Gastric cancer : staging, treatment, and surgical quality assurance

Dikken, J.L.

PART II

Multimodality treatment

CHAPTER 8

Preoperative chemotherapy does not influence the number of evaluable lymph nodes in resected gastric cancer

Johan L. Dikken[a,b], Nicole C.T. van Grieken[c], Pieta Krijnen[d], Mithat Gönen[e], Laura H. Tang[f], Annemieke Cats[g], Marcel Verheij[h], Murray F. Brennan[a], Cornelis J.H. van de Velde[b], Daniel G. Coit[a]

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Departments of Surgery[a], Epidemiology and Biostatistics[e], and Pathology[f], Memorial Sloan-Kettering Cancer Center, New York, USA
Department of Surgery[b], Leiden University Medical Center, Leiden, the Netherlands
Department of Pathology[c], VU University Medical Center, Amsterdam, the Netherlands
Comprehensive Cancer Center the Netherlands[d], Leiden, the Netherlands
Departments of Gastroenterology and Hepatology[g], and Radiotherapy[h], the Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands

ABSTRACT

BACKGROUND

While it is suggested that more than 15 lymph nodes (LNs) should be evaluated for accurate staging of gastric cancer, LN yield in western countries is generally low. The effect of preoperative chemotherapy on LN yield in gastric cancer is unknown. The aim of the present study is to determine whether preoperative chemotherapy is associated with any difference in the number of LNs obtained from specimens of patients who underwent curative surgery for gastric adenocarcinoma.

PATIENTS AND METHODS

In 1205 patients from Memorial Sloan-Kettering Cancer Center (MSKCC) and 1220 patients from the Netherlands Cancer Registry (NCR) who underwent a gastrectomy with curative intent for gastric adenocarcinoma without receiving preoperative radiotherapy, LN yield was analyzed, comparing patients who received preoperative chemotherapy and patients who received no preoperative therapy.

RESULTS

Of the 2425 patients who underwent a gastrectomy, 14% received preoperative chemotherapy. Median LN yields were 23 at MSKCC and 10 in the NCR. Despite this twofold difference in LN yield between the two populations, with multivariate Poisson regression, chemotherapy was not associated with LN yield of either population. Variables associated with increased LN yield were institution, female sex, lower age, total (versus distal) gastrectomy and increasing T-classification.

CONCLUSIONS

In this patient series, treatment at MSKCC, female sex, lower age, total gastrectomy and increasing primary tumor classification were associated with a higher number of evaluated LNs. Preoperative chemotherapy was not associated with a decrease in LN yield. Evaluating more than 15 LNs after gastrectomy is feasible, with or without preoperative chemotherapy.

INTRODUCTION

In addition to the number of lymph node (LN) metastases,[1,2] the total number of evaluated LNs is a strong predictor of survival after a curative resection for gastric cancer.[3] In node-negative patients a larger number of evaluated LNs is associated with better survival.[4] Although the minimum number of LNs that should be evaluated for definitive staging has not been defined,[5] a LN yield of 15 or more has been associated with improved overall survival.[6] More than 15 lymph nodes should be evaluated for accurate staging according to the American Joint Committee on Cancer (AJCC) staging manual.[7,8] A lower number of evaluated nodes could lead to *stage migration*, i.e. the migration of patients into a less advanced nodal stage by investigating fewer lymph nodes. When fewer nodes are examined, lymph node metastases could be missed that would have been demonstrated when more lymph nodes would have been investigated.[9] In Western countries, nodal yields are generally low. Studies report that only 29-32% of US patients who undergo a resection with curative intent have 15 or more nodes evaluated.[6,10]

With the increasing use of neoadjuvant therapy in the treatment of resectable gastric cancer,[11-13] the question arises whether lymph node yield is influenced by the use of preoperative chemotherapy. If preoperative chemotherapy decreases the number of evaluable lymph nodes, retrieval of more than 15 nodes would be more difficult to achieve. Retrospective analysis of a series of patients who underwent a curative resection for gastric cancer prior to 1999 showed that preoperative chemotherapy (cisplatin, leucovorin, fluorouracil) had a marked effect on tumor cells in regional lymph nodes, and that the extent of this effect could be correlated with the degree of pathologic response of the primary tumor to chemotherapy.[14] The MAGIC study, in which patients were randomized between surgery with preoperative and postoperative chemotherapy, or surgery alone, also showed that preoperative chemotherapy was associated with a lower number of tumor positive lymph nodes.[11] Neither study reported on differences in total LN yield.

In other malignancies, including rectal[15-17] and breast cancer,[18] preoperative therapy has been associated with a lower number of evaluated lymph nodes. For gastric cancer, data on this topic are not available. The aim of the present study was to determine if preoperative chemotherapy is associated with any change in the number of lymph nodes retrieved from surgical specimens of patients undergoing resection with curative intent for gastric cancer.

PATIENTS AND METHODS

MEMORIAL SLOAN-KETTERING CANCER CENTER

From a prospectively maintained database, 1921 patients were identified who underwent surgery for adenocarcinoma of the stomach (excluding tumors of the gastroesophageal junction) at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1985 and 2009. Patients who underwent surgery other than total or distal gastrectomy (N = 516), patients

with metastatic (M1) disease identified before or during surgery (N = 161), patients without tumor identified on postoperative pathology (N = 26; group was too small to analyze separately) and patients who received preoperative radiotherapy (N = 9) were excluded from the analyses. Of the remaining 1209 patients, 1205 (99.7%) had available information on the number of evaluated LNs. Data on individual patient and tumor characteristics, treatment, and survival were entered into the database.

Neoadjuvant chemotherapy was administered according to hospital practice or active trial protocols. Patients were registered to have received preoperative chemotherapy if they received at least one cycle of treatment. All patients were scheduled for a D2 lymphadenectomy with spleen preservation. Perigastric soft tissues were thoroughly examined in order to identify all possible lymph nodes, and multiple attempts were made in an effort to achieve more than 15 LNs in all specimens. The study was approved by the MSKCC Institutional Review Board.

NETHERLANDS CANCER REGISTRY

The Netherlands Cancer Registry (NCR) is a registry of all newly diagnosed malignancies in the Netherlands. Information in the NCR is routinely collected by trained registrars who extract this information from the hospital records. In the registry, information on patient and tumor characteristics is available as well as data on treatment and survival. Since the date of resection was not registered in the cancer registry, the date of histologically confirmed diagnosis was used to calculate patient's age at operation. Before 2005, no data were collected on the type of gastrectomy.

From the cancer registry, 1934 patients were selected who underwent resection for a primary adenocarcinoma of the stomach between 2005 and 2007. After exclusion of patients who underwent surgery other than total or distal gastrectomy (N = 460), patients with M1 disease (N = 107), patients without tumor identified on postoperative pathology (N = 16), patients without available data on the number of evaluated LNs (N = 89), unknown T-stage and stage group (N = 13) and unknown tumor location (N = 29), 1220 patients were available for analysis.

If a patient had received any preoperative chemotherapy, this was considered sufficient to register 'preoperative chemotherapy' use. Patients received surgery according to clinical guidelines for the treatment of gastric cancer in the Netherlands, advising at least a D1 lymphadenectomy. TNM classification and stage group were recorded by the registrar based on the 6th edition (2002) of the AJCC staging system. Since data in the NCR could not be fully translated into the 7th edition (2010), in this study, the 6th edition is used.

In the Netherlands, an official pathology guideline has been approved only last year. Before that, no official Dutch guideline was available. However, in the Netherlands the 6th edition of the AJCC staging manual was used in the study period, requiring more than 15 lymph nodes for accurate staging. The study was approved by the NCR Review Board.

Table 1. Patient characteristics

	MSKCC (N = 1205)		NCR (N = 1220)		*P*
	N	**%**	**N**	**%**	
Sex					
male	660	*55*	762	*62*	<0.001
female	545	*45*	458	*38*	
Age at diagnosis					
mean	65.3		68.5		
median (IQR)	68	*(57-75)*	70	*(61-77)*	<0.001
Type of surgery					
distal gastrectomy	812	*67*	729	*60*	<0.001
total gastrectomy	393	*33*	491	*40*	
Preoperative chemotherapy					
no	1020	*85*	1065	*87*	0.06
yes	185	*15*	155	*13*	
Tumor location					
proximal	151	*13*	144	*12*	<0.001
middle	413	*34*	277	*23*	
distal	593	*49*	563	*46*	
multiple	48	*4*	236	*19*	
Invasion depth					
T1	335	*28*	200	*16*	<0.001
T2	389	*32*	622	*51*	
T3	444	*37*	341	*28*	
T4	37	*3*	57	*5*	
Nodal status					
N0	541	*45*	487	*40*	<0.001
N1	400	*33*	488	*40*	
N2	182	*15*	194	*16*	
N3	82	*7*	51	*4*	
Number of nodes evaluated					
median (IQR)	23	*(16-32)*	10	*(6-16)*	<0.001
median positive (IQR)	1	*(0-5)*	1	*(0-5)*	0.21
>15 nodes evaluated	929	*77*	312	*26*	<0.001
Tumor differentiation grade					
well-moderate	350	*29*	301	*25*	*<0.001*
poor-undifferentiated	837	*69*	710	*58*	
unknown	18	*2*	209	*17*	
Stage Group AJCC 6th ed.					
I	499	*41*	443	*36*	<0.001
II	249	*21*	341	*28*	
III	351	*29*	341	*28*	
IV	106	*9*	95	*8*	

AJCC: American Joint Committee on Cancer, IQR: Inter Quartile Range, MSKCC: Memorial Sloan-Kettering Cancer Center, NCR: Netherlands Cancer Registry

STATISTICAL ANALYSIS

Differences between the MSKCC and NCR populations were analyzed with the Chi-square test for categorical variables, and the Mann-Whitney U test for continuous variables. LN yields were expressed as the mean and standard deviation of the number of LNs evaluated. Because of a twofold difference in LN yield between the two populations, separate analyses were performed for the MSKCC and NCR groups. Differences in LN yield between groups were calculated with two-sample t-tests. When more than

two subgroups were tested, for ordinal subgroups t-tests were performed between the consecutive groups, whereas for nominal variables the first subgroup was used as reference for the other groups. Multivariate Poisson regression was used to model the number of LNs retrieved as a function of demographic and clinical factors and to identify significant predictors of LN retrieval. Factors that were significant in univariate analysis were included in the multivariate model, except tumor location (which determined the type of surgery that was performed), nodal status (because it is dependent on the number of evaluated nodes), and stage group (because it is dependent on nodal status).
In the MSKCC group, patients with unknown differentiation grade (N = 18) were excluded from the multivariate analysis, because of overdispersion of the multivariate model with these patients included. Since preoperative chemotherapy might decrease the depth of invasion on postoperative pathology, a second multivariate analysis without tumor stage was also performed. All analyses were performed using SPSS (version 17.0.0).

RESULTS

A total of 2425 patients underwent a total or distal gastrectomy with curative intent for M0 gastric adenocarcinoma between 1985 and 2009 at MSKCC (N = 1205) or between 2005 and 2007 in the Netherlands (N = 1220). Patient characteristics are summarized in Table 1. Fifty-nine percent of the patients were male and the mean age was 66.9 years. About two-thirds of the patients underwent a distal gastrectomy. Preoperative chemotherapy was administered in 15% of the MSKCC patients, and in 13% of the NCR patients (P = 0.06). In the MSKCC population, 45% of the patients were node negative, and 55% had positive LNs. In the NCR population, 40% of all patients were node negative, and 60% of the patients had positive lymph nodes (P < 0.001). Large differences in LN yield were observed between MSKCC patients, with a median of 23 sampled nodes (Inter Quartile Range 16-32), and NCR patients, with a median number of 10 (IQR 6-16) sampled nodes (P < 0.001). The percentage of patients with more than 15 LNs examined was 77% in the MSKCC group, and 26% in the NCR group (P < 0.001). Stage group distributions were similar between MSKCC and NCR patients.

Table 2 summarizes differences in LN yield by patient, tumor, and treatment characteristics. Despite significant differences in nodal yield between the two populations, chemotherapy was associated with very little difference in the total number of nodes analyzed. The mean difference of two nodes in each population was significant in the NCR population, but not in the MSKCC group. Differences in LN yield per T-stage based on univariate analysis are depicted in Figure 1. Only in the NCR T2 tumor patient subgroup the number of evaluated lymph nodes was significantly higher after preoperative chemotherapy, likely a random observation. Figure 2 indicates a decrease in LN yield with increasing patient age, which is underscored for both groups in the multivariate analysis.
Despite wide variations in LN yield between the populations, on multivariate Poisson

Table 2. Univariate analysis on the number of evaluated lymph nodes for different patient characteristics, separately analyzed for the MSKCC and NCR population

	MSKCC (N = 1205)			NCR (N = 1220)		
Number of nodes	**Mean**	**± SD**	***P***	**Mean**	**± SD**	***P***
Sex						
male	23.8	± 12.6		11.2	± 7.7	
female	26.4	± 13.1	<0.001	12.0	± 8.7	0.09
Age at diagnosis						
<50	27.6	± 13.2		14.2	± 9.0	
50-69	25.1	± 12.5	0.03	12.5	± 8.2	0.08
≥70	24.0	± 13.1	0.17	10.4	± 7.7	<0.001
Type of surgery						
distal gastrectomy	23.5	± 12.3		10.3	± 7.5	
total gastrectomy	27.9	± 13.5	<0.001	13.3	± 8.6	<0.001
Preoperative chemotherapy						
no	24.7	± 13.0		11.3	± 8.1	
yes	26.1	± 12.3	0.18	13.3	± 7.8	0.004
Tumor location						
proximal	26.1	± 13.1		13.8	± 8.5	
middle	26.0	± 13.7	0.95 [a]	12.1	± 8.7	0.06 [a]
distal	23.5	± 12.0	0.62 [a]	10.9	± 7.6	<0.001 [a]
diffuse	29.0	± 14.2	0.18 [a]	10.8	± 8.0	<0.001 [a]
Tumor stage						
T1	22.9	± 12.7		8.8	± 7.0	
T2	25.2	± 12.4	0.02	11.3	± 7.9	<0.001
T3	26.0	± 12.9	0.36	13.3	± 8.6	<0.001
T4	28.4	± 16.8	0.28	12.5	± 7.7	0.47
Nodal status						
N0	23.1	± 12.7		8.9	± 7.7	
N1	23.9	± 12.5	0.36	10.9	± 6.7	<0.001
N2	27.2	± 11.8	0.003	15.8	± 6.0	<0.001
N3	37.1	± 11.0	<0.001	26.3	± 8.6	<0.001
Tumor differentiation grade						
well-moderate	24.7	± 13.6		10.5	± 7.6	
poor-undifferentiated	25.1	± 12.6	0.60	12.0	± 8.3	0.008
Stage group AJCC 6th ed.						
I	22.9	± 12.5		9.0	± 7.5	
II	25.0	± 13.0	0.04	10.6	± 7.1	0.002
III	24.5	± 11.7	0.68	13.2	± 7.1	<0.001
IV	35.7	± 13.2	<0.001	20.2	± 10.2	<0.001

P-values are based on comparison of consecutive categories, except for *Tumor Location*
MSKCC: Memorial Sloan-Kettering Cancer Center, NCR: Netherlands Cancer Registry
[a] as compared to proximal

regression (Table 3), preoperative chemotherapy was not associated with a significant difference in LN yield in either population. Factors that were associated with a significant increase in LN yield were the same for the MSKCC and NCR groups: female gender (+13.2% and +9.0%), decreasing age (+3.7% and +7.1% per 10 years), total gastrectomy (+17.4% and +20.8%) and increasing tumor stage. Excluding tumor stage from the multivariate model (not shown) only changed the effect of tumor grade in the NCR group: this became significant.

Figure 1. Univariate comparison of lymph node yield per T category, (a) MSKCC patients, (b) NCR patients

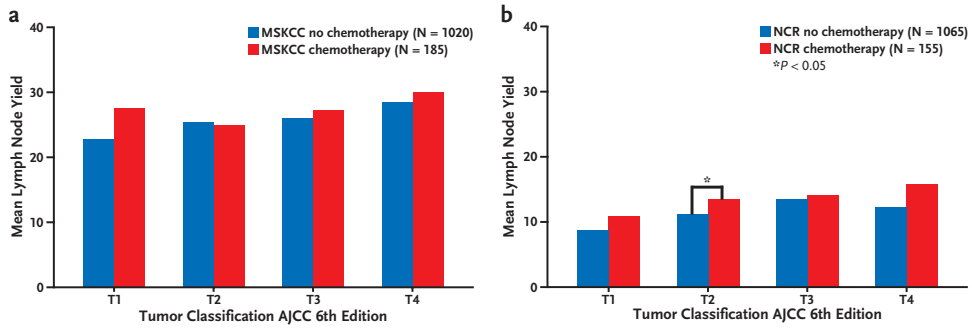
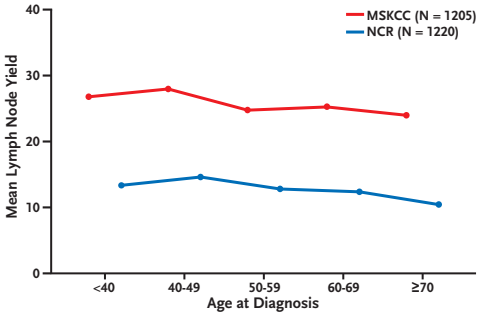


Figure 2. Univariate comparison of lymph node yield per age category



DISCUSSION

Although the use of preoperative chemotherapy has been associated with a decrease in tumor cells in regional lymph nodes in gastric cancer,[14] and has been associated with nodal downstaging in one recent randomized study,[11] there are no reports available on the association of preoperative chemotherapy on the total number of evaluated lymph nodes in gastric cancer.

In the present study, preoperative chemotherapy was not associated with any change in the number of evaluated lymph nodes in gastric cancer, either in a high-volume US center, or a population-based cancer registry. Performing this analysis in two entirely different populations increases the robustness of the results, given the comparable outcomes in both groups.

Comparing LN yield between the two populations reveals a large difference in the median number of evaluated nodes. Median LN yield is 23 in the MSKCC group and 10 in the NCR group. A US-population-based study on gastric cancer patients also found a median number of 10 evaluated nodes.[10] While for adequate staging more than 15 LNs should be evaluated,[7] in the current study, the percentage of patients with more than 15 LNs examined was 77% in the MSKCC group, but only 26% in the NCR group. These findings

Table 3. Multivariate Poisson regression on the number of evaluated lymph nodes, separately analyzed for the MSKCC and NCR population

	MSKCC (N = 1187)			NCR (N = 1220)		
	RR[a]	95% CI	*P*	RR[a]	95% CI	*P*
Sex						
male (ref)	1.000			1.000		
female	1.132	1.069-1.199	<0.001	1.090	1.009-1.178	0.03
Age at diagnosis[b]	0.963	0.942-0.985	<0.01	0.929	0.900-0.959	<0.001
Type of surgery						
distal gastrectomy (ref)	1.000			1.000		
total gastrectomy	1.174	1.104-1.248	<0.001	1.208	1.118-1.305	<0.001
Preoperative chemotherapy						
no (ref)	1.000			1.000		
yes	0.994	0.917-1.076	0.87	1.046	0.934-1.171	0.44
Tumor classification						
T1 (ref)	1.000			1.000		
T2	1.111	1.029-1.200	<0.01	1.274	1.130-1.437	<0.001
T3	1.118	1.035-1.209	<0.01	1.455	1.280-1.654	<0.001
T4	1.184	1.006-1.394	0.04	1.327	1.087-1.621	<0.01
Tumor differentiation grade						
well-moderate (ref)	1.000			1.000		
poor-undifferentiated	0.937	0.876-1.002	0.06	1.062	0.966-1.168	0.21
unknown	[c]			1.013	0.895-1.147	0.83

ref: reference category

[a] The RR (relative risk) of an increase in the lymph node yield for the covariate. For example, an RR of 1.132 means that females in the MSKCC group had 1.132 times as many lymph nodes examined (ie, a 13.2% increase).

[b] Estimates the ratio of a 10-year incremental increase in age

[c] 18 patients were excluded because the multivariate model was unable to fit this small group

reflect the experience of gastric cancer surgery and specimen processing of a dedicated cancer hospital in comparison to a nationwide group of academic and general hospitals where gastric cancer surgery is not centralized and is performed in lower volumes. A recent survey in Denmark, where gastric cancer surgery was centralized from 37 to 5 hospitals in 2003, showed an increase in the number of patients with at least 15 LNs evaluated from 19% to 75% in five consecutive years.[19]

In the current study, on univariate analysis, preoperative chemotherapy was associated with a statistically significant higher LN yield in the NCR (+2 nodes), but not in the MSKCC group. This is not a biologically significant difference, but a consequence of the smaller standard deviation in the NCR group.

With multivariate analysis, which adjusts for the other demographic and tumor characteristics, preoperative chemotherapy was not associated with a change in LN yield in either the high-volume center or the population-based registry. The difference with the univariate analysis may be explained by the higher percentage of patients receiving chemotherapy in the younger age group (<50: 29%) as compared to the older groups (50-69: 19% and ≥70: 6%), while the younger patients also have a higher LN yield. Adjusting for age group in the multivariate analysis offsets this effect. In the multivariate analysis,

female gender remained associated with an increase in LN yield in both groups, with 13% more nodes in the MSKCC group and 9% more nodes in the NCR population. This has previously been reported for gastric[10] and rectal cancer.[20] It can be hypothesized that differences in immune system that exist between males and females[21] might be responsible for this difference. Increased age was associated with a decrease in lymph node yield, also previously described for gastric,[10,22] colorectal,[15] and breast cancer.[23] This might be explained by a less aggressive lymph node dissection in elderly patients, or possibly a lower absolute number of lymph nodes present in the elderly, due to age-associated changes in the immune system.[24] The increase in LN yield from total as compared to a distal gastrectomy is an expected finding given the more extended operation. Increasing T-stage was also associated with an increasing LN yield. It has been suggested that larger tumors may cause a more intense immune response within the regional LNs, making them more visible to pathologic examination and possibly leading to higher LN yields.[25]

The relation between nodal status and LN yield is complex and is influenced by multiple factors. First, nodal status can have an effect on LN yield: LN metastases are often enlarged and easier to find during surgery and specimen processing by the pathologist. On the one hand, the presence of LN metastases could therefore lead to an increased LN yield; on the other hand, it could decrease LN yield if the surgeon or pathologist limits the search for extra nodes once positive nodes are identified.[26] The relatively uniform D2 dissection performed in the MSKCC dataset argues against this latter possibility. This problem might be overcome by using fat dissolving techniques to identify all LNs present in a specimen,[27] but this very labor intensive technique was not regularly performed in either of our patient populations. Secondly, LN yield determines AJCC N status (instead of nodal status determining LN yield), because the number of positive nodes can never be higher than the total number of LNs. Therefore, nodal status was left out of the multivariate regression model.

Similar studies have been performed for other cancer types. One study has analyzed the effect of preoperative chemoradiotherapy on nodal yield in adenocarcinoma and squamous cell carcinoma of the esophagus. No differences were detected in the number of lymph nodes sampled.[28] For rectal cancer, several studies report a lower total number of lymph nodes after preoperative (chemo)radiotherapy.[15-17,20,29] For breast cancer, conflicting results are found: some studies report a decrease in nodal yield after preoperative chemotherapy,[18,30] while others find no difference.[31,32] Overall, no uniform relation between preoperative therapy and nodal yield can be defined for all cancer types. It can however be hypothesized that preoperative radiotherapy does have an effect on LN yield, while for preoperative chemotherapy this effect might be dependent on the type of chemotherapy administered. Furthermore, different surgical and specimen processing techniques might influence the effect of preoperative therapy on nodal yield for different cancer types.

The number of evaluated LNs in a specimen is influenced by three main factors: First, patient and tumor-related factors contribute to LN yield. Age, gender, activity of the immune system all contribute to the absolute number of LNs present in a patient. Enlarged, tumor positive nodes will be found more easily, thereby increasing LN yield. Secondly, the surgeon determines the number of nodes that are dissected, by defining both the extent of gastrectomy, and the extent of the lymph node dissection performed. The third and potentially most important factor is the pathologist, who will find a certain number of LNs based on specimen processing protocols, and available resources. The only available pathologist related factor in the current series is the study population. By separately analyzing the two populations, an adjustment is made for high versus low volume center.

In conclusion, the increasing use of systemic therapy raises the question if preoperative chemotherapy reduces the number of evaluated lymph nodes in gastric cancer resection specimens. The current study was performed in two entirely different populations: a high-volume cancer center and a nationwide cancer registry. In both populations, the administration of preoperative chemotherapy was not associated with a difference in LN yield. Therefore the threshold of what is considered an adequate assessment of regional nodes in gastric cancer should not be changed for patients who have received neoadjuvant chemotherapy.

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