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Shall metastatic lymph node ratio be accepted as a prognostic factor in the patients underwent lymphadenectomy with inadequate lymph nodes for gastric cancer?

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ABSTRACT

A relation between the number of resected lymph node and the number of metastatic lymph nodes in gastric cancer is the ratio of lymph nodes demonstrating that pN category was influenced by the extension of the lymphadenectomy. The necessity of accurate lymph node staging has been stated vital while evaluating different treatment consequences. This study evaluates use of ratio of lymph nodes as a prognostic factor in the patients with gastric cancer who underwent the surgery with inadequate lymph nodes removal. Eighty-eight gastric cancer patients with average age 64.3 and male/female ratio 1.3/1 were reviewed. The relation between the number of resected lymph nodes and the number of metastatic lymph nodes was analysed according to 2 different staging systems and evaluated against the other prognostic factors too. Pearson correlation of the variables and multivariate analysis then ROC curve analysis were used to collate the ratio and the pN stage. The number of lymph node metastases increased with the number of resected lymph nodes but the number of metastatic lymph node was not adequate to make the staging true (<15). Though the lymph node ratio is supposed to be a better prognostic factor than the number of metastatic lymph nodes no difference had been exposed favoring the ratio of lymph nodes in the study. ROC curve of both variables did not show difference (0.692 and 0.709, respectively) but both variables were used as a significant prognostic factor (p<0.0001). According to the multivariate analysis the hazard ratio for the pN stages showed a significant increase (p=0.006, HR=1.8, 95% CI=1.184-2,671) with significant difference, which favored pN stages as a better prognostic factor against the ratio. The ratio of the lymph nodes seems not to be a good prognostic factor in the patients underwent lymphadenectomy with 15 lymph nodes or lower. However it needs further evaluation. [Turk J Cancer 2009;39(4):146-154]

KEY WORDS: Gastric cancer, lymph node ratio, lymphadenectomy

INTRODUCTION

Lymph node metastasis is a vital prognostic factor for survival after surgery for gastric cancer. Authors have accepted more proper pathologic staging of the disease and a survival advantage may be given by a curable surgery with the extended lymph node dissection (D2) (1,2). The optimal number of lymph nodes has to be retrieved and examined in order to make reliable staging of the disease. But how is less clear now. Based on different procedural systems using a range of data sets the suggested number

for adequate staging of gastric cancer has been debated in a spectrum from 15 to 25 lymph nodes (1,3). American Joint Committee on Cancer (AJCC)-TNM classification has recommended that more than 15 lymph nodes must be examined (4,5). The less number of nodes reflect the surgery with limited lymph node dissection involving perigastric nodes (D1) (6). To make a true stage grouping with 30 nodes or more (D2 and D3 according to the Japanese Gastric Cancer Association (JGCA)) have been used routinely in Japan (7,8). While the range of lymph nodes retrieved by different surgeons, even when performing the same extent of lymphadenectomy it has not been possible to make a uniform strategy (3,6,9). These conditions result in insufficient staging according to the AJCC suggestion. The ratio of metastatic to resected lymph nodes (the ratio of lymph nodes-RLN) has been used to improve the accuracy of staging. The papers about RLN mostly are from eastern countries related with the patients with 15 or more lymph nodes resected during surgery (10-12). In small volume centers with less extensive lymph nodes resection the RLN should be confirmed because this approach is signified to predict patient survival and avoid stage migration (13,14). In this study, we evaluated the prognostic significance of the RLN in 88 patients with gastric cancer staged according to AJCC classification retrospectively in a single center.

PATIENTS AND METHODS

From January 1996 to December 2006 109 patients with gastric cancer were admitted in the study. Patients were treated in a single center. Of 109 patients 13 were lost to follow up-probably most of all died- and 8 were operated in accordance to the recurrence with severe morbidity, which were not included in the study. Eighty-eight patients were evaluated retrospectively. None had preoperative treatments. Patients with distant metastasis and with recurrence were also excluded. Out of 88 patients 25 were women ranging in age from 44 to 83 years with a mean age of 64.3±9.3 years. Total gastrectomy was performed in 48 patients, distal subtotal gastrectomy was performed in 32 and proximal gastrectomy was performed in 8 patients. Lymphatic dissection was performed in 27 patients with D1, in 58 patients with D2 and in 3 patients with D3 lymphadenectomy.

Lymph nodes were identified and taken back from formalin-fixed specimen. Paraffin embedded nodes were stained by using the haematoxiline-eosin dye, and then inspected for metastasis under the view of a microscope. No particular staining technique was used. Pathologic evaluation of the number of resected and metastatic lymph nodes was performed. Pathologic reports stated 2 early adenocancers, 43 diffuse infiltrative adenocancers, 23 invasive ulcerative type adenocancers, and the rest as polypoid type (fungating) adenocancers. The pathologic outcomes were evaluated in accordance with the principles of the TNM classification of the 6th edition criteria of the International Union against Cancer (UICC) (4,15). Additionally node regions for staging were evaluated according to the criteria of the Japanese Gastric Cancer Association (JGCC) (7).

N ratio intervals were settled on using the optimum cut off value and regarding patients' survival as the dependent variable (log-rank test). Analyses were performed by using the favorable cut off values. The RLN were stratified into 6 subgroups, RLN 0, 0%; RLN 1, 1-19%, RLN 2, 20-39%; RLN 3, 40-59%; RLN 4, 60-79%; RLN 5, 80-100%. We used RLN reclassified into 4 groups, RLN 0%, <30%, 30-60% and >60%.

Follow up for each patient was quit at the last day of January 2007 when was 25.2 (SD:16.9) months (range for survival time, 2-71). During the time period 41 (46.6%) patients died for recurrence or distant metastasis.

Overall survival (OS) and 95% confidence interval (CI) were determined by using Kaplan-Meier test. The log rank test was used to discover differences in the groups of patients. Following independent variables were analyzed; age (in 5 different groups followed each other in a 10-year interval), sex (male vs. female), tumor site (cardia, fundus, corpus, antrum, and linitis plastic), type of resection (R0-R2), T stage (T1-mucosa, sub-mucosa, T2- muscularis propria, subserosa, T3-serosa, T4- expansion to other tissues), Lauren type histology (diffuse, intestinal and mixed type), the number of metastatic lymph nodes (N0-N3), a ratio between metastatic and examined lymph nodes (from the RLN 0 to the RLN 5).

ROC curve analysis was used to compare the RLN and pN stages to identify as a prognostic factor in the diagnosing of gastric cancer.

RESULTS

From 1996 to 2006 88 patients with gastric cancer were enrolled in the study. A curative intended surgery was performed for each patient. Patients' demographics displayed a male/female ratio 1.3/1. Predominant tumor localization was the distal part of the stomach (corpus-antrum) with a greater frequency of intestinal forms at the histological examination. Tumors were mostly identified as locally advanced in the study. The mean number of resected lymph nodes was 14.9 (SD 8.2) (range 6-61). The metastatic number of nodes was 4.5 (SD 5.0) (range 0-20) nodes (Table 1). Ratio of lymph nodes (RLN) was 53.8% (95% CI 47.1-60.5%).

Table 1
Clinical and pathological features

Factor	Group	N
Age (mean ±SD) (year)		64.3 (±9.3)
Sex	Female	26
	Male	42
Localization	Cardia	15
	Fundus	6
	Corpus	26
	Antrum	27
	Linitis	14
Histologic type	Diffuse	33
	Intestinal	39
	Mixed	16
Depth of tumor	T1	6
	T2	20
	T3	39
	T4	23
Number of metastatic nodes	0 (0)	23
	1-6 (1)	38
	7-15 (2)	21
	>15 (3)	6
The ratio of lymph nodes	(0) 0	23
	(1) 1-19	26
	(2) 20-39	11
	(3) 40-59	10
	(4) 60-79	10
	(5) 80-100	8

Six groups of RLN were analyzed for the three subsets of lymph node numbers separately. The comparison between RLN and pN stages done by regression analysis gave a negative correlation between pN stages and survival which was statistically significant (p=0.033). But the correlation between RLN and survival was positive. Cox analysis was done for both variables having been correlated with survival. It was displayed that the pN stages had the highest HR (HR=1.778). It was identified that a significant correlation between the number of metastatic and resected lymph nodes was found in the series (Pearson: 0.321, p<0.0001). The estimation completed by using Cox analysis stated that the ratio of lymph nodes was not the more reliable prognostic factor when comparing to the total number of metastatic lymph nodes criteria (included pN stages) (RLN: p=0.333, HR=1.107 95%CI=0.902-1.358; pN stages: p=0.0006, HR=1.778, 95% CI=1.184-2.671) (Table 2).

Table 2A
Multivariate analysis of both classifications of the RLN and the three subsets of lymph node number

	Standardized Coefficients Beta	t	p
pN stages	-0.321	-2.152	0.033
Reclassified RLN	-0.320	-1.415	0.159
RLN	0.214	1.087	0.278

Table 2B
Same variables were evaluated by using Cox regression

	p	HR	95% CI for Exp(B)	
			Lower	Upper
LN_ratio	0.333	1.107	0.902	1.358
pN stage	0.006	1.778	1.184	2.671

Table 3
The ratio of lymph node classifications

	β	p	HR	95.0% CI for HR	
				Lower	Upper
RLN (0%)		0.000			
RLN (<1-19%)	-1.590	0.000	0.204	0.099	0.419
RLN (20-39%)	0.002	0.998	1.002	0.319	3.149
RLN (40-59%)	-0.412	0.548	0.662	0.172	2.545
RLN (60-79%)	0.362	0.591	1.436	0.384	5.371
RLN (80-100%)	-0.236	0.506	0.790	0.394	1.583
Reclassified RLN (<30%)		0.064			
Reclassified RLN (30-60%)	-1.275	0.022	0.279	0.094	0.832
Reclassified RLN (>60%)	-0.680	0.269	0.506	0.152	1.693

RLN: The ratio of lymph nodes, HR: Hazard ratio, CI: Confidence interval

The metastatic lymph node ratio was classified to six subgroups (from 0% to 100% with each part was of 20%, except 0%). A significant increase in the relative risk was not showed in the subgroups the RLN (Table 3). The subgroups 4-6 and 3-5 did not have statistical significance and the hazard ratios of those were similar. It was decided that a re-staging should be necessary to identify statistically. We categorized into three different groups (0, <30, 30-60, >60). Rearrangements of the new categorization's outcomes were listed in the table 3. RLN gave the similar outcomes as the previous one which defined that was not a reliable prognostic factor against pN stages (Beta:-0.321, p=0.033) (Table 2A).

The ROC curve analysis was performed to make a representation of the tradeoffs between sensitivity and specificity of both the RLNs and the pN stages. Areas under the curve for the tests were almost identical with statistical significance of variables (Table 4). Both tests were capable to display how specific and sensitive when comparing with the prognostic factors. However the areas under the receiving operator characteristic curve of 0.69-0.71 remained overall low. An accuracy measured by the area under the ROC curve was classified as "fair" in the traditional academic point system. Thus there was no tendency in order to decide on the one.

Table 4
Area under curve identified by ROC curve analysis for RLN and pN stages

Variables	Area under curve	Std. Error	p	95% CI Lower	95% CI Upper
Reclassified RLN	0.707	0.036	0.000	0.636	0.778
pN stage	0.709	0.036	0.000	0.638	0.780
RLN	0.692	0.037	0.000	0.620	0.763

CI: Confidence Interval, RLN: The ratio of lymph node

Different prognostic factors were analyzed by using Cox regression analysis. When the different factors were used to evaluate the RLN for metastatic lymph node it was displayed that the hazard ratios decreased regarding the prognostic factors but it kept continuing to be inferior to the pN stages for total number of involved lymph node criteria. In the other factors histological type of tumors and localization had statistical difference with little increased hazard ratio. However the locations of the tumor had also significant difference without hazard ratio increase (Table 5A and 5B).

The similarity between the survival graphs of RLN 0-39% was similar. The survival plot of the RLN with 60-79% was similar to 80-100%. However the other two graphs demonstrated considerable changes in figures 1 and 2. Then when the survival plots of RLN and reclassi-

Table 5A
Multivariate analysis of prognostic data

	β	P	HR	95.0% CI for HR	
				Lower	Upper
Age	0.026	0.029	1.026	1.003	1.051
Sex	0.349	0.179	1.417	0.852	2.357
Depth of tumor					
T1		0.225			
T2	0.285	0.692	0.752	0.184	3.077
T3	0.408	0.414	0.665	0.250	1.771
T4	0.307	0.450	1.360	0.613	3.017
pN stage					
N0		0.001			
N1	1.486	0.001	0.226	0.093	.552
N2	0.998	0.018	0.369	0.162	.840
N3	0.294	0.446	0.745	0.350	1.589
Histologic type					
Diffuse		0.008			
Intestinal	0.134	0.695	-1.143	0.586	2.232
Mixed	0.797	0.010	-2.218	1.211	4.065
Localisation of tumor					
Cardia		0.0			
Fundus	2.348	0.000	0.096	0.035	.260
Corpus	2.881	0.000	0.056	0.013	.238
Antrum	2.423	0.000	0.089	0.035	.223
Linitis plastica	1.897	0.000	0.150	0.057	.395

RLN: The ratio of lymph node, HR: Hazard ratio, CI: Confidence interval

Table 5B
Multivarite analysis of prognostic data with the ratio of lymph nodes

	β	p	HR	95.0% CI for HR	
				Lower	Upper
Age	0.018	0.130	1.018	0.995	1.043
Sex	0.404	0.137	1.497	0.879	2.549
Depth of tumor					
T1		0.203			
T2	0.429	0.549	0.651	0.160	2.647
T3	0.591	0.228	0.554	0.212	1.448
T4	0.160	0.691	1.174	0.532	2.593
Histologic type					
Diffuse		0.005			
Intestinal	0.176	0.614	1.193	0.602	2.364
Mixed	0.918	0.007	2.505	1.290	4.864
Localization of tumor					
Cardia		0.0			
Fundus	2.488	0.000	0.083	0.031	0.226
Corpus	2.987	0.000	0.050	0.012	0.216
Antrum	2.504	0.000	0.082	0.032	0.209
Linitis plastica	1.967	0.000	0.140	0.053	0.370
The RLN					
Reclass. RLN(0%)		0.000			
Reclass. RLN(<30%)	-1.160	0.002	0.313	0.151	0.651
Reclass. RLN(30-60%)	-0.856	0.014	0.425	0.215	0.840
Reclass. RLN(>60%)	0.521	0.162	1.683	0.812	3.491

RLN: The ratio of lymph node, HR: Hazard ratio, CI: Confidence interval

fied RLN had been compared by Log-Rank test there was no statistical significance (Table 6A and 6B).

DISCUSSION

The results from the study with limited series unfortunately did not support the evidence from Western and Japanese series pointing out RLN as an important prognostic factor in patients with gastric cancer (10-12, 14, 16-18). The Japanese Gastric Cancer Association (JGCA) lymph node staging system has provided a comprehensive guide to the treatment of gastric cancer and its metastases, otherwise the 6th edition AJCC lymph node staging system is recently good, safe and reasonable prognostic issue. However both staging systems involve the situation of stage migration in the majority of percentage of cases. The ratio has been suggested by some investigative groups as another staging system which has tried reducing the stage migration (12-14, 19). Numerous studies have displayed that the number of removed lymph nodes de-

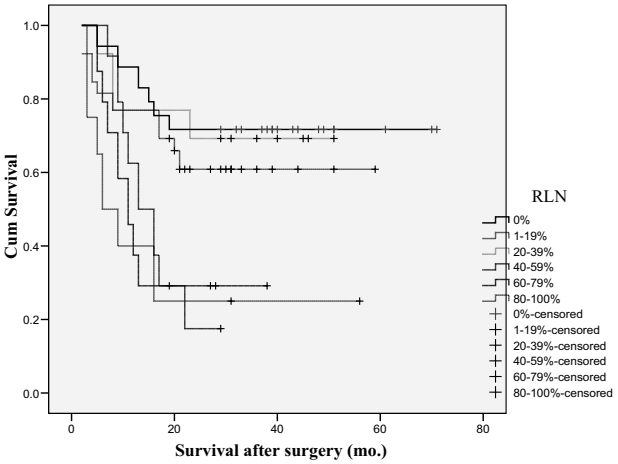

Fig 1. Survival due to the ratio of lymph nodes. The survival plot of RLN 20-39 was similar to RLN with 0% and 1-19%. The survival plot of the RLN with 60-79% was similar to 80-100%.

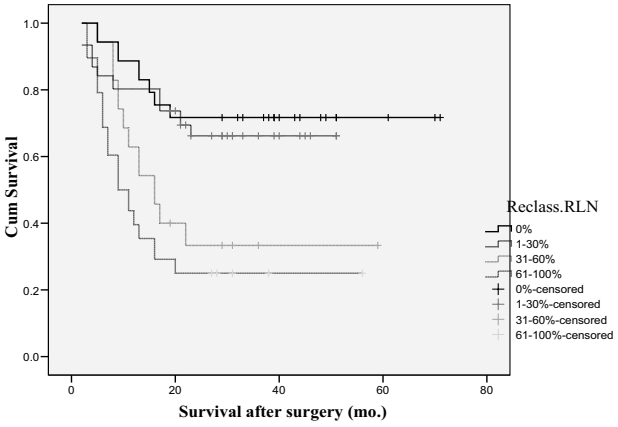

Fig 2. Survival curves of the reclassified RLN

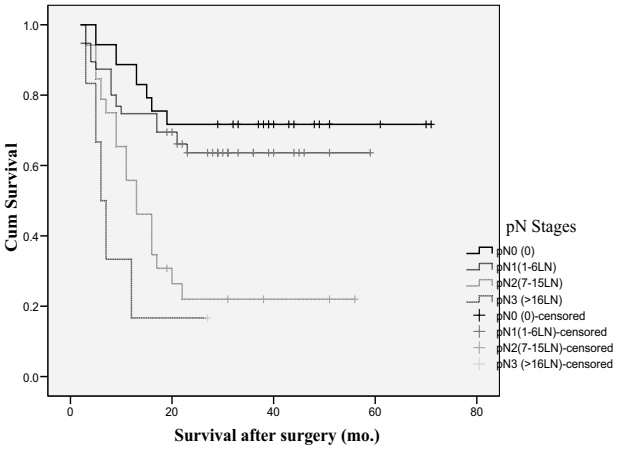

Fig 3. Survival after surgery due to pN Stages

termines the correctness of tumor staging and minimizing the condition of stage migration (3,20). Authors' reports emphasizing the number of metastatic lymph nodes along with the specimen as an important prognostic factor in gastric cancer has influenced some changes in AJCC classification of gastric cancer in 1997 Edition which required removal of at least 16 lymph nodes to allow accurate staging (4,21). Although inadequate lymph node retrieval from the specimen and inter-personality difference in the number of lymph nodes at the particular stations causes limited lymph node removal, the most common reason is the insufficient dissection of the lymph nodes. Wagner (22) showed the number of perigastric and celiac lymph nodes had big variations, which was from 16 to 93 in the patient underwent the same type D2 lymphadenectomy. In this limited series the reason that the average number of lymph nodes was less than 16 (14.9) could be related to the surgical technique and the prior one. The great amount of patient-based studies from the centers has showed that lymph node dissection is unsatisfactory in bigger percentage of patients (6,23). That causes an important problem as correct staging of patients is the main factor to be treated by aggressive adjuvant chemotherapy. Some authors suggested that better disease control could be achieved by the reduction of the tumor aggressiveness (the number of metastatic lymph nodes) by widening the number of removed lymph nodes (patients immunity), which was the RLN (24,25). The concept of the stage migration could be explained like the more increased the observed survival of patients the larger the number of removed lymph nodes. Persiani (26) stated that RLN had the lowest error margin when D1 limited dissection had been done. Then the hypothesis like RLN could act as a good prognostic factor was accepted regardless of the extent of lymph dissection. Except few data about the applicability of RLN in patients underwent surgery with a low number of removed lymph nodes prevents nodal grouping due to the AJCC principles. In the study to establish the best cut-off value the estimation of the increasing of the hazard ratio had been used. Because the average number of removed lymph nodes was less than 16 it was not easy to determine a statistical difference for the stages pN3 and the last subgroup of the RLN (>60% which corresponded to pN3 stage) (Table 5). The survival diagrams for the RLN classified into 6 subgroups showed that the survival curves of the patients were not expected so that curves had some stage migrations. However the survival curves of different total nodal stage were similar to the curves from 4 subgroups of the RLN. According to the Youden's index the maximum J values (j=sensitivity+specificity-1) for

Table 6A
The comparisons between the subgroups of pN stages and the subgroups of reclassified RLN

pN stages	Reclassified RLN	1-30%		31-60%		61-100%	
		Chi-Square	p	Chi-Square	p	Chi-Square	p
pN0 (0 LN)*	1-30%						
	31-60%						
	61-100%						
pN1 (1-6LN)	1-30%			0.973	0.324	0.866	0.352
	31-60%	0.973	0.324			1.313	0.252
	61-100%	0.866	0.352	1.313	0.252		
pN2 (7-15LN)	1-30%			5.068	0.024	2.934	0.087
	31-60%	5.068	0.024			0.048	0.826
	61-100%	2.934	0.087	0.048	0.826		
pN3 (>16LN)*	1-30%						
	31-60%						
	61-100%						

*Comparisons cannot be performed because there is only one valid factor

Table 6B
The comparisons by mantel-Cox test between the subgroups of pN stages and the subgroups of Reclassified RLN

Reclassified RLN	RLN (%)	1-19%		20-39%		40-59%		60-79%		80-100%	
		Chi-Sq.	p	Chi-Sq.	p	Chi-Sq.	p	Chi-Sq.	p	Chi-Sq.	p
0%*	1-19										
	20-39										
	40-59										
	60-79										
	80-100										
1-30%	1-19			3.706	0.054						
	20-39	3.706	0.054								
	40-59										
	60-79										
	80-100										
31-60%	1-19			1.635	0.201	3.218	0.073				
	20-39	1.635	0.201			0.087	0.768				
	40-59	3.218	0.073	0.087	0.768						
	60-79										
	80-100										
61-100%	1-19					3.000	0.083	0.087	0.768	0.197	0.657
	20-39										
	40-59	3.000	0.083					2.302	0.129	0.308	0.579
	60-79	0.087	0.768			2.302	0.129			0.515	0.473
	80-100	0.197	0.657			0.308	0.579	0.515	0.473		

*Comparisons cannot be performed because there is only one valid factor.
RLN: The ratio of lymph nodes, pN: the number of metastatic lymph nodes

RLN, reclassified RLN and pN stages were 0.371, 0.294 and 0.393, respectively. The cut offs of RLN, reclassified RLN and pN stages were 20-39%, <40% and pN1, respectively. Under these conditions the sensitivities of variables were 85%, 82% and 88%, respectively. ROC curve demonstrated no statistical differences between the RLN, reclassified RLN and pN stages as prognostic factors on the patients' survival despite of the fact that those had significant importance on the survival after surgery for gastric cancer with statistically significant p values ($p<0.0001$) (Table 4). That could depend on the limited series or the unsatisfactory surgical procedure with less than 16 lymph nodes. In the Marchet's study (27) analyzing the impact of RLN in 432 patients underwent surgery with less than 15 lymph nodes RLN was superior to AJCC lymph node stages to predict survival. In the study we did not reveal similar outcomes.

The outcomes of multivariate analysis of several prognostic factors in the limited series, age and 2 histological types were described as statistically significant independent prognostic factors, which were reported by some centers where age and depth of tumor were the prognostic predictive value on survival (16,22,24,28). We could not find severe impact of the location of tumor on patients' survival, which was of statistically significant difference for each part of stomach. A multivariate analysis was done for the RLN and the pN stages; the latter one had significant difference and increased hazard ratio on the patients' survival (HR=1.78, 95% CI=1.184-2.671).

Analyzing the survival of the pN stages was not determined by the RLN only to prevent a possible lymph node staging migration. The survival curve for the subgroups of the RLN demonstrated upmigration in the subgroups with 20-39% and 60-79% but downmigration was also displayed in the one with 40-59%. That migration was proposed to the reclassifying of the RLN. The reclassified RLN made the survival plots clear and improved. Otherwise, the downmigration was noticed if the number of removed lymph nodes was lower than that was accepted (14) [14]. We could explain the occurred downmigration in the study with the same argument. Between the two migrations, the upmigration should be preferred because upmigration allows improvement in reliability of the N stages.

In conclusion we confirmed that the stage migration can be induced in the UICC N staging system when the total number of metastatic lymph nodes is used by different investigators. Such stage migration could be adjusted by the RLN based on survival time. But the RLN was not demonstrated an eventful variable which was a prognostic factor for survival when comparing with pN stages while the surgery provided less than 16 lymph nodes removed along with the whole specimen.

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