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Impact on long-term survival of the number of lymph nodes resected in patients with pT1N0 gastric cancer after R0 resection
A multicenter study in China

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Abstract

Although studies on the association between the number of lymph nodes resected and prognosis in patients with pT2–4N0 stages of gastric cancer have reported consistent results, there is no consensus on the optimal number of lymph nodes to be examined for pT1N0 stage gastric cancer. The aim of this study was to evaluate the long-term effect of the number of lymph nodes removed on the outcomes of patients with pT1N0 stage gastric cancer after R0 resection.

From December 2009 to December 2011, 227 patients undergoing R0 resection of pT1N0 stage gastric cancer at 4 Chinese centers were enrolled in this study. Patients were assigned to 2 groups according to the number of lymph nodes dissected (≤15 or >15). Standard survival methods and restricted multivariable Cox regression models were applied.

More women ($P = 0.031$) were in the ≤15 group than in the >15 group. The mean number of lymph nodes removed from women was greater than that from men ($P = 0.007$). The 5-year survival rate was significantly higher in the >15 lymph nodes resected group than the ≤15 group. The number of lymph nodes resected was identified as an independent prognostic factor and was significantly correlated with overall survival (OS).

A lymphadenectomy with dissection of more than 15 lymph nodes improved the long-term survival of patients with pT1N0 gastric cancer after R0 resection. Therefore, it is necessary to consider removing more than 15 lymph nodes among such patients.

Abbreviations: AJCC = American Joint Committee on Cancer, OS = overall survival.

Keywords: gastric cancer, lymph node, survival

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1. Introduction

Gastric cancer is still one of the most common causes of cancer-related death worldwide. Many factors influence the prognosis of gastric cancer after surgery. Besides depth of invasion, lymph node metastasis is the most important prognostic factor in gastric cancer patients undergoing curative resection.[1,2] Moreover, it is generally accepted that patients may show greater survival benefit by receiving a standardized pattern of lymph node dissection. According to the latest version of the American Joint Commission for Cancer (AJCC) classification and the National Comprehensive Cancer Network (NCCN) Guidelines, sampling an adequate number of regional lymph nodes (15 or greater) is recommended for evaluating nodal metastatic status.[3–5]

Some studies have investigated the association between the number of dissected lymph nodes and the prognosis of gastric cancer.[6–8] In addition, several studies also found that the prognosis of patients with node-negative gastric cancer was related to the number of dissected lymph nodes.[9–18] Most of these studies indicated that the prognosis of pT2–4N0 stage node-negative gastric cancer patients was improved when a sufficient number of nodes were dissected.

Several studies have investigated the factors related to lymph node metastasis of gastric cancer. In addition to the already known factors such as tumor size, histological characteristics, depth of tumor invasion, and lymphovascular invasion, it was observed that the ethnicities of patients and/or their geographic differences influenced lymph node metastasis and aberrant metastatic behavior of early gastric cancer.[19,20]

However, the correlation between the number of dissected nodes and the prognosis of pT1N0 stage gastric cancer patients remains unclear and controversial because there are only a few studies focused on this population. In addition, the outcomes from these studies have been inconsistent. Moreover, with the widespread use of screening programs in gastric cancer, the number of cases of pT1N0 stage early gastric cancer has increased in recent years.[21] Endoscopic resection of early gastric cancer has long-term survival outcomes similar to those obtained with surgical resection, and it is minimally invasive and has a lower cost. Thus, endoscopic resection is becoming an increasingly acceptable therapeutic option for early gastric cancer. However, endoscopic resection does not consider the risk for lymph node metastasis, which is an expanded criterion for surgery.[22]

Hence, it is important to determine the effect of lymph node removal on their prognosis, and identifying the optimal number of lymph nodes to resect in these patients also appears to be of particular importance. Therefore, the present study was conducted. The aim of the work was to evaluate the long-term effect of number of dissected nodes on the outcomes of patients with pT1N0 gastric cancer after R0 resection.

2. Methods

2.1. Ethics statement

The study was approved by National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, and Affiliated Hospital of Qinghai University. Written informed consent was obtained from each patient.

2.2. Study population

Between December 2009 and December 2011, 227 consecutive patients histologically diagnosed with pT1N0 stage primary gastric cancer at the Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Affiliated Hospital of Qinghai University, People's Hospital of Qinghai Province, and Qinghai Red Cross Hospital were enrolled in this study. All patients were treated with curative resection (R0, i.e., microscopically negative) and underwent a lymph node dissection. Patients who had cancer beyond pT1N0 stage, who were complicated with other malignancies, treated with non-R0 resection, or unavailable, or who had incomplete data were excluded from the study.

The clinicopathological characteristics of all patients were collected retrospectively from medical databases at the participating hospitals. Data for the following clinicopathologic features were collected: age (>60 vs ≤60 years), sex (male vs female), tumor site (cardia gastric cancer, in which tumors arise 2–5 cm from the gastric mucosa distal to the esophagogastric junction,[23,24] vs non-cardia gastric cancer, in which tumors originate from the gastric mucosa distal to the cardia), pT category, World Health Organization (WHO) histopathologic classification, WHO histologic grade (moderate to well, moderate, and poor to moderate), lymphatic vessel invasion, perineural invasion, lymph node involvement, the number of lymph nodes dissected (>15 vs ≤15), (neo)adjuvant chemotherapy, (neo) adjuvant radiotherapy, and follow-up. The pT and pN categories were based on the criteria of the AJCC, seventh edition, pTNM classification.

2.3. Treatment modalities

All of the participating hospitals followed the Japanese Gastric Cancer Association published guidelines.[4] Basically, D1, D1+, or D2 gastrectomy was selected on the basis of the guidelines. Moreover, according to the guidelines, radical total or subtotal gastrectomy with D2 lymph node dissection is the standard surgical therapy for advanced gastric cancer and most cases of early-stage gastric cancer. Information on patients treated with chemotherapy and chemoradiotherapy, if applicable, was also noted.

2.4. Survival data

After surgery, all of the patients were subjected to a routine follow-up examination every 3 months for the first 2 years, every 6 months from the third to fifth years, and annually thereafter. The follow-up examination was performed by trained investigators through inpatient visits, outpatient visits, mailings, telephone calls, or visiting patients. Overall survival (OS) was defined as the time from the date of surgery until death or last follow-up. Cancer-related death was considered as a positive endpoint and was used as a prognostic parameter.

2.5. Statistical analysis

Statistical analyses were performed using SPSS version 19.0 (Statistical Package for the Social Sciences, Chicago, IL). Two independent sample tests for quantitative data and the Chi-square test or Fisher exact test for categorical data were performed. Survival curves were calculated by using the Kaplan–Meier method and compared by the log-rank test. Differences between groups were assessed by univariate analyses using Pearson Chi-square and analysis of variance (ANOVA) for categorical and continuous data, respectively. A multivariate analysis of prognostic factors related to patient gastric cancer-specific survival was performed by using the Cox proportional hazards model and a stepwise procedure. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated. All statistical tests were conducted 2-sided, and P values < 0.05 were considered to be statistically significant.

3. Results

3.1. Demographics and clinicopathological features

During the period from December 2009 to December 2011, 227 consecutive patients with pT1 stage and lymph node negative gastric cancer were treated with R0 resection at the participating hospitals and were included in the study. There were 57 (25.11%) women and 170 (74.89%) men. The mean age of all of the patients was 57.15 ± 10.48 years, and the mean age of the women was younger than that of the men (54.37 ± 10.01 vs 58.04 ± 10.51, $P = 0.022$).

Patients were categorized into 2 groups according to the number of lymph nodes resected: ≤15 and >15. Table 1 summarizes the demographic data and clinicopathological features of pT1N0 gastric cancer patients undergoing R0 resection stratified according to the number of examined lymph nodes. No difference was noted in terms of age, tumor site, or tumor grade between the 2 groups. More women ($P = 0.031$) were in the ≤15 group than in the >15 group. The recurrence rate was 8.91%, 6.35%, in ≤15 group and >15 group ($P < 0.001$), respectively. With respect to factors including neural invasion,
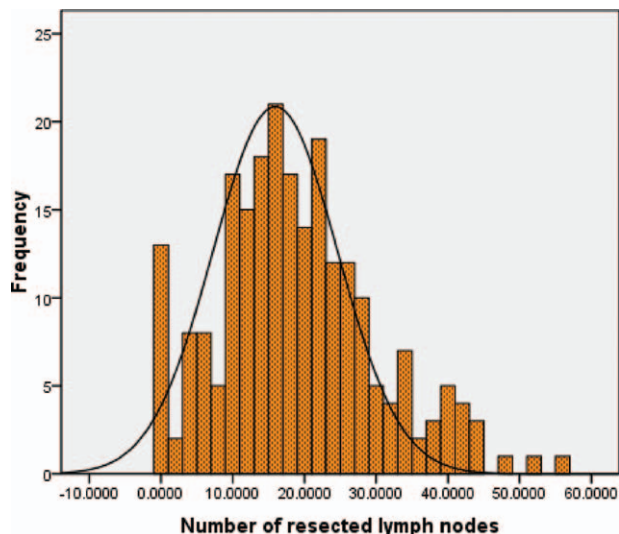
Table 1

Demographics and clinicopathological features of pT1N0 stage gastric cancer patients undergoing R0 resection, stratified by 15 examined lymph nodes.

Variable	No. of examined		P
	≤15 (n = 101)	>15 (n = 126)	
Age, y			0.099
≤60	57	85	
>60	44	41	
Gender			0.031
Male	83	87	
Female	18	39	
Tumor site			0.056
Cardia cancer	24	17	
Noncardia cancer	77	109	
Tumor grade			0.812
Moderate to well	11	16	
Moderate	27	28	
Poor to moderate	43	71	
Not reported	20	11	
Adjuvant chemotherapy alone			0.523
Yes	13	12	
No	88	114	

Table 2

Clinicopathological features and univariate analysis of overall survival in patients with node-negative gastric cancer.

Variable	N	5-year overall survival rate (%)	P
Age, y			0.532
≤60	142	97.14	
>60	85	91.56	
Gender			0.998
Male	170	95.11	
Female	57	96.43	
Tumor site			0.667
Cardia cancer	41	85.30	
Noncardia cancer	186	96.72	
Tumor grade			0.812
Moderate to well	27	96.30	
Moderate	55	98.08	
Poor to moderate	114	93.55	
Not reported	31	96.77	
Adjuvant chemotherapy alone			0.020
Yes	55	91.83	
No	202	95.71	
Lymph node			0.009
≤15	101	90.52	
>15	126	99.17	

ethnicity, receiving D1 or endoscopic resection, lymphatic/venous invasion, neoadjuvant chemotherapy, neoadjuvant chemoradiotherapy, and adjuvant chemoradiotherapy, data were not further analyzed due to insufficient number of events.

3.2. Univariate analysis

The frequency distribution of removed lymph nodes for the entire cohort of patients is shown in Fig. 1. For all patients, the mean number of dissected lymph nodes was 18.51 ± 11.02. When the number of lymph nodes was stratified according to sex, the mean number of lymph nodes removed from women was 21.89 ± 12.43, which is more than the number from men 17.37 ± 10.30 ($P = 0.007$).

The OS rates of the 2 groups are summarized in Table 2 and Fig. 2. The OS rate was significantly higher in the >15 lymph nodes resected group. The 5-year survival rate was 90.52% and 99.17% for the ≤15 lymph nodes resected group and the >15 lymph nodes resected group, respectively ($P = 0.009$). Six variables, including age, sex, tumor site, tumor grade, adjuvant chemotherapy alone, and the number of lymph nodes resected, were used to evaluate the prognostic factors by Kaplan–Meier survival analysis. Univariate analysis found that adjuvant chemotherapy alone and the number of lymph nodes resected were statistically significantly associated with OS ($P = 0.020$ and 0.009, respectively), while the others were not related to OS (P for all >0.05).
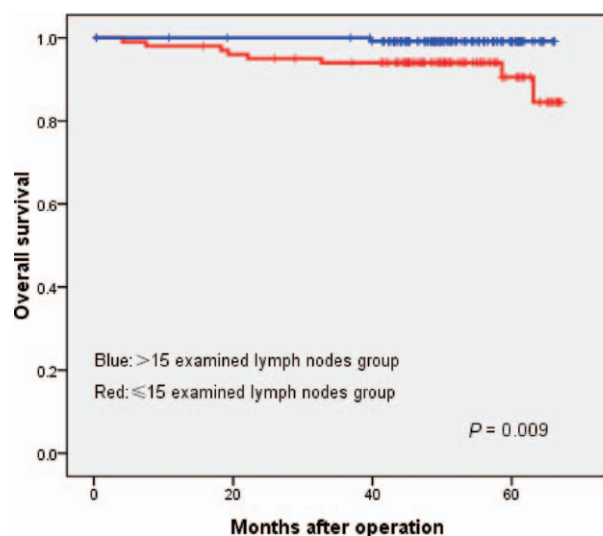

Figure 1. The frequency distribution of examined lymph nodes for the entire cohort of patients with pT1N0 gastric cancer after R0 resection.

Figure 2. Gastric cancer-specific survival rates associated with >15 examined lymph nodes and ≤15 examined lymph nodes in pT1N0 gastric cancer patients undergoing R0 resection. The 5-year survival rate is significantly higher in the >15 examined lymph nodes group than in the ≤15 examined lymph nodes group.

	Multivariate analysis		
	P^*	95% CI	Hazard ratio
Age, y			
≤60	Ref		
>60	0.419	0.40–8.84	1.88
Gender			
Female	Ref		
Male	0.384	0.08–2.67	0.46
Tumor site			
Cardia cancer	Ref		
Noncardia cancer	0.796	0.23–6.89	1.25
Tumor grade			
Moderate to well	Ref		
Moderate	0.556	0.03–7.22	0.43
Poor to moderate	0.804	0.14–13.19	1.33
Not reported	0.794	0.03–13.78	0.67
Adjuvant chemotherapy alone			
No	Ref		
Yes	0.067	0.91–17.83	4.02
Lymph node			
≤15	Ref		
>15	0.034	0.01–0.83	0.09

95% CI = 95% confidence interval.
* Cox proportional-hazards model.

3.3. Multivariate analysis

The Cox proportional hazards model was used to identify the independent predictors of OS. Details of the results are presented in Table 3. The analysis revealed that only the number of lymph nodes resected was an independent prognostic factor and was significantly correlated with OS ($P = 0.034$).

4. Discussion

Studies have revealed that undergoing R0 resection is the strongest prognostic factor for patients with gastric cancer. Moreover, it is the only chance to cure gastric cancer and obtain a better long-term survival.[25,26] Therefore, the surgical approach in the treatment of gastric cancer has been substantially extended over the last decades,[26,27] and D2 lymphadenectomy has been recommended as the standard of care by the Japanese Surgical Society as the optimal surgical option for gastric cancer treatment.[4] After R0 resection, lymph node involvement has been demonstrated to be the most powerful prognostic factor for patients with resectable gastric cancer.[28–30] Accordingly, the UICC/AJCC TNM classification recommends that at least 15 lymph nodes should be retrieved for an adequate evaluation of the pN category of gastric cancer.[31,32] However, only 29% of gastric cancer patients have more than 15 lymph nodes dissected despite the AJCC/UICC guidelines.[33]

Another question that must be considered is while the research on the association between the number of lymph nodes resected and prognosis in patients with pT2–4N0 stage gastric cancer has yielded consistent results, there is no consensus on the optimal number of examined lymph nodes for pT1N0 stage gastric cancer. In fact, accurate assessment of the lymph node stage is critical in gastric cancers that are classified as pN0.[34] In addition, it is especially important to optimize the treatment and prognosis of patients with pT1N0 stage gastric cancer.[33,35] With

the increasing rates of diagnosis of early gastric cancer, this problem has become prominent. However, how many lymph nodes should be removed in patients with pT1N0 gastric remains unclear and controversial, as several earlier studies showed different outcomes.

In 2005, Smith et al[14] investigated the prognostic factors in 953 T1–2N0 gastric cancer patients undergoing R0 resection on the basis of information from the Surveillance, Epidemiology, and End Results (SEER), and found that 5-year OS increased from 61% (for 1–10 lymph nodes examined) to 93% (for >40 lymph nodes examined). They reported that the OS of patients with gastric cancer who had >25 lymph nodes removed had better outcomes than those with fewer than 25 lymph nodes removed. Furthermore, the multivariate analyses revealed that the number of lymph nodes examined was an independent prognostic factor in these patients.[14] Moreover, Son et al[34] also evaluated the prognostic value of the number of examined lymph nodes during curative resection for gastric cancer, including T1N0 cases. They concluded that the outcomes of T1N0 stage patients in whom the number of examined lymph nodes during curative gastrectomy was ≤15 were worse than patients in whom >15 lymph nodes were examined. In addition, ≤15 examined lymph nodes was an independent prognostic factor for T1N0 stage patients.[34]

However, some other studies do not support the above conclusions. Wang et al[15] reported that retrieval of more than 25 nodes did not improve the survival of T1N0 stage patients in a study including 57 T1N0 cases in 2012. Similarly, Chu and Yang[16] found that a lymphadenectomy with more than 15 lymph nodes removed did not benefit survival among 54 T1–2N0 stage patients in 2015. Another study from Song et al[17] concluded that >15 examined lymph nodes were not correlated with survival time in 90 T1N0 stage patients who underwent gastrectomy in 2014. Hsu et al[18] also report that ≤15 examined lymph nodes did not affect the OS rates for 496 patients with T1N0 gastric cancer in 2013.

To the best of our knowledge, this is the first study that specifically assessed the relationship between long-term survival and the number of lymph nodes removed during R0 resection in patients with pT1N0 gastric cancer. In addition, our study had a relatively large patient group. The results from our current work demonstrated that patients with pT1N0 gastric cancer and R0 resection who have >15 lymph nodes resected had a higher survival rate than those with ≤15 lymph nodes removed. The recurrence rate in ≤15 group was higher than in >15 group. These results are in accordance with the studies from Smith et al[14] and Son et al[34]; however, it is not consistent with several other studies.[15–17] One potential reason for this difference may be that the relatively small sample sizes (no more than 100 patients in each study) among these 3 studies that might have resulted in selection biases.[15–17] Moreover, the proportion of pT1N0 gastric cancer patients receiving ≤15 lymph node resection reported by another study was 29.23%,[18] much less than the 44.49% in our study, which may also lead to different research results.

It is also worth noting that some other variables, including sex, tumor site, tumor grade, and adjuvant chemotherapy were not confirmed by us as independent prognostic factors for pT1N0 gastric cancer patients. This is consistent with the results from Wang et al[15] but not with those obtained by Son et al.[14] To date, there are only 2 studies (Wang et al[15] and Son et al[34]) that evaluated the role of the number of dissected lymph nodes on the prognosis of pT1N0 gastric cancer patients by univariate and

multivariate analysis at the same time. In addition to the number of dissected lymph nodes, Son et al[34] also identified age >60 years and being male as predictors of a poor outcome for these patients. However, the study from Wang et al[15] does not present such outcomes.

The different populations enrolled in the various studies may be the reasons for the differences. For all stages of gastric cancer patients undergoing R0 resection, the impact of the tumor site, tumor grade, and adjuvant chemotherapy on prognosis is still unclear because the results of some previous studies are inconsistent.[36,37] In addition, our other study also supported the idea that cardia and noncardia gastric cancer have similar stage-for-stage prognoses.[30] Moreover, ethnicity and geographic differences also influence the survival of patients with gastric cancer. For example, the 5-year survival rate in Romanian patients is less than 15%, whereas, in Japanese patients, it is 70%. In Poland, the 5-year relative survival rate was 12.94/100,000 in male patients and 4.68/100,000 in female patients.[38]

Another issue that needs to be noted is that the mean number of dissected lymph nodes in our study was more than that of several previous studies.[14,16] This may be associated with the implementation of D2 gastrectomy for gastric cancer among the participating hospitals. One other important thing to note is that the mean number of examined lymph nodes in women was greater than that in men. The younger mean age of the women may be a reason for this. That is, surgeons are accustomed to removing more lymph nodes from younger patients.

The present study, however, has some possible limitations. First, this was a retrospective study. However, the accurate statistical methods used in this study could strengthen its value. Second, a significantly higher proportion of D2 lymphadenectomy was performed among the participating hospitals.

In conclusion, although the survival benefit of removing more than 15 lymph nodes is disputed in different studies, this study suggests that a lymphadenectomy with dissection of more than 15 lymph nodes might improve the long-term survival of patients with pT1N0 gastric cancer after R0 resection. Therefore, careful management is warranted when such patients have less than 15 lymph nodes removed. Thus, effective sentinel node mapping in patients with early gastric cancer, who are undergoing surgical excision, could detect possible skip metastasis.[39] Although pT1N0 gastric cancer patients have an excellent prognosis, identifying the optimal number of lymph nodes to remove could further improve survival in these cases.

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