

Effects of extended lymphadenectomy and postoperative chemotherapy on node-negative gastric cancer

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Author contributions: Wang XN, Zhang RP and Liang H performed the majority of experiments; Deng JY provided vital reagents and analytical tools and was also involved in editing the manuscript; Xue Q co-ordinated and provided the collection of all the human material in addition to providing financial support for this work; Xue Q designed the study and wrote the manuscript.

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Abstract

AIM: To investigate the effects of extended lymphadenectomy and postoperative chemotherapy on gastric cancer without lymph node metastasis.

METHODS: Clinical data of 311 node-negative gastric cancer patients who underwent potentially curative gastrectomy with more than 15 lymph nodes resected, from January 2002 to December 2006, were analyzed retrospectively. Patients with pT4 stage or distant metastasis were excluded. We analyzed the relationship between the D2 lymphadenectomy and the 5-year survival rate among different subgroups stratified by clinical features, such as age, tumor size, tumor location and depth of invasion. At the same time, the relationship between postoperative chemotherapy and the 5-year survival rate among different subgroups were also analyzed.

RESULTS: The overall 5-year survival rate of the entire

cohort was 63.7%. The 5-year survival rate was poor in those patients who were: (1) more than 65 years old; (2) with tumor size larger than 4 cm; (3) with tumor located in the upper portion of the stomach; and (4) with pT3 tumor. The survival rate was improved significantly by extended lymphadenectomy only in patients with pT3 tumor ($P = 0.019$), but not in other subgroups. Moreover, there was no significant difference in survival rate between patients with and without postoperative chemotherapy among all of the subgroups ($P > 0.05$).

CONCLUSION: For gastric cancer patients without lymph node metastasis, extended lymphadenectomy could improve the survival rate of those who have pT3-stage tumor. However, there was no evidence of a survival benefit from postoperative chemotherapy alone.

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Key words: Gastric cancer; Lymph node negative metastasis; Extended lymphadenectomy; D2 lymphadenectomy; Chemotherapy

Core tip: Little information is available regarding the effects of D2 lymphadenectomy and postoperative chemotherapy in patients with node-negative early gastric cancer. Data of 311 gastric cancer patients without lymph node metastasis were analyzed retrospectively. Results showed that D2 lymphadenectomy could improve the survival rate of patients with pT3-stage tumor. However, there was no evidence of a survival benefit from postoperative chemotherapy. In conclusion, it is recommended that D2 lymphadenectomy with gastrectomy be applied for node-negative patients with pT3 gastric cancer whereas the effects of postoperative chemotherapy in patients with node-negative early gastric cancer need to be further studied.

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INTRODUCTION

Gastric cancer is one of the most common malignancies worldwide, with a high mortality rate^[1]. Many studies indicate that, in gastric cancer, the presence or absence of lymph node metastasis is an important prognostic factor that could influence the prognosis of patients following curative gastrectomy^[2-5]. It has been shown that an extended (D2) lymphadenectomy could bring benefits to the long-term survival rate of patients with node-positive gastric cancer^[6,7], and D2 lymphadenectomy has become a standard surgical procedure for curative treatment in South Korea and Japan^[8]. However, recurrence and metastasis are also noted in node-negative gastric cancer after curative resection, and there are few studies on the effects of D2 lymphadenectomy in patients with node-negative gastric cancer. At the same time, postoperative chemotherapy is considered an effective treatment option for patients with advanced gastric cancer^[9-11], nevertheless, whether it could bring benefit to node-negative gastric cancer patients who received curative gastrectomy still needs to be further elucidated. Hence, the aim of this study was to investigate whether extended lymphadenectomy and postoperative chemotherapy could bring a survival benefit to patients with node-negative gastric cancer.

MATERIALS AND METHODS

Between January 2002 and December 2006, 867 patients diagnosed with gastric adenocarcinoma were treated with curative gastrectomy (R0 resection) and with more than 15 lymph nodes resected at the Department of Gastric Cancer Surgery, Tianjin Medical University Cancer Hospital and City Key Laboratory of Cancer Prevention and Therapy, Tianjin, China. Of these patients, 311 had lymph node-negative metastasis. There were 230 males and 81 females with ages ranging from 21 to 82 years (60.0 ± 11.2 years). Patients with pT4 stage or distant metastasis were excluded. D2 lymphadenectomy was performed according to the guidelines of lymph node stations defined by the Japanese Gastric Cancer Association^[12].

Patients were stratified according to clinical features including age, sex, tumor size, location, Borrmann type, depth of invasion, and pathologic examination. Furthermore, patients with poor prognosis were stratified into subgroups according to the number of resected lymph nodes (LNs) and whether they received postoperative chemotherapy. According to the number of resected LNs, patients were divided into a 15-24 subgroup and a ≥ 25 subgroup. Patients were also divided into groups according to whether or not they received postoperative chemotherapy.

Table 1 Clinicopathologic factors of patients with node-negative gastric cancer

Characteristics	n	5-yr survival rate	χ^2	P value
Gender			1.416	0.234
Male	230	67.40%		
Female	81	72.80%		
Age (yr)			4.979	0.026
< 65	156	75.20%		
≥ 65	155	62.40%		
Tumor size (cm)			5.930	0.015
≤ 4	166	73.80%		
> 4	145	63.00%		
Tumor location			8.721	0.033
Upper	103	58.70%		
Middle	45	67.90%		
Lower	150	76.50%		
Total	13	68.40%		
Borrmann type			3.834	0.280
I	60	71.60%		
II	129	74.20%		
III	108	62.80%		
IV	14	57.10%		
Depth of invasion			13.676	0.001
T1	22	100.00%		
T2	69	78.40%		
T3	220	62.20%		
Pathology			2.689	0.101
Differentiated	124	73.90%		
Undifferentiated	187	65.30%		

Patients received postoperative chemotherapy (FOLF-OX6): oxaliplatin (100 mg/m²) and leucovorin (400 mg/m²), followed by 5-FU (400 mg/m²) bolus, then a 46 h continuous infusion of 5-FU (3000 mg/m²). The regimen was repeated every 2 wk for 6-8 cycles and follow-up was conducted until November 2011 or until death. Data collection was based on review of clinical charts and on telephone interviews with discharged patients.

Statistical analysis

The analysis was performed using the Statistical Package for Social Science (SPSS), version 13.0 for Windows. Actuarial survival rate was determined *via* the Kaplan-Meier method, and univariate comparisons of survival between different groups were performed using the log rank test. Significance of differences was accepted at *P* value < 0.05.

RESULTS

The overall 5-year survival rate (5-YSR) of the entire cohort was 63.7%. Factors influencing the 5-YSR were as follows: age (*P* = 0.026), tumor size (*P* = 0.015), tumor location (*P* = 0.033) and depth of invasion (*P* < 0.001). The survival rate was lower in patients who were more than 65 years old, with tumor size larger than 4 cm, with tumor located in the upper portion of the stomach, or with pT3 status. Gender (*P* = 0.234), Borrmann type (*P* = 0.280) and pathological types (*P* = 0.101) had no significant influence on the survival rate. The clinicopathological variables tested in the univariate analysis are shown in Table 1.

The survival rate of different groups divided by the

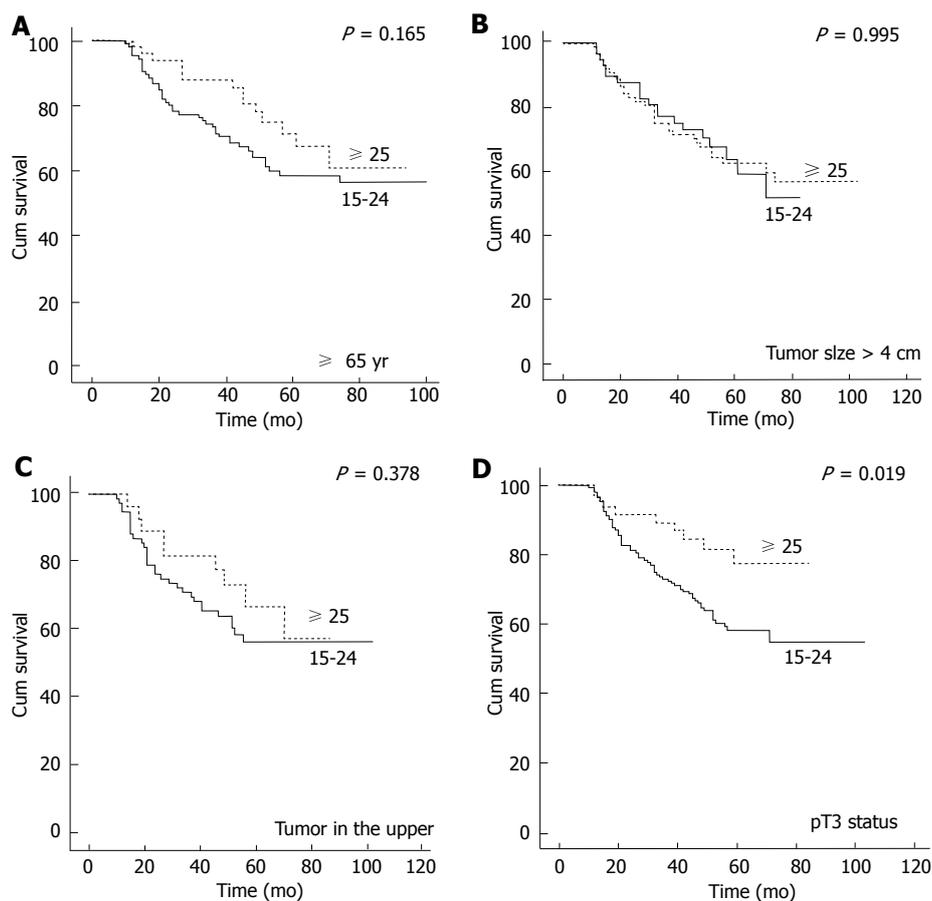


Figure 1 Five-year survival curve for patients with N0 gastric cancer according to the number of resected lymph nodes. A: In ≥ 65 years group, survival curve for 155 patients with N0 gastric cancer according to the number of resected lymph nodes (15-24 and ≥ 25); B: In tumor size > 4 cm group, survival curve for 145 patients with N0 gastric cancer according to the number of resected lymph nodes (15-24 and ≥ 25); C: In the upper location group, survival curve for 103 patients with N0 gastric cancer according to the number of resected lymph nodes (15-24 and ≥ 25); D: In pT3 group, survival curve for 220 patients with N0 gastric cancer according to the number of resected lymph nodes (15-24 and ≥ 25).

Table 2 Major postoperative complications observed in the study

Type of complications	15-24 LNs removed (n = 189)	Above 25 LNs removed (n = 122)	χ^2	P value
Pulmonary	16	13		
Abdominal abscess	15	9		
Pancreatic fistula	5	3		
Anastomotic leak	2	2		
Lymphorrhhea	4	3		
Paralytic ileus	2	2		
Others	3	2		
Total	47	34	0.347	0.556

LNs: Lymph nodes.

number of resected LNs and whether patients received post-operative chemotherapy were compared between groups stratified by age, tumor size, tumor location and pT status. In patients who were more than 65 years old, with tumor size larger than 4 cm, with tumor located in the upper portion of the stomach, the survival rate was not significantly different between the two subgroups of patients with 15-24 and ≥ 25 LNs dissected ($P = 0.165, 0.995, 0.378$, respectively). However, for patients with pT3 cancer, the survival rate in patients with ≥ 25 LNs dissected was significantly higher than that of patients with 15-24 LNs dissected ($P = 0.019$). The survival curves are presented in Figure 1.

There was no significant difference in survival rates between patients with or without postoperative chemotherapy in all 4 groups, divided according to whether patients were more than 65 years old, with tumor size larger than 4 cm, with tumor located in the upper portion of the stomach or in pT3 status ($P = 0.632, 0.917, 0.580, 0.632$, respectively). The survival curves are shown in Figure 2.

Eighty-one of the 311 patients developed postoperative general and surgical complications (morbidity: 26.0%), such as pulmonary affections, abdominal abscess, pancreatic fistula, anastomotic leak, lymphorrhhea, paralytic ileus, and no patients died during the perioperative period. Forty-seven patients with complications were in the patient group with 15-24 LNs dissected, and thirty-four were in the group with ≥ 25 LNs dissected. There was no significant difference in the post-operative complication rate between these two groups ($P = 0.556$). Table 2 lists the type of complications and their frequency.

DISCUSSION

Nowadays, due to the significant improvements in diagnosing techniques as well as the popularization of health screening, gastric cancers tend to be detected in their early stages. Of all the patients with gastric cancer treated in our hospital, 35.9% were in the early period. It is commonly considered that lymph node metastases is one of the most important prognostic factors for patients with gastric cancer after curative surgery^[13]. What's more, re-

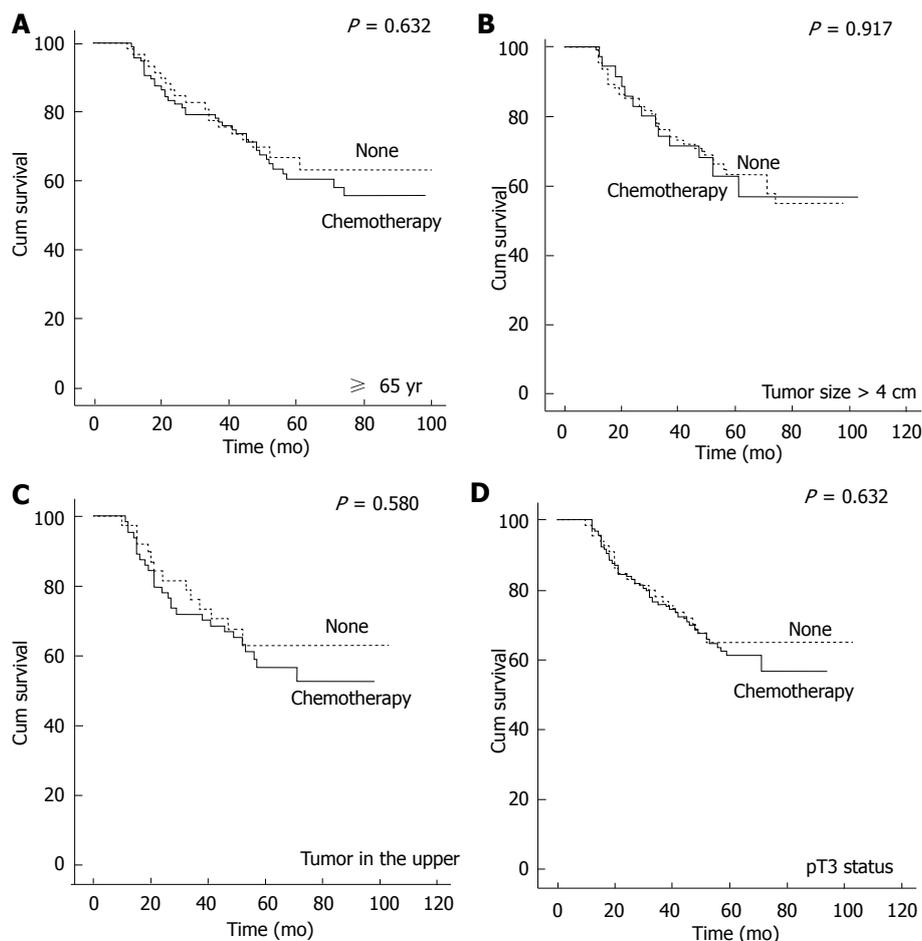


Figure 2 Five-year survival curve for patients with N0 gastric cancer according to whether patients received postoperative chemotherapy. A: In ≥ 65 years group, survival curve for 155 patients with N0 gastric cancer according to whether patients received postoperative chemotherapy; B: In tumor size > 4 cm group, survival curve for 145 patients with N0 gastric cancer according to whether patients received postoperative chemotherapy; C: In the upper location group, survival curve for 103 patients with N0 gastric cancer according to whether patients received postoperative chemotherapy; D: In pT3 group, survival curve for 220 patients with N0 gastric cancer according to whether patients received postoperative chemotherapy.

currence and metastasis were also noted in gastric cancer without lymph node metastasis after curative resection. The recurrence rate of early gastric cancer (EGC) was reported as 1.7%-3.4%^[14-17]. In previous studies^[18-20], it was reported that some variables such as pT status, tumor size, tumor location, Lauren type and the number of resected LNs were associated with survival in pN0 gastric cancer. According to our study, the survival rate was lower in patients whose age was more than 65 years old, tumor size was larger than 4 cm, tumor location was in the upper portion of the stomach, or tumor stage was pT3.

Studies have shown that D2 lymphadenectomy could improve the overall survival of patients with advanced node-positive gastric cancer^[21,22]. D2 lymphadenectomy for pN0 gastric cancer patients who received gastrectomy has been a topic of much discussion. Some recent studies reported that D2 lymphadenectomy with gastrectomy could prolong the survival rate of patients with node-negative advanced gastric cancer^[23-25]. Consistently, in this study we found that the survival rate of node-negative patients with pT3 gastric cancer could be improved by D2 lymphadenectomy ($P = 0.019$). One possible reason is that the node and tissue with micrometastasis were removed by D2 lymphadenectomy. In one recent study^[26] it is reported that lymph node micro-metastasis was detectable in 10% of node-negative EGC patients, and occurred more frequently in cases with larger tumor,

lymphatic invasion, or venous invasion. Based on these results, it is recommended that, for node-negative patients diagnosed with pT3 gastric cancer by endoscopic ultrasound preoperatively or at operation, the D2 lymphadenectomy should be performed even without clinically detectable node metastases. However, for other patients with poor survival rate, the effect of D2 lymphadenectomy is inconspicuous.

Previously, it was claimed that the postoperative morbidity and mortality may be increased by D2 lymphadenectomy^[27,28]. However, with the improvement of surgical techniques, this situation has been changed. As reported in one study^[29], there was no difference in the incidence of four major complications (anastomotic leak, pancreatic fistula, abdominal abscess, pneumonia) between the D2 group and D2 plus group. In this study, we also found that the mortality of postoperative general complications was not significantly different between two groups with and without D2 lymphadenectomy (24.9% *vs* 27.9%, $P = 0.556$).

To date, it has been recommended that postoperative chemotherapy should be used in advanced gastric cancer^[9-11,30,31]. The efficacy and safety of FOXFOL6 regimen for advanced gastric cancer has been demonstrated by a phase II study^[32]. However, the therapeutic value of chemotherapy for pN0 gastric cancer is still unclear and scarcely reported. Inconsistent with results

from advanced gastric cancer, we found that the survival rate of pN0 gastric cancer patients with postoperative chemotherapy was not significantly different from that of patients without chemotherapy, regardless of whether patients were more than 65 years old ($P = 0.632$), with tumor size larger than 4 cm ($P = 0.917$), with tumor located in the upper portion of the stomach ($P = 0.580$) or in pT3 status ($P = 0.632$).

There were several limitations to the current study. First, in this study, the overall survival is evaluated as an endpoint, while disease-free or recurrence-free survival was not investigated, which are also important for patients with gastric cancer. Second, the extent of lymphadenectomy was variable according to the decisions made by different surgeons, which may affect the results of this study. Finally, as this is a retrospective study, the regimen and dose of chemotherapy might be multifarious, which may affect the accuracy of the comparison of groups.

In conclusion, it is recommended that D2 lymphadenectomy with gastrectomy be applied for node-negative patients with pT3 gastric cancer. However, the effect of postoperative chemotherapy in pN0 gastric cancer patients still need to be further studied.

COMMENTS

Background

Many studies have shown that D2 lymphadenectomy could bring benefits to the long-term survival rate of patients with node-positive gastric cancer, however, little information is available regarding its effects in patients with node-negative gastric cancer. At the same time, although the efficacy and safety of FOXFOL6 regimen for advanced gastric cancer has been validated by many studies, the effects of postoperative chemotherapy for pN0 gastric cancer are still unclear and scarcely reported.

Research frontiers

Some recent studies reported that D2 lymphadenectomy with gastrectomy could prolong the survival rate of patients with node-negative gastric cancer, whereas the impact of postoperative chemotherapy on the survival is scarcely reported.

Innovations and breakthroughs

The authors retrospectively reviewed 311 patients with node-negative gastric cancer, who were treated with curative gastrectomy and with more than 15 lymph nodes resected at a hospital in Tianjin between 2002 and 2006, to assess whether D2 lymphadenectomy and postoperative chemotherapy may affect their survival rate.

Applications

The authors suggest that, for node-negative patients diagnosed with pT3 gastric cancer, D2 lymphadenectomy be performed even without clinically detectable node metastases. However, for other patients with poor survival rate, the effect of D2 lymphadenectomy is less obvious.

Peer review

This article demonstrated the necessity of extended lymphadenectomy for gastric cancer patients without lymph node metastasis. In this study, the authors found that the survival rate of node-negative patients with pT3 gastric cancer could be improved by D2 lymphadenectomy.

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