such a low NALN is subject to a high rate (47%) of misclassification[6, 9]. We have previously reported that the survival rate of GC in the I.R. of Iran is relatively lower than that in other countries, even in earlier stages of the disease[30-33]. The five-year survival rate for stomach cancer in stage I and stage II has been estimated to be 41% and 30%, respectively, and the survival rates reported for patients in stage IIIA and stage IIIB are 9% and 10%, respectively, indicating a similar survival rate for stage II and stage III patients[23]. We think that stage migration could play a significant role in the underestimation of the patient stage. Inap-

propriate staging of patients could be one reason for the similar survival in stage II and III patients. Misclassification of disease stage not only will lead to a biased estimate of patient survival, but it may also influence the treatment plan and affect patient outcomes. For instance, patients with no lymph node involvement will not receive adjuvant chemotherapy, which is recommended for early-stage patients[17].

Although different thresholds have been suggested for the ideal NALN, varying from 10 to 25, almost all guidelines recommend the evaluation of 10-15 lymph nodes for appropriate staging of GC[6,20,29]. A recent meta-analysis suggested that the NALN should be 16 and supported the recommendations of the AJCC for staging GC. Therefore, surgeons and pathologists should work together and set a goal of 16 NALN for all GC patients[6].

Training of the pathologist and surgeons for meticulous lymphadenectomy and lymph node assessment is suggested to improve the NALN and staging of GC[34-36]. Mahar et al., in a qualitative study conducted to evaluate gastric cancer specimen processing in pathological examinations suggested education and evidence-based procedural guidelines for pathologists and surgeons involved in GC patient care as a way to improve the procedure[34]. Qureshi et al. conducted a survey and reported that 94% of pathologist agreed on the value of further training for appropriate staging in GC[35]. They believed that there is a wide gap between the knowledge of the pathologist and the surgeon regarding existing recommendations and clinical practice guidelines for GC staging.

International differences in the standards of lymph node resection exist for GC patients. The Japanese Gastric Cancer Association has published detailed guidelines for the pathological assessment and staging of GC, describing the 16 nodal compartments as N1, N2, and N3. A more extensive lymph node dissection including dissection of N1 and N2 nodes is called D2 lymphadenectomy, and D1 lymphadenectomy is restricted to the resection of N1 nodes. D2 lymphadenectomy during gastrectomy increases the NALN[37]. Although there is strong supportive evidence from Asia and some European centers for D2 lymphadenectomy, several randomized control trials have failed to show a survival benefit for these patients, leading to controversy among surgeons about the necessity of extended lymphadenectomy[37, 38]. Many investigators believe that moving from incomplete surgery to D1 lymphadenectomy is more critical than performing D1 or D2 lymphadenectomy. Two major clinical trials were conducted in a European Medical Research Council (MRC) Randomized surgical trial in[38], and the Dutch trial[37] compared the effectiveness of D1 and D2 lymphadenectomy. When D1 resection was mandated for the patients, the overall five-year survival rate of the D1 group jumped from 20% to 34% in the British trial and 45% in the Dutch trial[5,10,17]. An autopsy study showed that the median number of LN that can be harvested in D1 lymphadenectomy is 15[12]. In addition, surgical resection studies have reported that it is possible to assess 26 LNs by D1 resection, indicating that D2 resection is not necessary to remove 16 LN as a goal for NALN[6,37]. Therefore, it is important to emphasize appropriate LN dissection both in D1 and D2 lymphadenectomy and a careful evaluation of specimens in pathology labs to achieve the standard goals for NALN and proper staging of GC patients.

In this study, we reported NALN in gastric cancer patients operated on at three referral hospitals. The results of this study could be seen as representative data for Iranian GC patients who have undergone this operation in the entire country. A large sample size, thorough statistical analyses and evaluation of risk fac-

tors for misclassification of N staging and low NALN are among the strong points of this study. However, a limitation of this study was that we could not follow up the patients and evaluate patient survival and its association with N stage and NALN. In addition, we did not have access to data about the surgery method, i.e. partial or total gastric resection, the extension of lymph node dissection, and the skill and experience of the surgeons and the pathologist. An evaluation of these variables in future studies could clarify the reason behind the low NALN and stage migration in the I.R. of Iran. In conclusion, this study demonstrated a low NALN for GC and provided evidence for stage migration and underestimation of the true stage among Iranian GC patients. The variation in NALN in these three hospitals emphasizes the development and implementation of a national clinical practice guideline in the I.R. Of Iran. Developing a national guideline, training surgeons and pathologists and conducting regular audits are necessary to increase NALN and improve the staging of patients.

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Human rights statement and informed consent:

All procedures and methods were in accordance with the national ethical standards involving human subjects and with the Helsinki Declaration of 1964 and later versions. The study was conducted after approval of the ethics committee of Tehran University of Medical Sciences. All patients were provided a general informing consent upon the admission to the hospitals and agreed with the usage of their data in medical research. Because this study used the archived material of the patients who were admitted to the hospital in previous years, ethics committee waived obtaining additional informing consent from the patients for this study.

CONFLICT OF INTEREST:

All authors declared no conflict of interest.

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