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Retrospective Study

Prognostic significance of 14v-lymph node dissection to D2
dissection for lower-third gastric cancer

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Author contributions: Zheng C and Gao S designed research; Gao ZM, Sun AQ and Wang ZN treated patients and collected material and clinical data from patients; Zheng C and Huang HB performed the assays; Zheng C and Gao S analysed data; Zheng C and Li K wrote the paper.

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Abstract

BACKGROUND

Radical gastrectomy with D2 lymph node (LN) dissection is the standard surgical procedure for patients with resectable gastric cancer (GC). In the fifteenth edition of the Japanese Classification of Gastric Carcinoma, the 14v LN (LNs along the root of the superior mesenteric vein) was defined as the regional gastric LN. The efficacy of 14v LN dissection during radical distal gastrectomy for lower-third GC remains controversial.

AIM

To analyze whether the addition of 14v LN dissection improved the survival of patients with lower-third GC.

METHODS

The data from 65 patients who underwent 14v LN dissection and 65 patients treated without 14v LN dissection were selected using the propensity score-matched method from our institute database constructed between 2000 and 2012. Overall survival was compared between the groups.

RESULTS

Overall survival was similar between patients with 14v LN metastasis and those with distant metastasis ($P = 0.521$). Among patients with pathological stage IIIA disease, those who were treated with 14v LN dissection had a significantly higher overall survival than those treated without it ($P = 0.020$). Multivariate analysis showed that age < 65 years and pT2-3 stage were independent favorable prognostic factors for prolonged overall survival in patients with pathological stage IIIA disease. Patients with No. 1, No. 6, No. 8a, or No. 11p LN metastasis were at higher risk of having 14v LN metastasis.

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CONCLUSION

Adding 14v LN dissection to D2 dissection during radical distal gastrectomy may improve the overall survival of patients with pathological stage IIIA lower-third GC.

Key words: Gastric cancer; No. 14v lymph node; Lymphadenectomy; Prognosis; Propensity score matching

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Core Tip: The efficacy of 14v lymph node (LN) dissection during radical distal gastrectomy for lower-third gastric cancer (GC) remains controversial. The present propensity score-matched study indicated that among pathological stage lower-third GC IIIA patients, 14v LN dissection resulted in longer survival compared to treatment without it. The overall survival of patients with 14v LN metastasis was similar with that of patients with distant metastasis.

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INTRODUCTION

Gastric cancer (GC) is the fifth most common malignancy and the third leading cause of cancer death worldwide^[1]. Radical gastrectomy with D2 lymph node (LN) dissection is the standard surgical procedure for patients with resectable GC^[2-8]. LNs along the root of the superior mesenteric vein are defined as the 14v LNs. In the fifteenth edition of the Japanese Classification of Gastric Carcinoma, the 14v LN was defined as the regional gastric LN^[9]. The fifth edition of the Japanese Gastric Cancer Treatment Guidelines states that D2 gastrectomy does not include dissection of the 14v LNs, but D2 (+14v LN) dissection may be beneficial for tumors with apparent metastasis to the No. 6 LN^[10,11].

The prognosis of patients with 14v LN metastasis is poor^[12-14]. Whether metastasis to the 14v LNs are classified as regional gastric LN metastasis or distant metastasis (M1) remains controversial. An *et al*^[12] found that the 14v LN should be excluded from regional gastric LNs, as the survival of patients with 14v LN metastasis was similar with that of patients with M1 stage disease. The efficacy of prophylactic 14v LN dissection during radical distal gastrectomy for lower-third gastric cancer (LTGC) remains unclear^[15,16].

Therefore, the aims of the present study were to (A) compare the prognosis of patients with 14v LN metastasis and those with M1 stage disease; (B) evaluate the prognostic significance of adding 14v LN dissection to D2 dissection during radical distal gastrectomy for patients with LTGC; and (C) aid in patient selection for 14v LN dissection.

MATERIALS AND METHODS

Patients

Between January 2000 and December 2012, data from 1510 patients with GC who underwent distal gastrectomy at the Department of Surgical Oncology, First Affiliated Hospital of China Medical University were collected retrospectively. The eligibility criteria were as follows: (A) Diagnosis of gastric adenocarcinoma; (B) Presence of primary tumors in the lower third of the stomach; (C) Undergoing distal gastrectomy; (D) Receiving at least D2 LN dissection; (E) Absence of microscopic residual tumor; (F) No history of gastrectomy or other malignancy; (G) No history of preoperative chemotherapy or radiotherapy; and (H) Absence of distant metastasis.

A total of 96 patients with M1 stage disease satisfied the inclusion criteria but were only included for comparing the prognosis of M1 stage patients with 14v LN

metastasis. Ultimately, 1004 patients were included in this study. Of these patients, 65 underwent 14v LN dissection [the 14vD (+) group], and the remaining 939 patients did not undergo 14v LN dissection [the 14vD (-) group]. The 14vD (+) group included patients with 14v LN metastasis and those without 14v LN metastasis. After propensity score matching, we included 65 patients in the 14vD (+) group and 65 patients in the 14vD (-) group.

There were no predefined indications for adding 14v LN dissection to lymphadenectomy. The decision to perform 14v LN dissection was made at the surgeon's discretion^[12]. The TNM stage was defined according to the AJCC guidelines, eighth edition^[17]. The extent of lymphadenectomy and LN stations were defined according to the fifteenth edition of the Japanese Classification of Gastric Carcinoma^[9]. Eligible patients underwent postoperative chemotherapy with 5-fluorouracil or platinum-based regimens.

The entire study population was followed up *via* phone and/or outpatient clinic consultation until death or the last follow-up date (December 31, 2017). The Institutional Ethics Committee of China Medical University approved this study. As this was a retrospective study, formal patient consent was not required.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences version 24.0 for Windows (SPSS Inc., Chicago, IL, United States). The chi-squared test was used for categorical variables. Overall survival (OS) was analyzed using Kaplan-Meier analysis and compared using the log-rank test. Univariate analysis was performed using the log-rank test. Multivariate analysis for prognostic factors was conducted using the Cox proportional hazard model. The hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazard model. A two-tailed *P*-value < 0.05 was considered statistically significant.

Propensity score matching was used to reduce the effects of selection bias and potential confounding factors. Propensity scores were calculated using a logistic regression model for the following covariates: Age, gender, pT stage, and pN stage. Patients in the 14vD (+) group were matched in a 1:1 ratio with those in the 14vD (-) group using imposed propensity scores with a 0.02 caliper width. We performed propensity score matching using SPSS 24.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Patient characteristics

Table 1 shows the comparison of the clinicopathological characteristics of the 14vD (+) and the 14vD (-) groups (*n* = 65 each). Of the 65 patients in the 14vD (+) group, 8 (12.31%) had 14v LN metastasis. There were no significant differences in age, gender, tumor size, histologic grade, pT stage, pN stage, pTNM stage, and postoperative chemotherapy between the 14vD (+) and 14vD (-) groups (all *P* > 0.05).

Patient survival

OS was similar between the 14vD (+) and 14vD (-) groups (HR: 1.01, 95% CI: 0.64–1.58, *P* = 0.980; **Figure 1A**). After stratified analysis, patients with 14v LN metastasis had a significantly shorter OS than the 14vD (+) and 14vD (-) groups (HR: 3.35, 95% CI: 1.51–7.45, *P* = 0.002; **Figure 1B**). The OS of patients with 14v LN metastasis in the 14vD (+) group was similar to that of patients with M1 stage disease (HR: 0.79; 95% CI 0.38–1.65; *P* = 0.521; **Figure 1B**).

Univariate and multivariate survival analyses for the entire population Univariate analysis indicated that pT stage and pN stage were prognostic factors for OS. Multivariate analysis showed that pT stage and pN stage were independent prognostic factors, while the status of 14v dissection was not a prognostic factor (**Table 2**).

Subgroup analysis

The forest plot showed that the OS of the 14vD (+) group was similar to that of the 14vD (-) group considering the pathological tumor stage and LN stage (**Figure 2**). **Figure 3** shows the OS according to the status of 14v dissection for each pathological stage. Among patients with pathological stages I, II, and IIIB/IIIC GC, OS was not significantly different between the 14vD (+) and 14vD (-) groups (*P* = 0.916, *P* = 0.802, and *P* = 0.541, respectively); however, the 14vD (+) group had better OS compared with the 14vD (-) group for pathological stage IIIA GC (*P* = 0.020).

Univariate and multivariate survival analyses for stage IIIA GC

Table 1 Clinicopathological characteristics of the entire study population, *n* (%)

| Characteristics | Propensity score matched patients (n = 130) | | | P-value |
|----------------------------|---|-------------------|-----------------|---------|
| | 14vD (-) (n = 65) | 14vD (+) (n = 65) | | |
| | | LNM (-) (n = 57) | LNM (+) (n = 8) | |
| Age group | | | | 0.323 |
| < 65 yr | 45 (69.2) | 43 (66.2) | 7 (10.8) | |
| ≥ 65 yr | 20 (30.8) | 14 (21.5) | 1 (1.5) | |
| Gender | | | | 0.149 |
| Male | 36 (55.4) | 37 (56.9) | 7 (10.8) | |
| Female | 29 (44.6) | 20 (30.8) | 1 (1.5) | |
| Tumor size | | | | |
| < 4 cm | 33 (50.8) | 27 (41.5) | 3 (4.6) | 0.559 |
| ≥ 4 cm | 32 (49.2) | 30 (46.2) | 5 (7.7) | |
| Histologic grade | | | | 0.537 |
| Differentiated | 17 (26.2) | 11 (16.9) | 3 (4.6) | |
| Undifferentiated | 48 (73.8) | 46 (70.8) | 5 (7.7) | |
| pT stage | | | | 0.488 |
| T1 | 9 (13.9) | 6 (9.2) | 0 | |
| T2 | 16 (24.6) | 17 (26.2) | 2 (3.1) | |
| T3 | 13 (20.0) | 19 (29.3) | 1 (1.5) | |
| T4a | 26 (40.0) | 14 (21.5) | 5 (7.7) | |
| T4b | 1 (1.5) | 1 (1.5) | 0 | |
| pN stage | | | | 0.788 |
| N0 | 27 (41.6) | 22 (33.8) | 0 | |
| N1 | 8 (12.3) | 6 (9.2) | 1 (1.5) | |
| N2 | 14 (21.5) | 15 (23.2) | 1 (1.5) | |
| N3a | 13 (20.0) | 14 (21.5) | 4 (6.2) | |
| N3b | 3 (4.6) | 0 | 2 (3.1) | |
| pTNM stage | | | | 0.288 |
| IA | 8 (12.3) | 3 (4.6) | 0 | |
| IB | 11 (16.9) | 7 (10.8) | 0 | |
| IIA | 3 (4.6) | 10 (15.4) | 0 | |
| IIB | 12 (18.5) | 13 (20.0) | 0 | |
| IIIA | 16 (24.6) | 14 (21.5) | 3 (4.6) | |
| IIIB | 13 (20.0) | 10 (15.4) | 4 (6.2) | |
| IIIC | 2 (3.1) | 0 | 1 (1.5) | |
| postoperative chemotherapy | | | | 0.856 |
| Yes | 24 (36.9) | 22 (33.8) | 3 (4.6) | |
| No | 41 (63.1) | 35 (53.9) | 5 (7.7) | |

P-value is the result of comparison of the 14vD (-) group and the 14vD (+) group. LNM (-): Without 14v lymph nodes metastasis; LNM (+): With 14v lymph nodes metastasis.

On univariate analysis, the status of 14v dissection significantly affected the prognosis. Multivariate analysis indicated that the independent prognostic factors for prolonged OS were age < 65 years ($P = 0.018$) and pT2-3 stage ($P = 0.006$; Table 3).

Frequency of metastasis to each LN station according to the presence of 14v LN metastasis

Tumors with 14v LN metastasis metastasized more often to LN stations 1, 3, 4, 5, 6, 8a, and 11p. This difference was significant for LN stations 1, 6, 8a, and 11p ($P < 0.001$). These results may indicate that the presence of 14v LN metastasis can be predicted based on the presence of metastasis to LN stations 1, 6, 8a, and 11p (Figure 4).

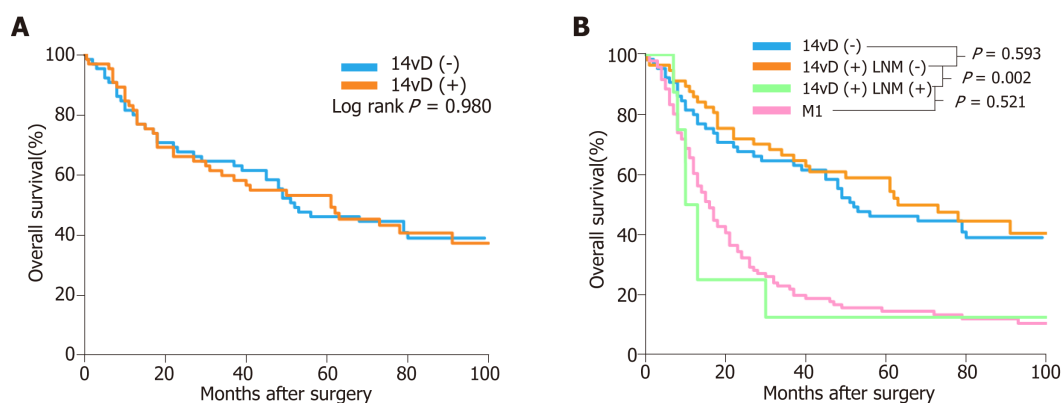


Figure 1 Overall survival curves of patients. A: Overall survival curves of patients in the 14vD (-) and 14vD (+) groups; B: Overall survival curves of patients in the 14vD (-) group, the 14vD (+) group with and without 14v lymph nodes metastasis, and patients with distant metastasis. LNM (-): Without 14v lymph nodes metastasis; LNM (+): With 14v lymph nodes metastasis.

DISCUSSION

In the present study, we found that the OS of patients with 14v LN metastasis was comparable to that of patients with M1 stage tumors, similar to previous findings^[12]. However, previous studies have also shown that GC patients with 14v LN metastasis without other distant metastasis had a significantly better OS compared to patients with M1 stage GC ($P < 0.001$)^[18,19]. Given the differences in the results, we cannot directly classify patients with 14v metastasis as having M1 stage GC, and we cannot ignore the potential survival benefits of 14v LN dissection^[20,21]. Therefore, it is important to select appropriate candidates who will benefit from the addition of 14v LN dissection. Some studies supported the addition of 14v LN dissection to D2 gastrectomy for patients with LTGC^[19,20,22-31]. Eom *et al*^[24] showed that 14v LN dissection was an independent prognostic factor for patients with clinical stage III/IV GC in the middle or lower third of the stomach. Liang *et al*^[25] argued that 14v LN dissection might improve the 3-year OS for distal pathological stage IIIB/IIIC GC. Additionally, Chen *et al*^[19] found that adding laparoscopic 14v dissection to laparoscopic-assisted radical distal gastrectomy might improve the OS of cT2-3 patients.

In the present study, we found that, among patients with pathological stage IIIA GC, the 14vD (+) group had better OS compared with the 14vD (-) group ($P = 0.020$). The TNM stage used in our study was defined according to the AJCC eighth edition, while the sixth edition was used in the study by Eom *et al*^[24] and the seventh edition in the studies by Liang *et al*^[27] and Edge *et al*^[32,33]. Moreover, our study demonstrated that adding 14v LN dissection had survival benefits for stage IIIA patients, and these results are similar to those obtained by Eom *et al*^[24] and Liang *et al*^[27]. The latter studies evaluated patients with advanced-stage tumors, while the patients in our study had early stage GC. To the best of our knowledge, the present study is the first to evaluate the role of adding 14v LN dissection for patients with different pathological stage GC according to the AJCC eighth edition. We found no effect of adding 14v LN dissection on the OS of patients with pathological stage I and II LTGC. This result could probably be attributed to the rarity of 14v LN metastasis in these diseases. In the studies by An *et al*^[12] and Kong *et al*^[34-36], the incidence of 14v LN metastasis was 0% and 2%-3% in stages I and II GC, respectively. Considering the low incidence of 14v LN metastasis in pathological stage I/II LTGC, 14v LN dissection was not recommended for these patients. Moreover, in the current study, 14v LN dissection did not result in better OS of patients with pathological stage IIIB and IIIC LTGC probably because patients with stage IIIB and IIIC GC have more extensive tumor invasion and tend to develop systemic disease.

The 14v LNs are anatomically downstream of the No. 6 LN considering the lymphatic flow for patients with LTGC. In theory, once the No. 6 LN is invaded, there is a high risk of metastasis to the 14v LNs. An *et al*^[12] reported that metastasis to the No. 6 LN was a useful predictive factor for 14v LN metastasis, with an accuracy rate of 99.0% and false-negative rate of 1.9%^[10]. In the present study, all patients with 14v LN metastasis had No. 6 LN metastases. Thus, our study results may indicate that the presence of 14v LN metastasis could be predicted based on the presence of metastasis to LN stations 1, 6, 8a, and 11p.

The present study has some limitations. First, this was a retrospective cohort study, and the clinicopathological features were different between the two groups.

Table 2 Univariate and multivariate analyses of prognostic factors for the entire study population

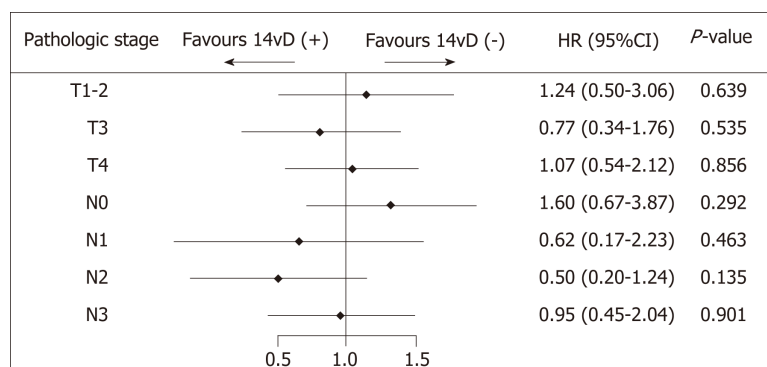
| Variable | Univariate analysis | | Multivariate analysis | |
|----------------------------|----------------------|---------|-----------------------|---------|
| | Hazard ratio (95%CI) | P-value | Hazard ratio (95%CI) | P-value |
| Status of 14v dissection | | 0.980 | | 0.900 |
| 14vD (-) | 1 (ref) | | 1 (ref) | |
| 14vD (+) | 1.01 (0.64-1.58) | | 0.97 (0.59-1.60) | |
| Age group | | 0.569 | | 0.234 |
| < 65 yr | 1 (ref) | | 1 (ref) | |
| ≥ 65 yr | 1.15 (0.71-1.86) | | 1.40 (0.80-2.45) | |
| Gender | | 0.781 | | |
| Male | 1 (ref) | | 1 (ref) | 0.721 |
| Female | 0.94 (0.60-1.46) | | 0.91 (0.56-1.50) | |
| Tumor size | | 0.455 | | 0.448 |
| < 4 cm | 1 (ref) | | 1 (ref) | |
| ≥ 4 cm | 1.19 (0.76-1.86) | | 0.82 (0.50-1.56) | |
| Histologic grade | | 0.275 | | 0.162 |
| Differentiated | 1 (ref) | | 1 (ref) | |
| Undifferentiated | 1.34 (0.80-2.24) | | 1.51 (0.85-2.71) | |
| pT stage | | 0.004 | | 0.033 |
| T1 | 1 (ref) | | 1 (ref) | |
| T2 | 4.88 (1.13-20.99) | | 4.97 (1.11-22.28) | |
| T3 | 8.32 (1.96-35.29) | | 6.58 (1.45-29.92) | |
| T4 | 9.17 (2.2-38.21) | | 7.87 (1.84-33.74) | |
| pN stage | | 0.002 | | 0.018 |
| N0 | 1 (ref) | | 1 (ref) | |
| N1 | 2.29 (1.07-4.90) | | 2.08 (0.92-4.67) | |
| N2 | 2.18 (1.20-3.97) | | 2.01 (1.06-3.81) | |
| N3a | 3.11 (1.71-5.63) | | 2.82 (1.49-5.36) | |
| N3b | 4.30 (1.46-12.65) | | 3.90 (1.22-12.45) | |
| Postoperative chemotherapy | | 0.799 | | 0.368 |
| No | 1 (ref) | | 1 (ref) | |
| Yes | 1.06 (0.67-1.70) | | 0.78 (0.46-1.33) | |

Therefore, we performed propensity score matching analysis to minimize these differences caused by nonrandom assignments. Second, the number of patients was small, especially for subgroup analysis, thereby possibly influencing the results. Third, we could not obtain information about surgical-related safety assessment, postoperative complications, and postoperative mortality; therefore, it was impossible to compare whether the risk of 14v LN dissection increased. Accordingly, in the future, high-quality multicenter clinical randomized controlled studies are needed to evaluate the effect of 14v LN dissection on OS.

In conclusion, the present study demonstrated that OS was similar between patients with 14v LN metastasis and those with M1 stage disease. Patients with No. 1, No. 6, No. 8a, or No. 11p LN metastasis were at a higher risk of 14v LN metastasis. The addition of 14v LN dissection to D2 dissection during radical distal gastrectomy may improve the OS of patients with pathological stage IIIA LTGC.

Table 3 Univariate and multivariate analyses of prognostic factors for patients with pathological stage IIIA gastric cancer

| Variable | Univariate analysis | | Multivariate analysis | |
|----------------------------|----------------------|---------|-----------------------|---------|
| | Hazard ratio (95%CI) | P-value | Hazard ratio (95%CI) | P-value |
| Status of 14v dissection | | 0.027 | | 0.342 |
| 14vD (-) | 1 (ref) | | 1 (ref) | |
| 14vD (+) | 0.39 (0.17-0.90) | | 0.61 (0.22-1.70) | |
| Age group | | 0.331 | | 0.018 |
| < 65 yr | 1 (ref) | | 1 (ref) | |
| ≥ 65 yr | 1.53 (0.65-3.64) | | 7.23 (1.41-37.06) | |
| Gender | | 0.986 | | 0.930 |
| Male | 1 (ref) | | 1 (ref) | |
| Female | 0.99 (0.44-2.24) | | 1.05 (0.36-3.09) | |
| Tumor size | | 0.091 | | 0.091 |
| < 4 cm | 1 (ref) | | 1 (ref) | |
| ≥ 4 cm | 0.46 (0.19-1.13) | | 0.37 (0.12-1.17) | |
| Histologic grade | | 0.220 | | 0.091 |
| Differentiated | 1 (ref) | | 1 (ref) | |
| Undifferentiated | 1.71 (0.73-4.02) | | 2.71 (0.85-8.60) | |
| pT stage | | 0.154 | | 0.006 |
| T2-3 | 1 (ref) | | 1 (ref) | |
| T4 | 1.35 (0.89-2.04) | | 14.15 (2.11-95.06) | |
| pN stage | | 0.886 | | 0.335 |
| N0-1 | 1 (ref) | | 1 (ref) | |
| N2 | 0.86 (0.33-2.25) | | 1.77 (0.55-5.72) | |
| N3a | 0.74 (0.22-2.49) | | 3.69 (0.64-21.37) | |
| Postoperative chemotherapy | | 0.936 | | 0.586 |
| No | 1 (ref) | | 1 (ref) | |
| Yes | 0.96 (0.39-2.37) | | 0.75 (0.27-2.11) | |

**Figure 2** Forest plot of overall survival. The hazard ratios for adding 14v lymph node dissection were obtained via Cox proportional hazard model for pathologic T stage and pathologic N stage.

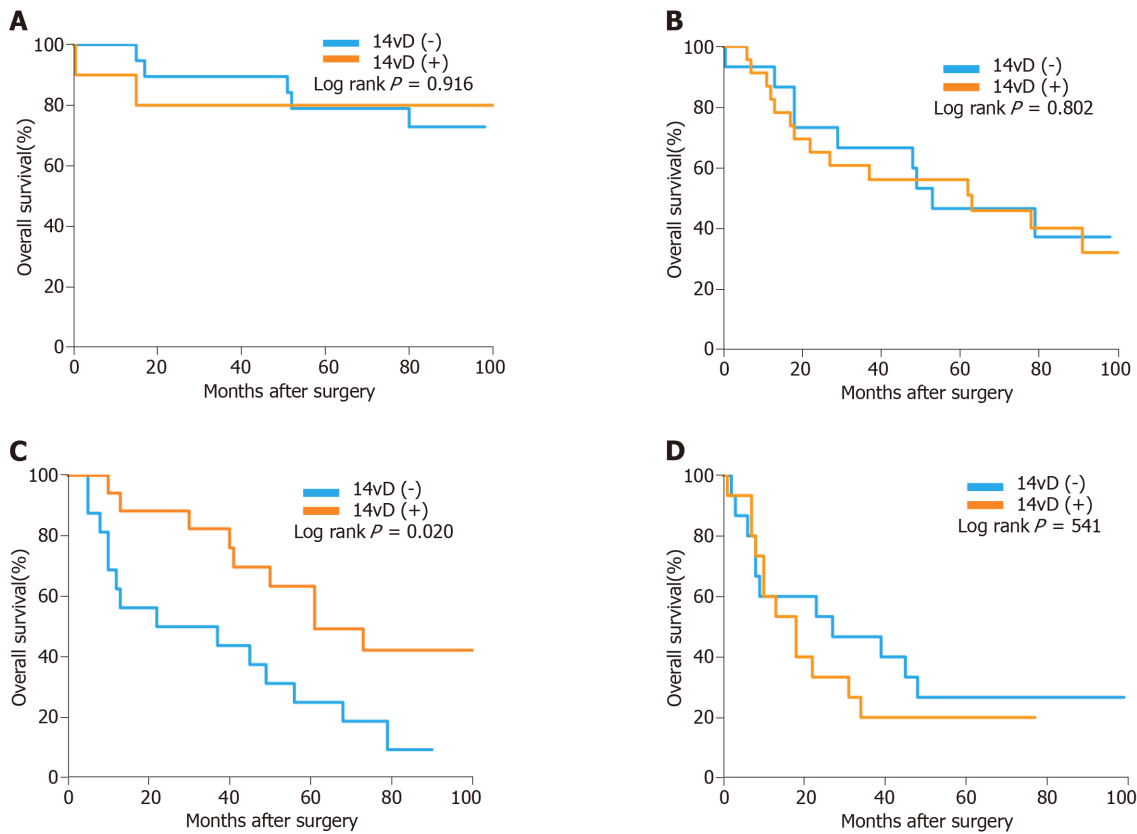


Figure 3 Overall survival according to 14v lymph node dissection in gastric cancer patients. A: Pathologic stage I; B: Pathologic stage II; C: Pathologic stage IIIA; D: Pathologic stages IIIB/IIIC gastric cancer patients.

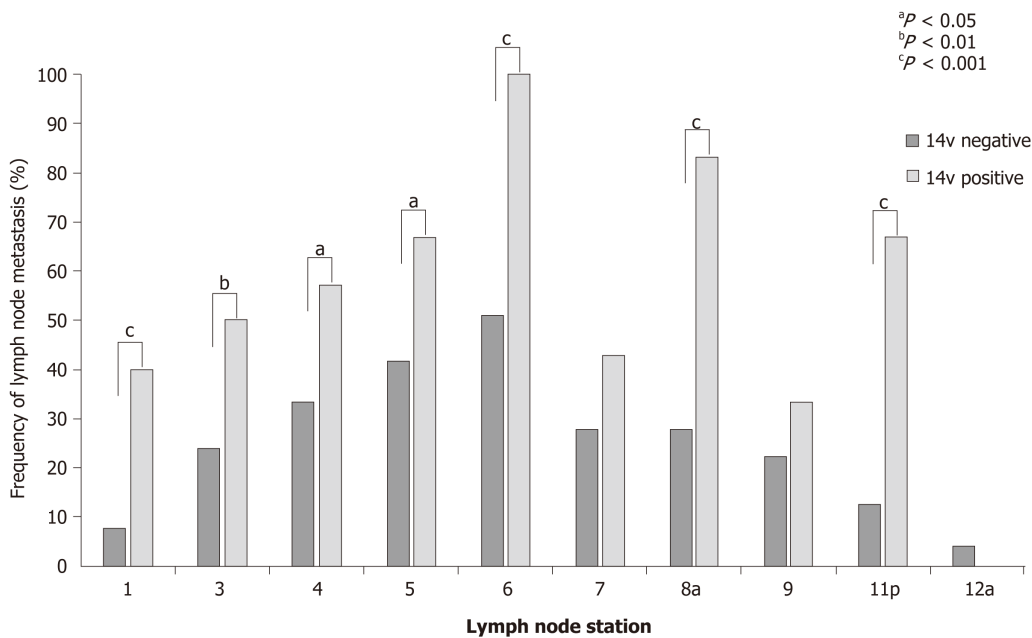


Figure 4 Frequency of metastasis to each lymph node station according to the presence of station 14 lymph node metastasis in the entire study population.

ARTICLE HIGHLIGHTS

Research background

In the fifteenth edition of the Japanese Classification of Gastric Carcinoma, the 14v lymph node (LN) (LNs along the root of the superior mesenteric vein) was defined as the regional gastric LN.

Research motivation

The efficacy of 14v LN dissection during radical distal gastrectomy for lower-third gastric cancer (GC) remains controversial.

Research objectives

To analyze whether the addition of 14v LN dissection improved the survival of patients with lower-third GC.

Research methods

Using the propensity score-matched method from our institute database constructed between 2000 and 2012, overall survival (OS) was compared between the patients with and without 14v LN dissection.

Research results

OS was similar between patients with 14v LN metastasis and those with distant metastasis. Among patients with pathological stage IIIA disease, those who were treated with 14v LN dissection had a significantly higher OS than those treated without it.

Research conclusions

Adding 14v LN dissection to D2 dissection during radical distal gastrectomy may improve the OS of patients with pathological stage IIIA lower-third GC.

Research perspectives

In the future, high-quality multicenter clinical randomized controlled studies are needed to evaluate the effect of 14v LN dissection on OS.

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