



A retrospective study comparing D1 limited lymph node dissection and D2 extended lymph node dissection for N3 gastric cancer

Xing Luo¹, Ming-Xiu Zhou^{1,2}, Wei Tian^{2,3}, Ming Zeng^{1,2}, Jian-Ling Xia¹, Gao-Ping Zhao⁴, Hong-Lin Hu¹, Xin-Bao Hao⁵, Liang-Fu Han⁶, Hao Liu¹, Yang-Ke He¹, Xue-Qiang Zhu¹, Liang Liang¹, Min Wei⁷, Li-Li Deng⁸

¹Cancer Center, Hospital of University of Electronic Science and Technology of China and Sichuan Provincial People's Hospital, Chengdu 610072, China; ²School of Medicine, University of Electronic Science and Technology of China, Chengdu 610072, China; ³Operations Management Department, Hospital of University of Electronic Science and Technology of China and Sichuan Provincial People's Hospital, Chengdu 610072, China; ⁴Department of Gastroenterology, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, Chengdu 610072, China; ⁵Sino-America Cancer Center, Hainan Medial University, Haikou 570100, China; ⁶Department of GI Surgery, Xijing Hospital, Xi'an 710000, China; ⁷Cancer Center, Ziyang People's Hospital, Ziyang 641300, China; ⁸Cancer Center, Sichuan Friendship Hospital, Chengdu 610072, China

Contributions: (I) Conception and design: X Luo, MX Zhou, W Tian, M Zeng; (II) Administrative support: M Zeng; (III) Provision of study materials or patients: MX Zhou, JL Xia, GP Zhao; (IV) Collection and assembly of data: X Luo, HL Hu, XB Hao, LF Han, H Liu; (V) Data analysis and interpretation: X Luo, YK He, XQ Zhu, L Liang, M Wei, LL Deng, H Bai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Ming Zeng. Cancer Center, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital, #32 West #2 Section, First Ring Road, Chengdu 610072, China. Email: miller2002@yahoo.com.

Background: In countries in East Asia, the typical treatment for curable gastric cancer is gastrectomy with D2 lymphadenectomy. However, whether D2 lymphadenectomy is beneficial for high-risk N3 node disease remains controversial. We conducted a multi-institution retrospective study on patients with high-risk, locally advanced gastric cancer. To compare the rates of disease-free survival (DFS) and overall survival (OS) between radical D2-type gastric resection and lymphadenectomy and the more limited D1 type resection and lymphadenectomy.

Methods: From July 2010 to June 2015, 74 patients out of 949 who underwent curative-intent R0 surgery were selected in pairs to compare the survival outcomes between those who underwent radical D2 type (n=37) *vs.* the more limited D1 type (n=37) gastric resection and lymphadenectomy.

Results: The median DFS was 9.72 and 7.81 months for the D2 and D1 types, respectively (P=0.746), and the OS was 16.39 and 15.85 months for the D2 and D1 types, respectively (P=0.937).

Conclusions: No statistically significant differences in DFS and OS were noted between D1 and D2 procedures for those with N3 disease. Our results support the hypothesis that a novel multidisciplinary approach rather than a surgical approach alone is needed to improve the survival outcomes of high-risk patients with N3 gastric cancer.

Keywords: Gastric cancer; chemoradiotherapy; surgery; D2 lymphadenectomy; D1 lymphadenectomy

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Introduction

Gastric cancer ranks globally as the second-highest contributor to cancer-related mortality, although its prevalence has been reducing (1). Eastern Asia accounts for

around 6 in 10 newly diagnosed cases of gastric cancer, and more than 2 million new cases are diagnosed annually in China alone. A multidisciplinary approach has been proven to improve the outcome for advanced-stage gastric cancer

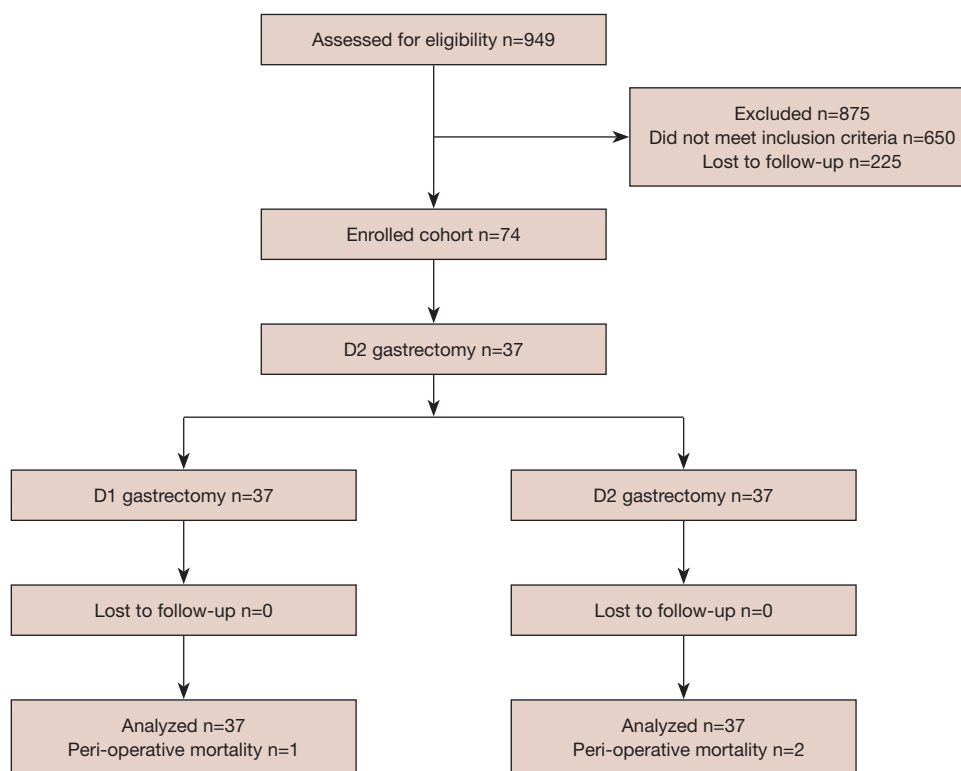


Figure 1 Patient selection.

patients, but surgical resection offers the most efficacy as a therapy for those with curable cases of the disease. Current data from level 1 evidence are based on N1 or N2 disease, and reports on N3 disease are limited (2-4).

The therapeutic value of limited (D1) *vs.* extended (D2) lymph node dissection for locally advanced gastric cancer remains controversial. The overall survival (OS) rate for N3 disease remains poor with radical surgery, including in Asian countries such as China, where extended lymph node dissection is practiced routinely. N3 disease was reported to have no survival benefits from any extensive surgery beyond D2, such as extensive para-aortic node dissection (D3) (5,6).

Whether D2 provides any survival benefits in the treatment of N3 disease remains unclear. This retrospective study compares two types of surgical management for lymph nodes of patients with gastric cancer, namely, D1 and D2 node dissection.

Methods

Among those who underwent R0 gastric resection from July 2010 to June 2015 in the 5 centers listed in the author's

information, 949 patients were identified and assessed for eligibility. Of these, 875 were deemed ineligible, leaving 74 (7.79%) patients eligible to undergo treatment: 37 to undergo D1 resection, and 37 to undergo D2 resection. The method used for patient selection is shown in *Figure 1*. The patients underwent D2 lymphadenectomy as part of standard radical gastrectomy. To best serve our research objective, the number of lymph nodes removed assisted in classifying lymphadenectomy. A total number of lymph nodes greater than 15 in the pathology report was defined as adequate D2, while a total less than or equal to 14 was defined as D1.

A D1 dissection involves the affected distal section of the stomach or the stomach in its entirety (subtotal or total resection) being removed, including the greater and lesser omenta (7-9). D2 dissection, meanwhile, sees the removal of the omental bursa as well as the front leaf of the transverse mesocolon, and the mentioned arteries are totally cleared. Resection of the spleen and the tail of the pancreas was considered to be required for the satisfactory removal of D2 lymph-node stations 10 and 11 in proximal tumors.

In contrast, in a D1 dissection, the spleen and tail of the

pancreas resections were carried out only in instances where removal was deemed necessary due to tumor invasion. Following the last pathological examination, the surgery was classified as R0 if the tumor was shown by microscopic evidence to have been entirely removed, if distant lymph nodes were not found to be involved, and if no malignant cells were discovered in the abdominal-washing fluid. No distal pancreatectomy and/or splenectomy was performed during D1 or D2 resection unless there was direct tumor invasion to the two organs at the time of presentation.

The percentage of positive node involvement (D+ %) was calculated as positive lymph node among total dissected lymph nodes. The positive node was defined as invasion in the dissected specimen, and pathologically confirmed lymph node involvement. Nodes with unknown status were excluded in the D+ % evaluation.

Patients who did not meet the criteria were excluded in this study. The criteria were individuals under the age of 75 years of age with histologically proven gastric adenocarcinoma, which was surgically removed with the D1 or D2 techniques. Further eligibility criteria, stemming from the intraoperative findings, were the detection of a stage T2b, T3, or T4 tumor, the absence of gross metastases in the abdominal cavity, and negative cytologic findings in the peritoneal-lavage fluid. All positive lymph nodes were diagnosed by dissection, not by examination of frozen sections. We ensured quality control by relating the number and location of lymph nodes identified through pathological examination. The detection of lymph nodes in stations besides those specified, or an inability to detect lymph nodes in stations that should have been dissected, led to the case being classified as unknown LN. The amounts of lymph nodes varied significantly at each station, and those stations defined may not have contained any lymph nodes (10,11). The study protocol was approved by the Ethics Committee of Sichuan Provincial People's Hospital. Informed consent was obtained from all patients before surgery was performed. For the purpose of the study, written consent was waived owing to the study's retrospective nature. Patients who underwent minimal invasive or open laparotomy were included in the study.

The clinical pathology, operative, and survival data were compared between the D1 and D2 groups. Patients were considered to have undergone additional organ resection when there was a record of the procedure in the patient's operative note or the pathological report. All disease stages were assigned using the 2017 American Joint Committee on Cancer TNM staging guidelines.

Chi-square analysis was applied to make comparisons based on the clinical pathology data. Parameters that influenced survival and recurrence were compared through the use of the Kaplan-Meier method with the log-rank comparison. A significant difference was indicated when P value =0.05. The results of significance between variables via univariate and multivariate analysis were not presented due to the small cohort size.

Results

A balance was maintained between the two groups in relation to age, sex, tumor size, the extent of resection, and pathology (*Table 1*). The median number of positive LNs removed from the D2 arm was significantly larger than in the D1 arm (11.19% *vs.* 9.03%, respectively; $P<0.007$).

No significant difference in postoperative morbidity was noted between the D1 (10.81%, $n=4$) and D2 treatment arms (18.9%, $N=7$) ($P=0.327$) (*Table 2*). Death within 90 days of surgery was considered as postoperative mortality, and a total of 3 patients died during this period: 1 (2.7%) from the D2 group and 2 (5.4%) from the D1 group (*Table 2*).

The most common site of recurrence was the peritoneum in both arms. The first site of recurrence was not significantly different between D1 ($n=16$, 43.2%) and D2 ($n=19$, 51.3%). Recurrences at the anastomotic site were less common in both groups (D1: $n=5$, 13.5% *vs.* D2: $n=4$, 10.8%). Overall, the rate of recurrence was higher in D1 ($n=35$, 94.5%) than in D2 ($n=31$, 83.7%) (*Table 3*).

Time to recurrence

There was a median follow-up period of 24 months (ranging from 7 to 40 months) for all patients who underwent R0 resection. A total of 66 (89.1%) patients in the entire population had recurrences, of which 44 (59.4%) were local, and 12 (16.2%) were distant. The median disease-free survival (DFS) was 9.72 and 7.81 months for the D2 and D1 groups, respectively ($P=0.746$). Meanwhile, the median OS was 16.39 and 15.85 months for the D2 and D1 groups, respectively ($P=0.937$). The incidence of recurrence between the two dissection groups was not significantly different (D1: 35/37, 94.5% *vs.* D2: 31/37, 83.7%; $P=0.261$). The median time to recurrence was 10 and 9 months in D2 and D1 groups, respectively. Among patients who underwent adjuvant therapy, the time to recurrence was significantly different between the two groups. Adjuvant treatment prolonged the recurrence from 6 months to 15 months

Table 1 Patient characteristics

Characteristic	D1	D2	t/ χ^2	P value [†]
Age (year)			-0.246	0.806
Mean	55.89	56.08		
SD	3.41	3.19		
Median	56	57		
Range	51–67	51–63		
Sex, n			0.000	1.000
F	18	18		
M	19	19		
Tumor location, n			0.897	0.639
Upper	8	7		
Mid	15	19		
Low	14	11		
Tumor size [‡] (cm)			0.689	0.493
Mean	6.51	6.06		
SD	2.94	2.61		
Median	6	6		
Range	1–13	1.7–14		
Clinical stage, n			–	0.736
T1–2	6	4		
T3–4	31	33		
Pathological stage, n			–	1.000
T1–2	5	5		
T3–4	32	32		
No. of positive lymph nodes			2.821	0.007
Mean	9.03	11.19		
SD	1.99	4.22		
Median	9	10		
Range	7–14	7–27		
R resection*, n			0.214	0.643
R0	34	35		
R1	3	2		
Type of resection, n			0.840	0.359
Total	8	5		
Subtotal	29	32		

[†], the T stage was determined according to the AJCC 2016 edition; [‡], P values were calculated using Fisher's exact test except for comparisons of age, tumor size, and number of positive lymph nodes; *, R0, no microscopic residual disease, R1 with microscopic residual disease.

Table 2 Morbidity and mortality from D1 or D2 surgery

Postoperative morbidity	Outcome*		P value
	D1	D2	
Total morbidity, n	4	7	0.327
Total death, n (%)	1 (2.7)	2 (5.4)	1.000

*, calculated using Fisher's exact test.

Table 3 Site of first tumor recurrence

Site	D1, n (%)	D2, n (%)	P value
Anastomosis site	5 (13.5)	4 (10.8)	1.000
Peritoneal/lymph node	16 (43.2)	19 (51.3)	0.642
DM (liver or lung)	7 (18.9)	5 (13.5)	0.528
Other	7 (18.9)	3 (8.1)	0.174
Total	35 (94.5)	31 (83.7)	0.261

DM, distant metastasis.

and from 5 months to 14 months in the D2 and D1 groups, respectively.

Survival

There was a median survival period of 15 months for the group as a whole. After excluding the patients lost to follow-up, the length of survival in the D1 group (median: 17 months) was not significantly better than in the D2 group (median: 15 months) (*Figure 2*). The median survival time for patients who underwent splenectomy was 15 months, and this rose to 16 months for patients who underwent pancreateosplenectomy. Analysis based on the disease stage (stages II to IV) revealed that survival was not significantly decreased by the removal of additional nodes in both D2 and D1 (*Figure 2*). Survival was not affected by the specific type of organ to be resected within each stage.

Discussion

Using multi-center data, we compared patients with N3 gastric cancer who underwent two types of surgical procedure, D1, and D2 curative resection, and found no significant differences in outcomes following surgery in these patients.

Primary surgery followed by adjuvant treatment remains the standard treatment for N3 gastric cancer, and neoadjuvant chemotherapy or chemoradiation in our

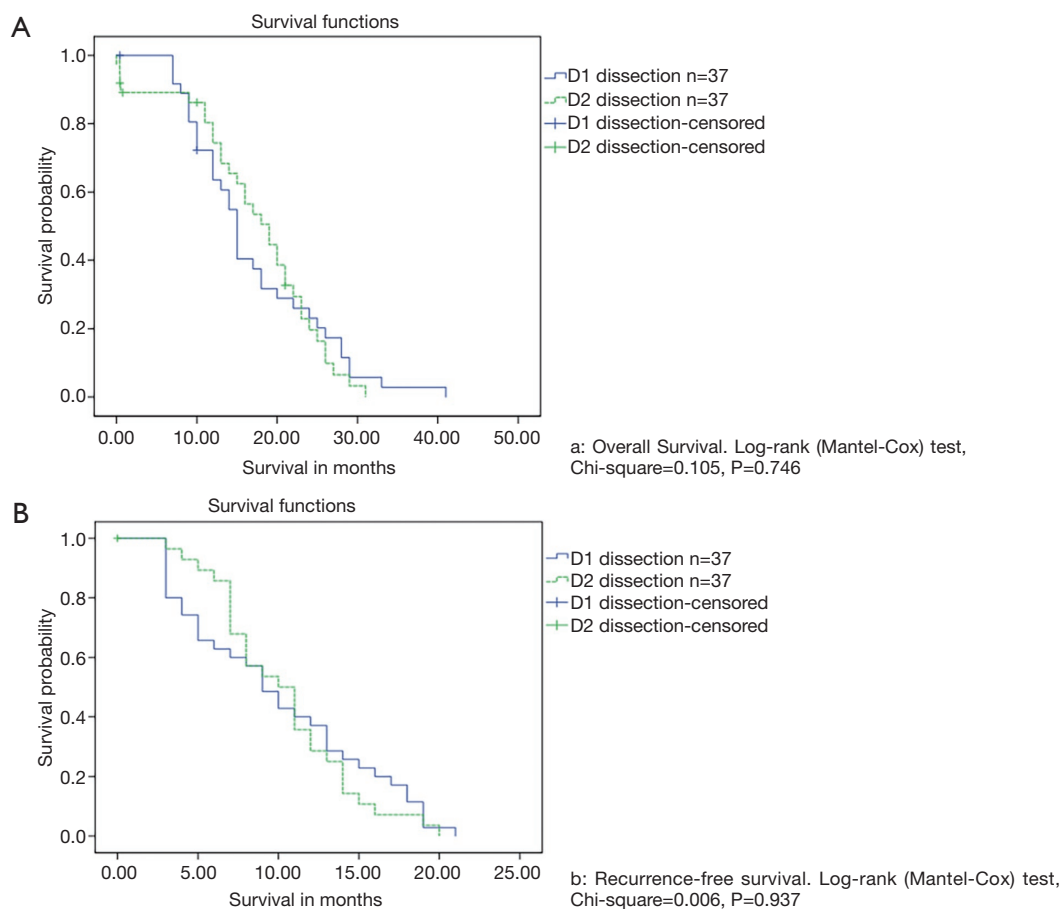


Figure 2 Kaplan-Meier estimates of overall survival (A) and recurrence-free survival (B).

study period was not the standard form of care. To avoid bias, patients who had received neoadjuvant treatment were excluded from the study. Overall, approximately 8% of patients in our cohort had N3, which is consistent with previous reports (12,13).

Our cohorts were all recruited from tertiary hospitals where more than 100 gastrectomy surgeries are performed annually. All of the surgeons were well trained, and each had more than 10 years' experience in related procedures. The volume-related quality issue raised by some authors (14) did not apply in this study.

The rate of surgical morbidity or mortality was not different between the D1 and D2 groups. Two large phases III trials—DGCT and MRC—reported high mortality rates after D2 dissection (15-17).

Our data did not show that extensive resection may have an adverse effect on prognosis. Zhang and Masahiro attributed this phenomenon to local tumor spillage from the

many divided lymphatic vessels (17,18). The mortality rate in the present study was consistent with that reported by Degiuli and Talaiezhadeh (19,20). The inconsistency in the rate of mortality in the two groups is likely due to differences in cohort size and types of analysis carried out. Future extended studies to confirm our findings are called for.

Studies have reported potential survival benefits from D2 dissection (3,6,21,22), which is inconsistent with our findings. However, those studies included patients from different populations and enrolled only those in the early stage of the disease. In their cohorts, patients with N3 accounted for less than 10%, and it is unclear whether the results of the subgroup analyses of the N3 patients could yield the same conclusion as those of the entire cohorts. Based on our results, we hypothesize that the extension of D2 lymph node dissection might hold benefits only as a treatment for early-stage diseases such as N1 or N2, but not for N3 or later-stage disease. This could be because N3 disease is already

systemic; as such, neither regional control nor survival can be influenced by intensive local lymph node dissection.

In China, the OS of gastric cancer patients has remained low over recent decades, and the 5-year cancer-specific mortality rate for stage III gastric cancer is higher than that in the United States, with approximately 72% vs. 56%, respectively (13). In contrast, in the same period, the Japanese Research Society for Gastric Cancer reported improved survival figures, with an OS of approximately 50% after resection (23). During this time, an increasing number of early-stage gastric cancer cases have been diagnosed via population-screening programs (24). Collectively, these improvements explain the improved Japanese survival data, as patients were diagnosed earlier. However, another study has suggested that the improved survival rate seen in Japan can be attributed to the adoption of radical surgery with lymphadenectomy (6). Such treatment modality was implemented in Japan based on the theory that effective locoregional control of cancer reduces recurrence in the gastric bed. If this theory is true, then extensive lymph node dissection would provide better local control for N3 disease.

However, evidence of the clinical benefit of extensive D2 lymph node dissection for locally advanced gastric cancer (LAGC) and N3 disease is lacking; thus, its role in the treatment of such patients remains controversial. Previous randomized control trials enrolled patients that have either N1 or N2 disease, and only a few have included those with N3 disease. To our knowledge, our study is the first to have focused on patients with N3 disease and compared the clinical benefit of D1 lymphadenectomy with D2 lymphadenectomy for gastric cancer. Our data show that patients with N3 disease may not benefit from D2 extensive node dissection.

Future efforts to improve the survival of patients with LAGC must concentrate on a multidisciplinary approach. The MAGIC study has demonstrated the survival benefits of perioperative chemotherapy for LAGC (25), and the ongoing TOPGEAR and President studies are expected to provide more data on the therapeutic value of neoadjuvant chemoradiation for treating gastric cancer (26).

This study had some limitations, including its retrospective nature and inconsistencies in data from the post-treatment review. Moreover, not all stations for positive nodes were matched, and a previous report showed that metastases in the station are predictive of OS (27).

In summary, our study demonstrated that patients with gastric cancer who have a high number of positive lymph

nodes have poor outcomes. Moreover, extensive node dissection did not improve the outcomes of such patients. Although Sasako *et al.* reported that extensive node dissection led to worse prognosis in node-positive patients (6), their study included patients with early-stage disease. Our findings should be interpreted with caution because this is a retrospective review and was thus subject to biases and errors and because there was no accurate manner in which to assess lymph-node metastases prior to surgery and intraoperative frozen-section diagnosis of all dissected lymph nodes was not feasible.

Given that our results show that D2 extended lymphadenectomy does not improve outcomes in patients with N3 gastric cancer, further research is needed to determine an alternative approach to improve the outcomes of these patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.42>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was reviewed and approved by the Ethics Committee of Sichuan Provincial People's Hospital (No: 2017-126-7). Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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