Impact of retrieved lymph nodes count on short-term complications in patients with gastric cancer

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Abstract

Background: It is well established that retrieved lymph nodes (RLNs) count were positively correlated with better overall survival in gastric cancer (GC). But little is known about the relationship between RLNs count and short-term complications after radical surgery.

Methods: A total of 1487 consecutive GC patients between January 2016 and December 2018 at Nanjing Drum Tower Hospital were retrospectively analyzed. Univariate analyses were performed to elucidate the association between RLNs count and postoperative complications. We further identified clinical factors that might affect the RLNs count.

Results: Among all of the patients, postoperative complications occurred in 435 (29.3%) patients. The mean RLNs count was 25.1 and 864 (58.1%) patients were diagnosed with lymph node metastasis. Univariate analyses showed no significant difference between RLNs count and postoperative complications (both overall and stratified by CDC grade). Univariate and multivariate analyses further revealed that type of resection, tumor invasion, and lymph node metastasis were associated with RLNs count.

Conclusions: The current study demonstrated that RLNs count was not associated with postoperative short-term complications following gastrectomy of GC, which provided a rationale for the determination of a proper RLNs count of curative gastrectomy.

Background

There are approximately one million new cases of gastric cancer (GC) each year worldwide, and half of them occur in Eastern Asia, including China, Japan, and South Korea[1]. Despite advances in early screening and comprehensive treatment of GC, it remains the third most common cause of cancer-related death in the world[2]. For advanced GC, a consensus has been reached of radical gastrectomy with D2 lymphadenectomy[3]. However, there is still controversy over the number of retrieved lymph nodes (RLNs) for accurate pathological staging.

Several studies have reported that RLNs count was positively correlated with better overall survival in GC, even in lymph node-negative GC[4-7]. An RLNs count of ≥16 has been recommended by the 8th edition TNM classification for GC to guarantee the accurate pN stage[8]. Moreover, Okajima *et al.* suggested an optimal RLNs count of ≥25 for nodal staging[9]. Recently, by stratum analysis of 7,620 patients, Deng *et al.* proposed an optimal RLNs count of ≥16 for lymph node-negative GC and >30 for lymph node-positive GC[10]. These above studies are all conducted by comparing the RLNs count with long-term survival. But little is known about the relationship between the RLNs count and short-term complications after radical surgery.

Postoperative complications of GC pose a significant impact on the length of postoperative stay and hospital charges, which further affect the quality of life[11]. Therefore, investigating the relationship

between RLNs count and postoperative short-term complications would provide more comprehensive evidence for selecting the appropriate RLNs count.

Methods

Patients

A total of 1487 consecutive GC patients between January 2016 and December 2018 at Nanjing Drum Tower Hospital were retrospectively reviewed. All patients underwent curative (R0) gastrectomy and were histologically confirmed. The exclusion criteria were as follows: (1) multivisceral resection; (2) patients accepting preoperative radiotherapy or chemotherapy; (3) patients with previous stomach surgery; (4) patients with incomplete clinical data. This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital.

Data collection

Data for preoperative characteristics, intraoperative index, and postoperative features were extracted. Preoperative characteristics included age, gender, body mass index (BMI), comorbidities, and laboratory data. The intraoperative index involved the American Society of Anesthesiologists (ASA) grade, surgical approach, type of resection, operation time, and blood loss. Postoperative features included depth of tumor invasion, tumor site, retrieved lymph node count, lymph node metastasis, lymph node ratio (LNR), log odds of positive lymph nodes (LODDS), pTNM stage, Lauren subtype, short-term complications, postoperative stay, and total hospital charges. LNR was defined as the ratio of positive to retrieved lymph nodes. LODDS was calculated by log [(positive lymph nodes + 0.5)/(total lymph nodes - positive lymph nodes + 0.5)][12]. The postoperative short-term complications occurring in the hospital or within 30 days were collected. All complications were evaluated according to the 1[13].

Statistical analysis

Statistical analyses were conducted by SPSS 19.0 (Chicago, IL, USA). Continuous variables were shown as means ± SD. Student's t test was applied for normally distributed data; Mann-Whitney U test was applied for non-normally distributed data. Categorical variable data were presented as numbers and analyzed using the Chi squared test or the fisher exact test. Univariate and multivariate analyses were performed to analyze risk factors associated with the postoperative complications or retrieved lymph node count. The optimal cut-off values of LNR and LODDS were determined by receiver operating characteristic (ROC) analysis. All statistical tests were conducted two-sided and statistical differences were termed as P value < 0.05.

Results

Patient characteristics

The background characteristics of the patients enrolled in this study were presented in Table 1. There were 1487 GC patients in all, including 1089 (73.2%) men and 398 (26.8%) women. The median age was 60 years with a range from 21 to 96 years. 1411 (94.9%) patients underwent open gastrectomy while 76 (5.1%) underwent laparoscopic surgery. The type of resection was distal gastrectomy in 617 (41.5%) patients, proximal gastrectomy in 163 (11.0%), and total gastrectomy in 707 (47.5%). Mean operation time was 232 min and mean intraoperative blood loss was 221ml. Pathological results were stage I/II/III/IV in 506/368/597/16 patients respectively. The mean RLNs count was 25.1 (range, 2-84) and 864 (58.1%) patients were tested with lymph node metastasis. Overall, postoperative short-term complications occurred in 435 (29.3%) patients. The mean postoperative stay was 12 days and mean total hospital charges were 7.5×10^4¥.

Association between perioperative characteristics and postoperative complications

As presented in Table 2, univariate and multivariate analyses indicated that postoperative short-term complications were significantly correlated with age, gender, level of preoperative serum albumin, and operation time. Stratified analyses by type of resection revealed that complications occurred frequently in proximal gastrectomy compared with total gastrectomy, while there was no significant difference between distal gastrectomy and total gastrectomy. No significant association was observed between RLNs count and overall postoperative complications.

Impact of RLNs count on postoperative complications

Of the total of 1487 patients, 435 (29.3%) developed complications; 74% (323 of 435) encountered a single complication, and 26% (112 of 435) encountered multiple complications. The details of patients with short-term complications based on the Clavien–Dindo classification are 15.5% for grade I, 9.2% for grade II, 4.0% for grade III, 0.3% for grade IV, and 0.2% for grade V. The rate of major complications (CDC grade ≥III) were 4.5%. The median RLNs count in this study was 24. So, we divided all patients into two groups based on the median RLNs count. Univariate analyses showed no significant difference between RLNs count and postoperative complications (both overall and stratified by CDC grade) (Table 3).

Factors associated with RLNs count

We further explored the potential factors associated with RLNs count. Univariate analyses revealed that preoperative serum albumin, type of resection, tumor invasion, lymph node metastasis, and pTNM stage were associated with RLNs count ($p < 0.05$; Table 4). Stratification by type of resection showed that RLNs count in either distal gastrectomy or proximal gastrectomy was significantly lower than that in total gastrectomy. Multivariate analyses further indicated that type of resection, tumor invasion, and lymph node metastasis were still significantly associated with RLNs count ($p < 0.05$; Table 4).

Discussion

Nodal involvement significantly affected the prognosis of GC patients because it is the major root of tumor relapse after surgery[14, 15]. Thus, standardized lymph nodes dissection is the basic requirement for curative (R0) gastrectomy. Curative gastrectomy with D2 lymphadenectomy has been considered as the standard fashion for decades in eastern Asia, especially in Japan[16, 17]. This procedure has been gradually accepted by Western countries in recent years[18, 19]. As for the RLNs count, the 8th edition TNM classification for GC recommended dissecting at least 16 lymph nodes. Moreover, emerging evidence revealed the positive correlations between RLNs count and overall survival of GC patients[4, 5, 20]. By comparing RLNs count to survival time, Okajima *et al.* suggested an optimal RLNs count of ≥25[9]; Deng *et al.* proposed an optimal RLNs count of ≥16 for lymph node-negative GC and >30 for lymph node-positive GC by stratum analysis of 7,620 patients[10]; Sano *et al.* reported that RLNs count preferably achieved 30 or more by a multicenter study enrolling 25,411 patients[20]. Additionally, LNR and LODDS were also reported to be associated with GC prognosis[21-23]. These above studies mainly focused on the relationship between RLNs count and long-term prognosis. However, little is known about its effects on postoperative short-term complications.

In this study, we concentrated on the association between RLNs count and short-term prognosis. Univariate analyses showed no significant difference between RLNs count and postoperative complications (both overall and stratified by CDC grade). Therefore, more lymph nodes were encouraged to be dissected from the perspective of short-term prognostic.

Although curative gastrectomy with D2 lymphadenectomy is considered a pivotal strategy for advanced GC, there are international and institutional differences in the number of RLNs count [24, 25]. Various factors were reported to influence the RLNs count, including the confidence and enthusiasm of doctors (both surgeons and pathologists), surgical situation, and innate lymph node count in each patient[7, 9]. In our study, we concluded that RLNs count was related to type of resection, tumor invasion, and lymph node metastasis. Of note, RLNs count was positively correlated with the lymph node metastasis rate, which underlined the importance of RLNs count for accurate staging.

Actually, for a thorough pathological examination, RLNs should be individually divided from a complete tissue sample after surgery. Owing to much time and effort was required during this procedure, it has not been widely implemented clinically. Therefore, the examined lymph nodes count by pathologists might be lower than the dissected lymph nodes count. Multiple attempts have been conducted to improve the

detection rate of lymph nodes[26-28]. Li *et al.* elucidated that the mean number of RLNs could be significantly elevated by injecting carbon nanoparticles before surgery compared with controls (38.33 vs 28.27)[26]. Bruno and colleagues reported a twofold lymph node pick up rate utilizing methylene blue staining than unstained groups (35 vs 17)[27]. Several dye materials were also used to increase the number of lymph nodes dissected during surgery, such as fluorescent indocyanine green (ICG) and 5-aminolevulinic acid (5-ALA)[29, 30].

We acknowledge that this study had some potential limitations. First, it was a retrospective, single center study, so the results might be flawed because of residual confounding factors. Second, the RLNs count was closely related to the quality of surgeons and pathologists. The perioperative variables might differ in different doctors. Therefore, multi-center studies are needed to confirm our results.

Conclusions

In conclusion, the current study demonstrated that RLNs count was not associated with postoperative short-term complications following gastrectomy of GC. Therefore, our analysis encouraged more lymph nodes to be dissected for accurate pathologic staging.

Abbreviations

BMI: body mass index; CRP: C-reactive protein; ASA: American Society of Anesthesiologists; RLNs: retrieved lymph nodes; LNR: lymph node ratio; LODDS: log odds of positive lymph nodes.

Declarations

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Availability of data and materials

Access to the data and the calculation method can be obtained from the authors by email (medsunfeng@163.com).

Authors' contributions

FS worked on the study design, collected data, and drafted the manuscript. SL contributed to the study design and data collection. PS was involved in data collection and extraction. CZ helped collect data. WG was involved in study design and data extraction. MW revised the manuscript. All authors have read and approved the final manuscript.

Ethics approval and informed consent to participate

This retrospective study was approved by the ethics committee of Nanjing Drum Tower Hospital, Medial School of Nanjing University. Due to the retrospective nature, the requirement for informed consent was waived by the IRBs from Nanjing Drum Tower Hospital, Medial School of Nanjing University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Demographic and clinical features of patients.

Characteristics	N=1487	Characteristics	N=1487
Age (y)	60.4±17.3	Tumor site	
Gender (n)		Cardia/fundus	452
Male	1089	Body	381
Female	398	Pylorus/antrum	654
BMI (kg/m^2)	23.0±3.5	RLNs count	25.1±9.1
Preoperative comorbidities (n)		Lymph node metastasis	
Previous abdominal surgery	209	Positive	864
Diabetes mellitus	131	Negative	623
Hypertension	488	LNR	0.17±0.24
Preoperative laboratory data		LODDS	-0.96±0.75
Serum albumin (g/L)	39.4±3.3	pTNM stage I/II/III/IV	506/368/597/16
CRP (g/L)	6.0±12.4	Lauren subtype	
ASA ≥3	884	Intestinal	620
Mode of surgical approach (n)		Diffuse	428
Laparoscopic	76	Mixed	401
Open	1411	Unknown	38
Type of resection (n)		Postoperative complications	
Distal gastrectomy	617	Positive	435
Proximal gastrectomy	163	Negative	1052
Total gastrectomy	707	Postoperative stay (days)	12.0±8.1
Operation time (min)	232.3±61.8	Total hospital charges (10^4¥)	7.5±3.5
Blood loss (ml)	221.8±204.5		
Tumor invasion			
T1-2	631		
T3-4	856		

BMI = body mass index; CRP = C-reactive protein; ASA = American Society of Anesthesiologists; RLNs = retrieved lymph nodes; LNR = Lymph node ratio; LODDS = Log odds of positive lymph nodes.

Univariate and multivariate analyses of characteristics associated with tive complications.

istics	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
	1.581	1.232-2.029	<0.001	1.578	1.219-2.044	0.001
	0.765	0.597-0.979	0.033	0.710	0.551-0.916	0.008
n^2)	0.988	0.956-1.020	0.449			
ive comorbidities						
abdominal surgery	0.996	0.722-1.374	0.982			
mellitus	1.156	0.787-1.700	0.460			
ısion	1.128	0.891-1.428	0.317			
ive laboratory data						
lbumin <35g/L	1.660	1.162-2.372	0.005	1.544	1.068-2.232	0.021
)g/L	1.315	0.892-1.938	0.167			
	1.047	0.834-1.315	0.693			
urgical approach						
copic	0.684	0.394-1.188	0.178			
section			0.067			0.025
strectomy		Reference			Reference	
strectomy	1.183	0.932-1.503	0.167	1.242	0.972-1.588	0.083
l gastrectomy	1.503	1.047-2.157	0.027	1.613	1.117-2.329	0.011
time	1.002	1.001-1.004	0.009	1.003	1.001-1.005	0.002
;	1.000	1.000-1.001	0.094			
e			0.780			
undus		Reference				
	1.054	0.811-1.370	0.693			
antrum	0.947	0.716-1.252	0.701			
asion (T3-4)	1.216	0.968-1.527	0.093			
	0.991	0.979-1.004	0.165			
de metastasis	1.044	0.832-1.310	0.707			
5	1.213	0.969-1.517	0.091			
-1.1	1.219	0.975-1.525	0.083			
ge (≥III)	1.036	0.826-1.300	0.757			
btype			0.952			
l		Reference				
	0.866	0.427-1.754	0.689			
	0.904	0.442-1.848	0.782			
n	0.925	0.452-1.894	0.832			

dy mass index; CRP = C-reactive protein; ASA = American Society of ologists; RLNs = retrieved lymph nodes; LNR = Lymph node ratio; LODDS = of positive lymph nodes; OR = odds ratio; CI = confidence interval.

Table 3. Univariate analyses of postoperative complications associated with RLNs count.

Characteristics	All	RLNs count		P value
		<25	≥25	
Overall (n)	435	248	187	0.062
Grade I (n)	231	132	99	0.198
Fever >37.5°C	144	85	59	
Emesis	156	83	73	
Pain	30	18	12	
Abdominopelvic collection	1	1	0	
Pleural effusion	4	4	0	
Grade II (n)	137	78	59	0.366
Blood transfusions	60	38	22	
Early postoperative bowel obstruction	2	1	1	
Gastroparesis	25	14	11	
Liver-function abnormalities	1	1	0	
Wound infection	8	5	3	
Pneumonia	27	15	12	
Intra-abdominal infections	20	12	8	
Urinary tract infection	4	0	4	
Enteritis	3	1	2	
Bacteremia	14	7	7	
Grade III (n)	59	32	27	0.878
Anastomotic leakage	23	14	9	
Lymphatic leakage	8	3	5	
Pancreatic fistula	2	0	2	
Biliary fistula	1	0	1	
Bleeding	8	5	3	
Abdominopelvic collection	1	1	0	
Pleural effusion	9	5	4	
Intra-abdominal abscess	2	1	1	
Wound disruption	3	3	0	
Delayed wound healing	4	3	1	
Gastroparesis	1	0	1	
Early postoperative bowel obstruction	1	0	1	
Splenic necrosis	1	0	1	
Grade IV (n)	5	4	1	0.452
Heart failure	1	1	0	
Kidney failure	1	1	0	
Brain infarction	1	0	1	
MODS	2	2	0	
Grade V (n)	3	2	1	1.000
Grade ≥III (n)	67	38	29	0.562

RLNs = retrieved lymph nodes; MODS = multiple organ dysfunction syndrome.

Univariate and multivariate analyses of factors associated with RLNs count ≥25.

istics	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P
	0.873	0.689-1.105	0.259			
	1.043	0.828-1.312	0.723			
n^2)	0.972	0.944-1.002	0.064			
ive comorbidities						
abdominal surgery	1.030	0.768-1.380	0.844			
mellitus	0.960	0.670-1.375	0.822			
ısion	0.852	0.685-1.059	0.148			
ive laboratory data						
lbumin <35g/L	1.484	1.048-2.102	0.026			
)g/L	1.195	0.827-1.726	0.343			
	0.892	0.725-1.098	0.282			
urgical approach						
copic	1.282	0.808-2.036	0.292			
section			<0.001			<0.001
strectomy		Reference			Reference	
strectomy	0.649	0.522-0.807	<0.001	0.716	0.572-0.896	0.004
l gastrectomy	0.334	0.231-0.485	<0.001	0.357	0.245-0.519	<0.001
time	1.001	1.000-1.003	0.086			
s	1.000	1.000-1.001	0.482			
e			0.304			
undus		Reference				
	0.903	0.709-1.148	0.404			
antrum	1.119	0.869-1.442	0.382			
asion (T3-4)	1.613	1.310-1.987	<0.001	1.299	1.010-1.670	0.042
de metastasis	1.585	1.286-1.952	<0.001	1.304	1.018-1.669	0.035
ge (≥III)	1.555	1.263-1.914	<0.001			
btype			0.082			
l		Reference				
	1.040	0.536-2.019	0.908			
	1.388	0.709-2.716	0.339			
n	1.328	0.677-2.603	0.409			

dy mass index; CRP = C-reactive protein; ASA = American Society of
ologists; RLNs = retrieved lymph nodes; OR = odds ratio; CI = confidence