

BRIEF ARTICLES

Prognostic impact of dissected lymph node count on patients with node-negative gastric cancer

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CONCLUSION: For node-negative gastric cancer, sufficient number of dissected LNs is recommended during D2 lymphadenectomy, to improve the long-term survival and reduce the recurrence. Suitable increments of the dissected LN count would not increase the post-operative complication rate.

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Abstract

AIM: To investigate the long-term effect of the number of resected lymph nodes (LNs) on the prognosis of patients with node-negative gastric cancer.

METHODS: Clinical data of 211 patients with gastric cancer, without nodal involvement, were analyzed retrospectively after D2 radical operation. We analyzed the relationship between the number of resected LNs with the 5-year survival, the recurrence rate and the post-operative complication rate.

RESULTS: The 5-year survival of the entire cohort was 82.2%. The total number of dissected LNs was one of the independent prognostic factors. Among patients with comparable depth of invasion, the larger the number of resected LNs, the better the survival ($P < 0.05$). A cut-point analysis provided the possibility to detect a significant survival difference among subgroups. Patients had a better long-term survival outcomes with LN counts ≥ 15 for pT1-2, ≥ 20 for pT3-4, and ≥ 15 for the entire cohort. The overall recurrence rate was 29.4% within 5 years after surgery. There was a statistically significant, negative correlation between the number of resected LNs and the recurrence rate ($P < 0.01$). The post-operative complication rate was 10.9% and was not significantly correlated with the number of dissected LNs ($P > 0.05$).

INTRODUCTION

Gastric cancer is a common malignancy worldwide. Despite its declining incidence, mortality of gastric cancer remains high^[1]. It is generally accepted that a higher survival rate benefits from a standardized pattern of lymph node dissection^[2-4]. Many studies favor an extended lymphadenectomy at the time of potentially curative gastrectomy for node-positive gastric cancer, and the risk of long-term death tends to decrease when the number of resected lymph nodes increases to about 25^[5-7]. However, there are few studies on how many nodes should be removed and examined when performing a radical gastrectomy for node-negative gastric cancer. Therefore, the aim of this retrospective study was to evaluate the long-term effect of the number of resected lymph nodes (LNs) on the prognosis of patients with node-negative gastric cancer.

MATERIALS AND METHODS

Materials

Between January, 1995 and March, 2004, 211 patients diagnosed with primary gastric cancer were treated with curative resection at the Department of Oncology,

Affiliated Union Hospital of Fujian Medical University, Fuzhou, China. The surgical procedure was defined as curative when no grossly visible tumor tissue (metastasis or LN involvement) remained after resection and when the resection margins were histologically normal. There were 164 males and 47 females whose age ranged from 29 to 84 years (57.4 ± 11.3 years). All patients received a D2 dissection according to the Japanese Classification of Gastric Carcinoma^[8]. Lymph nodes were meticulously dissected from the en bloc specimens, and the classification of the dissected LNs was determined by specialist surgeons who reviewed the excised specimens after surgery, based on the Japanese Classification of Gastric Carcinoma^[8]. All resected lymph nodes were proven to be without nodal involvement. The tumors' size was 4.2 ± 2.1 cm. Patients were divided according to the primary site of gastric cancer: 75 upper third (U) tumors; 40 middle third (M) tumors; and 96 lower third (L) tumors. Based on the Japanese Classification of Gastric Carcinoma^[8], there were 69 at stage pT1, 58 at stage pT2, 62 at pT3 and 22 at pT4. As far as the histological grades were concerned, there were 55 differentiated and 156 undifferentiated cases. Total gastrectomy, proximal subtotal gastrectomy and distal subtotal gastrectomy were carried out in 99, 15 and 97 cases, respectively. A total of 4649 LNs were taken for histological examination, and the median number of LN per patient was 22 (range, 6-48; mean 22.7 ± 7.0). Routine follow-up consisted of physical examination, laboratory tests (including measurement of carcinoembryonic antigen, CA19-9 and CEA levels), chest radiography, and abdominopelvic ultrasonography or computed tomography (CT). At the early stage (pT1), patients were followed every 6 mo during the first 2 years, and then yearly beyond the third year; at more advanced stages (pT2 or greater), follow-up was every 3 mo during the first year, every 6 mo or yearly beyond the second year, for a total of 5 years. Endoscopy was performed every 6 mo or yearly. All surviving patients were followed for more than five years. The survival time was the time from diagnosis until the last contact, the date of death, or the date that the survival information was collected. The rate of follow-up visits was 92.9%, with 196 cases involved.

Methods

Patients were stratified into five groups, based on the total number of LNs removed, as follows: < 15 LNs (18 cases), 15-19 LNs (49 cases), 20-24 LNs (63 cases), 25-29 LNs (44 cases) and ≥ 30 LNs (37 cases). The statistical analysis was performed with the Statistical Package for Social Science (SPSS), version 13.0 for Windows. Actuarial survival was determined *via* the Kaplan-Meier method, with univariate comparisons between groups through the log-rank test. Cox regression was used for multivariate analysis, with a backward elimination model for all covariates. Spearman rank correlation coefficient was used to analyze the relationship between the number of dissected LNs and recurrence rate. The correlation between the number of resected LNs and post-operative complication rate was analyzed with logistic regression model. Significance of differences was assumed at $P < 0.05$.

Table 1 Univariate analysis of variables in patients with node-negative gastric cancer

Characteristics	n	5-year survival rate (%)	χ^2	P value
Gender			1.887	0.170
Male	164	81.7		
Female	47	84.0		
Age (yr)			0.619	0.431
< 60	109	84.2		
≥ 60	102	79.9		
Tumor size (cm)			4.538	0.033
≤ 4	94	88.9		
> 4	117	76.8		
Tumor location			1.681	0.432
Upper	75	80.1		
Middle	40	81.7		
Lower	96	84.0		
Depth of invasion			27.698	0.000
T1	69	92.4		
T2	58	83.9		
T3	62	76.4		
T4	22	57.8		
Pathology			0.212	0.645
Differentiated	55	88.6		
Undifferentiated	156	80.0		
Surgical type			0.219	0.640
Total gastrectomy	99	80.5		
Subtotal gastrectomy	112	83.6		
Number of resected LNs			45.219	0.000
0-14	18	43.2		
15-19	49	76.8		
20-24	63	84.5		
25-29	44	90.6		
≥ 30	37	94.5		

Table 2 Multiple stepwise regression analysis with the Cox proportional hazards model

Characteristics	β	SE	Wald	P	RR	95% CI
Tumor size (cm)	0.223	0.319	0.487	0.485	1.249	0.668-2.335
Depth of invasion			8.802	0.032		
T2 vs T1	0.789	0.483	2.666	0.103	2.200	0.854-5.670
T3 vs T1	0.945	0.464	4.138	0.042	2.572	1.035-6.391
T4 vs T1	1.466	0.500	8.605	0.003	4.334	1.627-11.545
Number of resected LNs	-0.641	0.141	20.628	0.000	0.527	0.399-0.695

β : Coefficient of regression.

RESULTS

Univariate survival analysis

The five-year overall survival rate of the entire cohort was 82.2%. The clinicopathological variables tested in the univariate analysis are shown in Table 1. Factors influencing the 5-year survival rate were tumor size ($P = 0.033$), depth of invasion ($P < 0.001$) and number of resected LNs ($P < 0.001$). The covariates age ($P = 0.431$), gender ($P = 0.170$), tumor location ($P = 0.432$), pathological types ($P = 0.645$) and type of gastrectomy ($P = 0.640$) had no significant influence on the survival.

Multivariate survival analysis

Multiple survival analysis was calculated by the Cox's proportional hazard regression model. The prognostic

Table 3 Five-year overall survival by stage subgroups and total number of resected LNs *n* (%)

Depth of invasion	<i>n</i>	OS					<i>P</i>
		0-14	15-19	20-24	25-29	≥ 30	
T1	69	4 (37.5)	19 (83.9)	20 (88.9)	17 (100.0)	9 (100.0)	0.003
T2	58	4 (25.0)	14 (70.1)	20 (89.4)	11 (90.9)	9 (100.0)	0.005
T3	62	7 (57.1)	12 (72.7)	19 (83.5)	10 (88.9)	14 (92.3)	0.022
T4	22	3 (33.3)	4 (75.0)	4 (50.0)	6 (66.7)	5 (80.0)	0.045
Total	211	18 (43.2)	49 (76.8)	63 (84.5)	44 (90.6)	37 (94.5)	0.000

OS: Overall 5-year survival rate.

Table 4 Overall survival by total LN count and cut-point analysis per each stage subgroup

Depth of invasion	≤ 14 vs ≥ 15		≤ 19 vs ≥ 20		≤ 24 vs ≥ 25		≤ 29 vs ≥ 30	
	χ^2	<i>P</i>	χ^2	<i>P</i>	χ^2	<i>P</i>	χ^2	<i>P</i>
pT1-2	19.953	0.000	13.595	0.000	5.249	0.022	2.216	0.137
pT3-4	11.916	0.001	14.196	0.000	12.262	0.000	6.483	0.011
Total	32.824	0.000	26.679	0.000	16.109	0.000	7.572	0.006

Table 5 Impact of number of resected LNs on recurrence rate *n* (%)

Depth of invasion	No. of resected LNs	<i>n</i>	Recurrence rate ²	<i>r</i>	<i>P</i>
pT1-2	0-14	8	5 (62.5)	-0.253	0.001 ¹
	15-19	33	11 (33.3)		
	20-24	40	8 (20.0)		
	25-29	28	5 (17.8)		
	≥ 30	18	1 (5.6)		
pT3-4	0-14	10	8 (80.0)	-0.405	0.000 ¹
	15-19	16	9 (56.2)		
	20-24	23	8 (34.8)		
	25-29	16	4 (25.0)		
	≥ 30	19	3 (15.8)		

¹Significance of differences was assumed at $P < 0.01$; ²Recurrence within 5 years after surgery.

factors considered at univariate analysis were analyzed first by stepwise regression, including tumor size, depth of invasion and number of resected LNs. As a result, there were two independent, statistically significant prognostic parameters: depth of invasion ($P = 0.032$) and number of resected LNs ($P < 0.001$). The risk ratios and their 95% confident interval were listed in Table 2.

Impact of total LN counts by univariate survival analysis

The five-year survival, based on T category, showed considerable variations with increasing counts of resected LNs. An obvious trend toward better survival was observed for higher numbers of resected LN (Table 3).

Cut-point survival analysis

A cut-point analysis was performed to determine the numeric LN value that determines the greatest actuarial survival difference between pT1-2 and pT3-4 subgroups. We selected the ability to detect differences between groups based on the magnitude of the log-rank test χ^2 statistic. Results for all relevant cut points and stage subgroups are listed in Table 4. The cut-point analysis yielded the greatest survival difference at the levels of 15 (pT1-2), 20 (pT3-4) and 15 (entire cohort).

Impact of the number of resected LNs on recurrence rate

Within 5 years after surgery, a recurrence was confirmed by clinical, radiological examination or reoperation in 62 patients, with an overall recurrence rate of 29.4%. The number of patients with peritoneal and lymph nodes recurrence were 28 and 13 respectively. The most common site of haematogenous recurrence was the liver, occurring in 12 patients. Other patterns of recurrence were bone recurrence in 5 patients and lung recurrence in 4 patients. The relationship between the number of resected LNs and recurrence rate was analyzed by Spearman rank correlation coefficient (Table 5). For either pT1-2 or pT3-4 subgroups, there was a statistically significant, negative correlation between the number of dissected LNs and the recurrence rate ($P < 0.01$).

Correlation between number of resected LNs and post-operative complication rate

Twenty-three of the 211 patients (10.9%) experienced postoperative complications. These included pancreatitis (4 cases), anastomotic leakage (3), intra-abdominal abscess (4), postoperative ileus (1), stenosis (3), countercurrent esophagus (2), pancreatic leakage (2) and pneumonia (4). Logistic regression analysis revealed that the number of dissected LNs was not significantly correlated with the post-operative complication rate ($P = 0.214$).

DISCUSSION

It is commonly regarded that lymph node metastases is one of the most important prognostic factors in patients with gastric cancer after curative operation^[9,10]. Bruno *et al*^[11] pointed out that patients with node-negative gastric cancers have clinicopathological features similar to those with early gastric cancer and they showed also how those patients have a better prognosis than those with node-positive gastric carcinoma. The 5-year survival rate of patients with node-negative gastric carcinoma was 89.5%, based on the work by Wu *et al*^[12], whereas, based on our present data, this rate is

82.2%. The only potentially curative treatment for this disease is complete surgical resection, with an en bloc LN dissection. D2 lymph node dissection can increase the long-term survival of gastric cancer patients with lymph node metastases and it has become a standard surgical procedure for curative treatment in Korea and Japan^[13]. D2 lymph node dissection requires not only a specific anatomical extension (i.e. it must include both perigastric and suprapancreatic nodes), but also a certain number of resected LNs (at least 15). The number of dissected LNs is closely related to the postoperative pathologic staging and the prognostic assessment. Bouvier *et al*^[14] investigated 749 cases with gastric cancer, and the results showed that the risk of misclassification became significant, with an error rate of 47.1% in the pathology reports, when fewer than 10 lymph nodes were examined. They concluded that, in the latter cases, staging is not reliable. Karpeh *et al*^[15] reviewed 1038 patients with gastric cancer who had undergone gastrectomy with curative intent. They found that removal of ≥ 15 LNs appears to provide a considerable survival advantage, in comparison with the removal of < 15 LNs. In an attempt to improve staging accuracy, it was recommended that a minimum of 15 lymph nodes be examined. Based on our data, the median number of total LNs examined was 22 (mean 22.7 ± 7.0) per patient. In addition, the number of LNs dissected emerges as one of the most important prognostic indicators. Our present study shows that, with comparable depth of invasion, patients with a larger number of dissected LNs have a better survival rate ($P < 0.05$), consistent with the results of Smith *et al*^[16]. The contribution of negative LN counts to the prognosis of patients is partly due to LN micrometastases. In patients without LN metastases identified by HE staining, about 20% had LN micrometastases^[17]. Thus, it can be concluded that an extended lymphadenectomy contributes to decrease the number of residual tumor cells, leading to better prognosis. However, it is unclear how many LNs need to be removed in a D2 dissection in patients with node-negative gastric cancer. Giuliani *et al*^[18] suggested that patients with node-negative gastric cancer should undergo adequate lymphadenectomy to permit examination of ≥ 23 LNs, which would allow accurate identification of prognostic variables. From the cut-point analysis, we suggest that, to be adequate, the resection, at the time of a D2 radical dissection, should involve 15 LNs for pT1-2 and 20 LNs for pT3-4, and this based on an accurate survival estimates in patients with node-negative gastric cancer.

Despite improved prognosis, as a result of early diagnosis, radical operations and the development of adjuvant therapy^[9,19,20], death from gastric cancer is still almost entirely due to recurrent disease. About 5% of patients with early gastric cancer and 50% of patients with advanced gastric cancer die with recurrent disease, as reported by Böhner *et al*^[21]. In a large set of follow-up data from Japan, among 14000 patients with recurrent gastric cancer, the rate of loco-regional recurrence following potentially curative resection was 25.6%^[22]. This

may be due to the insufficient anatomical extension of the dissection at the time of the first surgery, including an insufficient gastrectomy or insufficient lymphadenectomy. The randomized Dutch gastric carcinoma study compared D1 and D2 lymphadenectomy and appeared to observe a significant reduction of the loco-regional recurrence rate after a more extended lymphadenectomy: following D1 lymphadenectomy, 36% of patients died with local recurrence, compared with 27% when a D2 lymphadenectomy was performed ($P < 0.05$)^[23]. Our present study shows that the overall recurrence rate is 29.4% within 5 years after surgery. The Spearman rank correlation coefficient analysis revealed that there was a statistically significant, negative correlation between the number of dissected LNs and the recurrence rate ($P < 0.01$). A lower recurrence rate was observed in cases with higher total LNs, indicating that a sufficient lymphadenectomy contributed to reduce the number of residual tumor cells. While correlating the number of dissected LNs with the post-operative complication rate, Zilberstein *et al*^[24] did not find any difference between the average number of dissected LNs in patients with and without complications. These authors suggested that the higher morbidity and mortality rates were not due to the extended lymphadenectomy. Those rates may be more likely correlated with the level of experience in gastroesophageal surgery, with the presence of an appropriate learning curve for radical gastrectomy and with the experience in the management of postoperative complications. The post-operative complication rate in our study was 10.9% and the logistic regression analysis showed that the number of dissected LNs did not correlate with the post-operative complication rate ($P > 0.05$). According to our results, it appears that a suitable increment of the number of dissected LN would not increase the post-operative complication rate if the surgery is performed by a trained surgical team.

COMMENTS

Background

Many studies have favored an extended lymphadenectomy at the time of a potentially curative gastrectomy for node-positive gastric cancer, and the risk of long-term death tends to decrease when the number of resected lymph nodes increases to about 25. However, few studies have assessed the relative contribution of the number of total resected lymph nodes to the outcome in patients with node-negative gastric cancers.

Research frontiers

It is generally accepted that a higher survival rate benefits from a standardized pattern of D2 radical dissection, which requires the removal of Group 1 and Group 2 lymph nodes (LNs). The number of dissected LNs is strongly correlated with patients' survival.

Innovations and breakthroughs

The authors retrospectively reviewed 211 patients with node-negative gastric cancer, who were treated with D2 radical resection at a hospital in Fujian between 1995 and 2004, to assess how the number of dissected LNs may affect their survival rate.

Applications

The authors suggest that importance should be attached to removing a sufficient number of LNs in order to improve the long-term survival and reduce the recurrence rate of patients with node-negative gastric cancer. Moreover, suitable increments of the number of dissected LNs would not increase the post-operative complication rate.

Peer review

The authors are to be congratulated on this paper, recording the effect of the number of lymph nodes resected in a large number of patients (211) with node negative gastric cancer and a remarkable survival rate of 82.2% at 5 years. The number of lymph nodes resected influenced the prognosis of the patients with node negative gastric cancer. This finding has important information for gastrointestinal surgeons.

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