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Association of lymphadenectomy extent with long-term survival in gastric cancer: a retrospective comparative cohort study

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ABSTRACT

Introduction: The optimal extent of lymphadenectomy for gastric cancer remains controversial, particularly in Western practice, where concerns regarding postoperative morbidity have historically limited the widespread adoption of D2 dissection. This study aimed to compare the perioperative safety and long-term oncological outcomes of D1 and D2 lymphadenectomy in patients undergoing curative gastrectomy.

Materials and Methods: A retrospective comparative cohort study was conducted involving 189 patients who underwent curative gastrectomy for gastric adenocarcinoma between 2014 and 2022. Fifty-seven patients underwent D1 lymphadenectomy, and 132 underwent standard D2 lymphadenectomy according to Japanese Gastric Cancer Association criteria. Baseline clinicopathological characteristics, postoperative outcomes, disease-free survival (DFS), and overall survival (OS) were analyzed. Survival outcomes were evaluated using Kaplan–Meier analysis and Cox proportional hazards regression.

Results: Baseline demographic, clinical, and pathological characteristics were comparable between the groups. The D2 group had a significantly greater number of harvested lymph nodes than the D1 group (median, 31 vs. 27; p=0.011), while postoperative morbidity (18.2% vs. 12.3%; p=0.429), hospital stay (p=0.400), recurrence (p=0.525), and 90-day mortality (p=0.533) were similar. Median overall survival was significantly longer following D2 lymphadenectomy (59 vs. 20 months). One-, three-, and five-year overall survival rates were consistently higher in the D2 group (83.3%, 59.5%, and 49.3%, respectively) than in the D1 group (64.6%, 35.6%, and 31.9%, respectively). Cox regression demonstrated that D2 lymphadenectomy reduced the risk of all-cause mortality by 41% (HR, 0.59; 95% CI, 0.40–0.87). Disease-free survival also favored D2 lymphadenectomy (HR, 0.62; 95% CI, 0.39–1.00), although the difference narrowly missed conventional statistical significance (p=0.052).

Conclusions: Standard D2 lymphadenectomy provides superior long-term survival without increasing perioperative morbidity or mortality when performed in experienced centers. These findings support D2 lymphadenectomy as the preferred surgical approach for patients undergoing curative gastrectomy for gastric cancer.

Keywords: D2 lymphadenectomy, disease-free survival, gastric cancer, gastrectomy, overall survival

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Introduction

Gastric cancer remains the fifth most commonly diagnosed malignancy worldwide and the fourth leading cause of cancer-related mortality, largely owing to its aggressive biological behavior and frequent presentation at advanced stages.[1] Curative-intent gastrectomy with adequate lymphadenectomy represents the cornerstone of treatment for localized and locally advanced disease. However, the optimal extent of lymph node dissection remains debated.

According to the Japanese Gastric Cancer Association guidelines, D1 lymphadenectomy includes removal of the perigastric lymph node stations, whereas D2 lymphadenectomy extends the dissection to second-tier nodal stations surrounding the major vascular structures.[2] Although D2 dissection has long been regarded as the standard approach in Eastern countries, its adoption in Western practice has historically been limited. Early randomized trials reported increased postoperative morbidity and mortality associated with D2 lymphadenectomy, largely because of the routine inclusion of splenectomy and distal pancreatectomy, without demonstrating a clear survival advantage.[3] Consequently, D1 lymphadenectomy remained widely accepted in many Western centers.

Subsequent evidence has challenged these initial concerns. Long-term follow-up studies and contemporary retrospective analyses have demonstrated that D2 lymphadenectomy provides superior oncological staging, improved locoregional disease control, and enhanced long-term survival outcomes without significantly increasing perioperative risk when performed in experienced centers using spleen- and pancreas-preserving techniques.[4,5] Furthermore, advances in perioperative management, minimally invasive surgery, and multimodal treatment strategies have substantially improved the safety profile of extended lymphadenectomy.

Despite these developments, real-world data comparing D1 and D2 lymphadenectomy in contemporary clinical practice remain limited, particularly in Western and transitional healthcare settings. Moreover, the survival benefit of D2 dissection in the era of modern perioperative treatment remains debated.

Therefore, this study aimed to compare perioperative outcomes, disease-free survival, and overall survival in patients undergoing curative gastrectomy with either D1 or D2 lymphadenectomy at a high-volume tertiary center. We hypothesized that standard D2 lymphadenectomy would provide superior long-term oncological outcomes without increasing postoperative morbidity or mortality.

Materials and Methods

Study Design and Ethical Approval

This retrospective comparative cohort study was conducted at a high-volume tertiary referral center specializing in gastric cancer surgery. Consecutive patients who underwent curative-intent gastrectomy between January 2014 and December 2022 were retrospectively reviewed. Patient selection is summarized in Figure 1.

The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Approval No. 2025/8676).

Patient Selection

A total of 292 consecutive patients who underwent subtotal or total gastrectomy for histologically confirmed gastric adenocarcinoma were initially screened. Patients with cardia tumors (n=43), those with linitis plastica (n=15), patients presenting with distant metastatic disease at diagnosis (n=8), those undergoing palliative procedures (n=12), those with microscopically or macroscopically positive resection margins (R1/R2) (n=9), and those with a history of gastric surgery (n=16) were excluded.

After application of the predefined exclusion criteria, 189 patients were included in the final analysis. Patients were categorized according to the extent of lymph node dissection performed based on the Japanese Gastric Cancer Association (JGCA) classification:

- D1 lymphadenectomy group (n=57)
- D2 lymphadenectomy group (n=132)

The study flowchart is presented in Fig. 1.

Surgical Procedure and Definition of Lymphadenectomy

The extent of lymphadenectomy was determined according to tumor characteristics, patient-related factors, and intraoperative assessment. Although D2 lymphadenectomy represents the recommended standard procedure for curative gastric cancer surgery, D1 dissection was selectively performed in patients considered to be at higher op-

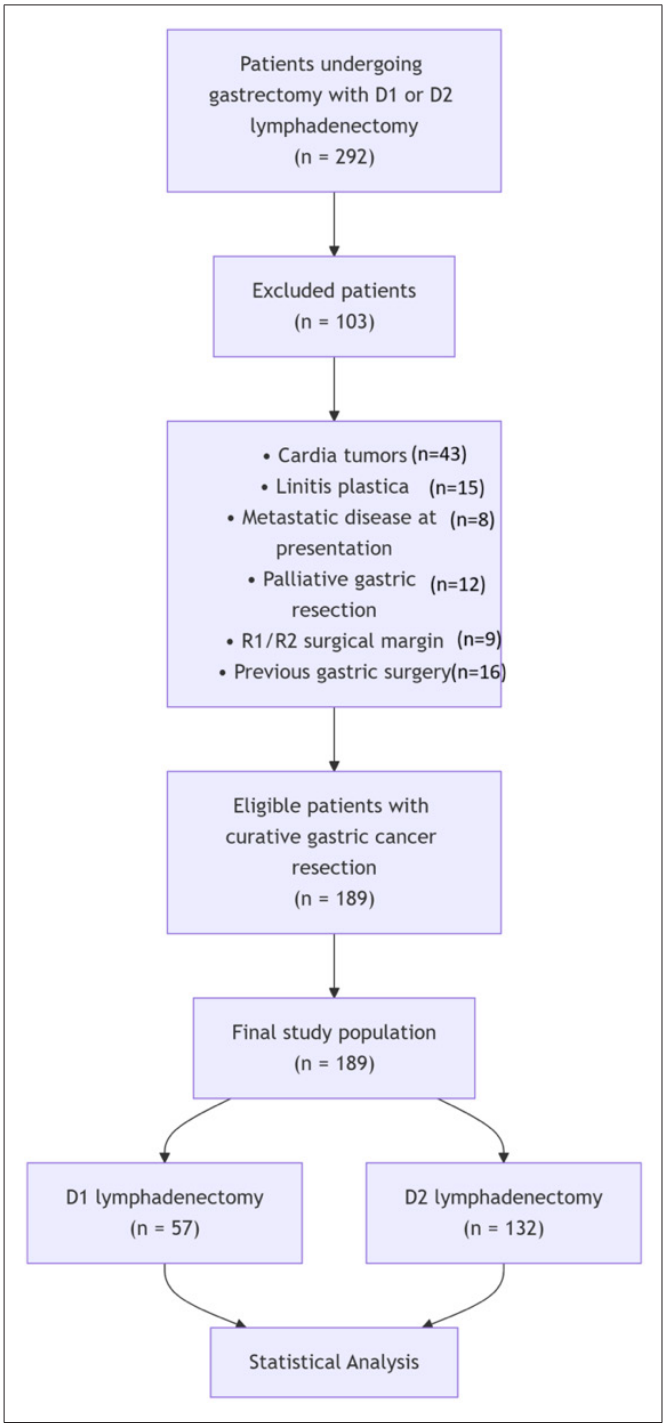

Figure 1. Flow diagram of patient selection. A total of 292 patients underwent gastrectomy with D1 or D2 lymphadenectomy during the study period. After excluding patients with cardia tumors, linitis plastica, metastatic disease at presentation, palliative gastric resection, R1/R2 resection margins, or previous gastric surgery, 189 patients were eligible for analysis, including 57 patients in the D1 lymphadenectomy group and 132 patients in the D2 lymphadenectomy group.

erative risk because of advanced age, substantial comorbidity burden, or unfavorable intraoperative findings.

All procedures were performed by experienced upper gastrointestinal surgeons in accordance with standardized institutional protocols and JGCA recommendations. The extent of lymphadenectomy was classified according to the Japanese Gastric Cancer Treatment Guidelines 2025 (7th edition), based on the operative notes.[4] D1+ lymphadenectomy was not used as a separate category in this cohort; all procedures were classified as either D1 or D2 as defined above.

D1 Lymphadenectomy

For distal gastrectomy, D1 lymphadenectomy included stations 1, 3, 4sb, 4d, 5, 6, and 7.

For total gastrectomy, lymph node stations 1–7 were removed.

Standard D2 Lymphadenectomy

- For distal gastrectomy, in addition to all D1 stations, standard D2 lymphadenectomy included dissection of stations 8a, 9, 11p, and 12a.
- For total gastrectomy, in addition to all D1 stations, standard D2 lymphadenectomy included dissection of stations 8a, 9, 11p, 11d, and 12a.

Extended lymphadenectomy (D2+) involving para-aortic nodal dissection or stations 8p and 11d was not performed.

Histopathological Assessment

All resected specimens were evaluated by dedicated gastrointestinal pathologists in accordance with the AJCC 8th Edition.[7]

The following variables were recorded:

- Tumor location
- Histological subtype
- Pathological T stage
- Pathological N stage
- AJCC 8th edition TNM stage
- Lymphovascular invasion (LVI)
- Perineural invasion (PNI)
- Serosal involvement (CERB positivity)

The total numbers of harvested and metastatic lymph nodes were documented for each patient.

Follow-up

Patients were followed according to institutional surveillance protocols. Clinical evaluations were performed every 3 months during the first 2 postoperative years, every 6 months between years 3 and 5, and annually thereafter.

Patients with locally advanced disease (T3–T4 and/or node-positive tumors) underwent thoracoabdominal computed tomography at 6–12-month intervals for up to 5 years. Patients undergoing subtotal gastrectomy received periodic endoscopic surveillance of the gastric remnant every 1–2 years. Nutritional assessment and support were provided throughout the follow-up period, and vitamin B12 levels were routinely monitored after total gastrectomy. The median follow-up period was 19.4 months in the D1 dissection group and 38.6 months in the D2 dissection group.

Study Outcomes

The primary outcomes were overall survival (OS) and disease-free survival (DFS).

Overall survival was defined as the interval between surgery and death from any cause or the date of last follow-up.

Disease-free survival was defined as the interval from surgery to the first documented recurrence, distant metastasis, death, or the last disease-free follow-up.

Secondary outcomes included postoperative morbidity, 90-day mortality, length of hospital stay, recurrence rate, and lymph node yield. Postoperative morbidity was assessed within 30 days of surgery, and surgical mortality was defined as death occurring within 90 days of surgery.

Statistical Analysis

Statistical analyses were performed using Jamovi software (version 2.7.13.0; The Jamovi Project, Sydney, Australia) and R software (version 4.5.2 GUI 1.82, High Sierra build 8556; R Foundation for Statistical Computing, Vienna, Austria).

Normality was assessed using the Shapiro–Wilk test. Continuous variables were expressed as medians and interquartile ranges (IQRs) and compared using the Mann–Whitney U test. Categorical variables were reported as frequencies and percentages and compared using Pearson's chi-square test or Fisher's exact test, as appropriate.

Overall survival and disease-free survival were estimated using the Kaplan–Meier method and compared using the log-rank test. Median survival times and corresponding 95% confidence intervals (CIs) were calculated. Univariable Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% CIs for the association between the extent of lymphadenectomy and overall and disease-free survival.

All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

Results

A total of 189 patients were included in the study, comprising 57 patients in the D1 lymphadenectomy group and 132 patients in the D2 lymphadenectomy group. Baseline demographic, clinical, and perioperative characteristics were generally comparable between the groups (Table 1). The median age was 66 years in the D1 group and 64 years in the D2 group (p=0.754), while the proportion of female patients was 75.4% and 63.6%, respectively (p=0.156). The distribution of ASA scores did not differ significantly between the groups (p=0.440). Similarly, tumor location, operative approach, rate of additional organ resection, preoperative serum tumor markers, and receipt of neoadjuvant therapy were comparable between the two cohorts.

Pathological findings are summarized in Table 2. The D2 group demonstrated a significantly greater lymph node yield than the D1 group (median 31 [IQR 22.8–43.3] vs 27 [IQR 19–34], p=0.011). In contrast, the number of metastatic lymph nodes was similar between the groups (p=0.460). No significant differences were observed in pathological T stage (p=0.917), N stage (p=0.124), overall TNM stage (p=0.639), lymphovascular invasion (p=0.716), or perineural invasion (p=0.531).

Postoperative outcomes are presented in Table 2. Length of hospital stay was comparable between the groups (median 8 days in both cohorts, p=0.400), as were postoperative morbidity rates (p=0.429). Although median disease-free survival was numerically longer in the D2 group (40.5 months) than in the D1 group (10 months), the difference did not reach statistical significance (p=0.052). Recurrence rates and 90-day mortality were likewise similar between the groups (p=0.525 and p=0.533, respectively).

Overall Survival

Long-term survival outcomes favored D2 lymphadenectomy. Median overall survival was 59.0 months (95% CI, 40.0–

Table 1. Baseline demographic, clinical, pathological, and perioperative characteristics of patients according to D1 and D2 lymphadenectomy groups

Variable	D1 lymphadenectomy (n=57)	D2 lymphadenectomy (n=132)	p
Gender, Female	43 (75.4%)	84 (63.6%)	0.156
Age (years), median (IQR)	66 (54–75)	64 (56.5–72)	0.754
ASA score			0.440
ASA 1	5 (8.8%)	13 (9.8%)	
ASA 2	32 (56.1%)	86 (65.2%)	
ASA 3	20 (35.1%)	32 (24.2%)	
ASA 4	0 (0.0%)	1 (0.8%)	
Tumor location			0.621
Corpus	10 (17.5%)	29 (22.0%)	
Antrum	47 (82.5%)	103 (78.0%)	
Operative technique			0.750
Open	39 (68.4%)	95 (72.0%)	
Laparoscopic	18 (31.6%)	37 (28.0%)	
Additional resection	6 (10.5%)	10 (7.6%)	0.701
CEA	2.46 (1.37–3.94)	1.80 (1.00–3.60)	0.284
CA19-9	9.50 (3.79–46.2)	8.50 (3.70–35.4)	0.405
Neoadjuvant therapy	37 (64.9%)	77 (58.3%)	0.492

Values are presented as number (percentage) or median (interquartile range), as appropriate. Categorical variables were compared using the Chi-square or Fisher's exact test, and continuous variables were compared using the Mann–Whitney U test. Statistical significance was set at $p<0.05$. ASA: American Society of Anesthesiologists score; CEA: Carcinoembryonic antigen; CA19-9: Carbohydrate antigen 19-9.

96.0) in the D2 group compared with 20.0 months (95% CI, 14.0–38.0) in the D1 group (Table 3). Correspondingly, 1-, 3-, and 5-year overall survival rates were consistently higher following D2 lymphadenectomy (83.3%, 59.5%, and 49.3%, respectively) than following D1 lymphadenectomy (64.6%, 35.6%, and 31.9%, respectively) (Fig. 2).

In univariable Cox regression analysis, D2 lymphadenectomy was associated with a significantly lower risk of all-cause mortality compared with D1 lymphadenectomy (HR, 0.59; 95% CI, 0.40–0.87), corresponding to a 41% lower hazard of death.

Disease-Free Survival

Disease-free survival analysis also favored D2 lymphadenectomy (Table 4). Median DFS was 28.0 months (95% CI, 12.0–not reached) in the D1 group, whereas median DFS was not reached in the D2 group during follow-up (95% CI, 46.0–not reached). Estimated DFS rates at 1, 3, and 5 years were higher in the D2 group than in the D1 group (79.6% vs 59.9%, 60.4% vs 42.8%, and 55.6% vs 40.3%, respectively) (Fig. 3).

Univariable Cox regression demonstrated a favorable effect of D2 lymphadenectomy on DFS, with a 38% relative reduction in the risk of recurrence or death (HR, 0.62; 95% CI, 0.39–1.00), although this association narrowly missed conventional statistical significance (p=0.050).

Discussion

The optimal extent of lymphadenectomy (D1 versus D2) in gastric cancer remains a longstanding and unresolved issue in surgical oncology. Early Western randomized trials reported increased postoperative morbidity and mortality associated with D2 dissection, largely attributed to the routine inclusion of splenectomy and distal pancreatectomy.[3,8] However, long-term follow-up data have demonstrated that spleen- and pancreas-preserving modified D2 lymphadenectomy may confer a survival advantage without a corresponding increase in perioperative risk.[9]

In the present study, no significant difference in postoperative morbidity or 90-day mortality was observed between the D1 and D2 groups, supporting the safety profile of

Table 2. Clinicopathological characteristics, surgical metrics, and survival outcomes stratified by D1 vs. D2 lymphadenectomy groups

Variable	D1 lymphadenectomy	D2 lymphadenectomy	p
Total LAP, median (IQR)	27 (19–34)	31 (22.8–43.3)	**0.011**
Pathological LAP, median (IQR)	8 (0–16)	5 (1–12.3)	0.460
T stage distribution			0.917
T1	7 (12.3%)	21 (15.9%)	
T2	4 (7.0%)	8 (6.1%)	
T3	22 (38.6%)	47 (35.6%)	
T4	24 (42.1%)	56 (42.4%)	
N stage distribution			0.124
N0	15 (26.3%)	23 (17.4%)	
N1	5 (8.8%)	28 (21.2%)	
N2	6 (10.5%)	18 (13.6%)	
N3	31 (54.4%)	63 (47.7%)	
TNM stage distribution			0.639
Stage I	8 (14.0%)	19 (14.4%)	
Stage II	12 (21.1%)	36 (27.3%)	
Stage III	37 (64.9%)	77 (58.3%)	
LVI (+)	49 (86.0%)	109 (82.6%)	0.716
PNI (+)	38 (66.7%)	80 (60.6%)	0.531
Hospital stay (days), median (IQR)	8 (6–14)	8 (6–10)	0.400
Recurrence	26 (45.6%)	52 (39.4%)	0.525
DFS (months), median (IQR)	10 (8–84)	40.5 (10–78.3)	0.052
Morbidity	7 (12.3%)	24 (18.2%)	0.429
3-month mortality	3 (5.3%)	3 (2.3%)	0.533

Data are presented as n (%) for categorical variables and median (interquartile range, IQR) for continuous variables. Bold face indicates statistically significant p-values (p<0.05). DFS: Disease-free survival; IQR: Interquartile range; LAP: Lymph nodes/lymphadenopathy; LVI: Lymphovascular invasion; PNI: Perineural invasion; TNM: Tumor-node-metastasis classification.

Table 3. Overall survival outcomes and univariable Cox regression analysis stratified by D1 vs. D2 lymphadenectomy groups

Stratification / Variable	Median OS, Months (95% CI)	1-Year OS Rate, % (95% CI)	3-Year OS Rate, % (95% CI)	5-Year OS Rate, % (95% CI)	Univariable HR (95% CI)	p
D1 lymphadenectomy	20.0 (14.0–38.0)	64.6 (53.2–78.3)	35.6 (25.0–50.8)	31.9 (21.7–46.9)	1.00 (Reference)	—
D2 lymphadenectomy	59.0 (40.0–96.0)	83.3 (77.1–89.9)	59.5 (51.6–68.5)	49.3 (41.3–58.9)	0.59 (0.40–0.87)	**0.007**

Continuous survival times and rates are presented with their respective 95% confidence intervals (CI). Boldface indicates statistical significance (p<0.05). CI: Confidence interval; HR: Hazard ratio; OS: Overall survival. Model Metrics: Total n=189 (Events: 115); Concordance index = 0.567 (SE=0.023); Likelihood ratio test p=0.009.

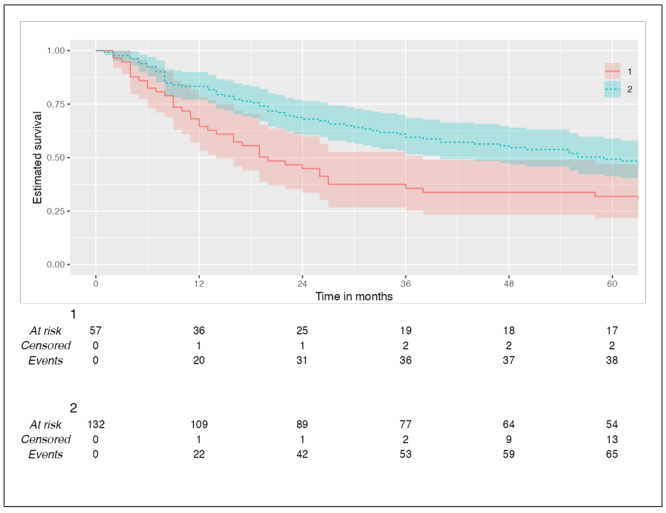

Figure 2. Kaplan-Meier overall survival curves for patients undergoing D1 (dashed line) versus D2 (solid line) lymphadenectomy.

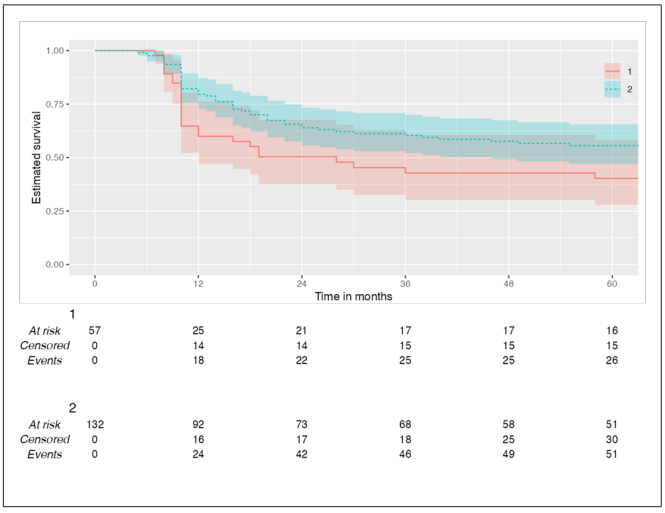

Figure 3. Kaplan-Meier disease-free survival curves for patients undergoing D1 (dashed line) versus D2 (solid line) lymphadenectomy.

modern modified D2 lymphadenectomy when performed in experienced centers. These findings are consistent with current international guidelines, which recommend D2 lymphadenectomy as the standard surgical approach for curative gastric cancer resection, particularly in high-volume institutions with appropriate surgical expertise.[4,6,10]

Long-term survival outcomes in our cohort demonstrated a significant benefit associated with D2 lymphadenectomy. Median overall survival was 59 months in the D2 group compared with 20 months in the D1 group (HR, 0.59; p=0.007). These results are consistent with the long-term follow-up of the Dutch Gastric Cancer Trial, which reported improved survival with D2 dissection after excluding routine splenectomy and pancreatectomy, particularly with extended follow-up.[9] Similarly, data from the Italian Gastric Cancer Study Group have suggested a survival benefit of D2 dissection in patients with node-positive disease and more advanced tumor stages.[11]

In addition to the survival benefit, the D2 group achieved a significantly higher lymph node yield than the D1 group (median 31 vs 27; p=0.011). Adequate lymph node retrieval is critical for accurate staging and prognostic stratification in gastric cancer,[12] and current guidelines recommend examination of at least 15 lymph nodes.[7] In this context, the higher nodal harvest observed in the D2 group suggests a more comprehensive oncological resection and may partially explain the observed survival advantage. Furthermore, several studies have demonstrated that increased lymph node yield is independently associated with improved staging accuracy and survival outcomes.[13–15]

Despite these findings, disease-free survival did not reach statistical significance between the groups, although a favorable trend was observed in the D2 cohort (p=0.052). This borderline result may be related to the limited sample size and the relatively short follow-up duration in a subset of patients and should therefore be interpreted cautiously.

Table 4. Disease-free survival outcomes and univariable Cox regression analysis stratified by D1 vs. D2 lymphadenectomy groups.

Stratification / Variable	Median DFS, Months (95% CI)	1-Year DFS Rate, % (95% CI)	3-Year DFS Rate, % (95% CI)	5-Year DFS Rate, % (95% CI)	Univariable HR (95% CI)	p
D1 lymphadenectomy	28.0 (12.0–NR)	59.9 (47.1–76.2)	42.8 (30.2–60.6)	40.3 (27.9–58.2)	1.00 (Reference)	—
D2 lymphadenectomy	NR (46.0–NR)	79.6 (72.7–87.3)	60.4 (52.1–70.0)	55.6 (47.1–65.5)	0.62 (0.39–1.00)	0.050

Continuous survival times and rates are presented with their respective 95% confidence intervals (CI). CI: Confidence interval; DFS: Disease-free survival; HR: Hazard ratio; NR: Not reached (due to survival probability remaining above 50%). Model Metrics: Total n=189 (Events: 78); Concordance index =0.556 (SE=0.028); Likelihood ratio test p=0.057.

The present study has several limitations. Its retrospective design introduces inherent risks of selection bias, as the choice of lymphadenectomy extent was influenced by patient comorbidities, tumor characteristics, and surgeon judgment rather than randomization. In addition, the single-center design and relatively small sample size may limit the generalizability of the findings. Nevertheless, the use of standardized surgical techniques and consistent pathological assessment strengthens the internal validity of the study.

Conclusion

D2 lymphadenectomy was associated with improved long-term survival compared with D1 dissection without an increase in perioperative morbidity or mortality in a contemporary surgical setting. These findings support the continued role of D2 lymphadenectomy as the standard surgical approach in curative gastric cancer surgery when performed in appropriately selected patients at experienced centers.

Disclosures

Ethics Committee Approval: The study was approved by the İnönü University Scientific Research Publication Ethics Board (approval number: 2025/8676, date: 18.11.2025).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare that they have no conflict of interest.

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