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Original Article

Survival outcomes after D1 and D2 lymphadenectomy with R0 resection in stage II–III gastric cancer: Longitudinal follow-up in a single center

Adam Uslu, Baha Zengel, Enver İlhan, Ahmet Aykas, Cenk Şimşek, Orhan Üreyen, Ali Duran, Gökalp Okut

ABSTRACT

Objective: D2 lymphadenectomy (D2-LND) with curative resection (R0) is the cornerstone of gastric cancer treatment. In this study, we compared survival outcomes of D2-LDN with D1-LDN in patients who had undergone curative resection for Stages II and III primary gastric adenocarcinoma.

Material and Methods: Between April 1996 and March 2014, 153 consecutive patients with adenocarcinoma of the stomach underwent total gastrectomy with D1-LND or D2-LND. Among those, 118 patients (38 D1 vs. 80 D2) with a complete history and having been followed for at least 1 year after surgery were enrolled.Both groups were compared in terms of demographic and clinico-pathologic characteristics.

Results: The mean follow-up was 42.6±52.5 months (mo.). The demographic characteristics of the groups were similar. The Tumor, Node and Metastases (TNM) stage distribution was 25% for Stage II and 75% for Stage III for both groups. Eighteen patients (47.4%) in the D1 and 47 patients (58.8%) in the D2 group were free from locoregional recurrence. The median disease-free survival was 22.0±4.1 mo. for the D1 and 28.0±4.3 mo. for the D2 group (p=0.36). Eight patients (21%) in the D1 and 39 patients (49%) in the D2 group were alive at the last follow-up. The median overall survival (OS) was 22.0±3.7 mo. for the D1 and 31.0±5.4 mo. for the D2 group (p=0.13). The 5-yeardisease-free survival and OS by the Kaplan–Meier estimates were 41% vs. 51% and 30% vs.42% in the D1 and D2 groups, respectively. The median 5-year OS for patients with Stages IIIB and IIIC tumors was 14.0±2.2 mo.for the D1 and 20.0±5.0 mo. for the D2 group, respectively (p: 0.048).

Conclusion: When compared to D1-LND, D2-LND with R0 resection have yielded a trend toward a better outcome in patients with primary gastric adenocarcinoma.

Keywords: R0 resection, D1 lymph node dissection, D2 lymph node dissection, total gastrectomy

ORCID IDs of the authors:
A.U. 0000-0003-2697-472X;
B.Z. 0000-0002-1812-6846;
E.İ. 0000-0003-3212-9709;
A.A. 0000-0003-0908-7766;
C.Ş. 0000-0002-9296-0097;
O.Ü. 0000-0002-7820-9088;
A.D. 0000-0002-2567-5317;
G.O. 0000-0002-3641-5625.

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Department of General Surgery, University of Health Sciences, Izmir Bozyaka Research and Training Hospital, İzmir, Turkey

Corresponding Author
Baha Zengel
e-mail: bahazengel@gmail.com

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INTRODUCTION

In the current era, both in Eastern and in Western populations, curative resection (R0) with D2 lymphadenectomy is accepted as the standard treatment for stomach cancer (1). The incorporation of D2 lymph node dissection (D2-LND) in routine practice has been materialized since 1960 in Japan and Korea, while it has recently appeared in Western guidelines (2, 3). Western surgeons were so far reluctant to establish D2 as a routine practice because of the reported-at least 10%-surgical mortality in two prospective randomized trials, while it was less than 3% in Japan for more than three decades (4, 5). However, this excess mortality was basically due to additional extended surgery, essentially the splenectomy with or without pancreatectomy. Besides, the best survival was obtained in patients who underwent spleen-sparing D2 resections (6, 7). A recent meta-analysis of eight prospective randomized trials including more than 2000 patients revealed a trend toward lower gastric-cancer-related mortality in patients who underwent D2 resection without splenopancreatectomy (8).

In this study, we evaluated the efficacy of limited (D1-LND) versus extended lymphadenectomy (D2-LND) for a consecutive group of patients with gastric adenocarcinoma, having been treated in a subspecialized oncologic surgery unit during the last two decades.

MATERIAL AND METHODS

Among 256 consecutive patients with adenocarcinoma of the stomach having been treated in University of Health Sciences, Izmir Bozyaka Research and Training Hospital, Department of General Surgery between April 1996 and March 2014, 103 patients were excluded because of the implemented palliative measures including subtotal gastrectomies, insertion of enteral feeding catheters and all bypass procedures, resections lesser than D1, and pathological assessment indicating Stage I tumors or R1 resections.

The inclusion criteria of the study were primary gastric adenocarcinomas with radiologic evidence of locoregional disease, total gastrectomy with D1 or D2 lymphadenectomy with ultimate pathology re-

Table 1. Adjuvant chemotherapy regimens and radiotherapy

Adjuvant Chemotherapy	D1-LND* group (n=38)	D2-LND** group (n=80)	p
Not received	2 (%5.3)	16 (%20.0)	0.053
MAYO protocol	9 (%23.7)	29 (%36.2)	
CISPLATIN+UFT protocol	17 (%44.7)	18 (%22.5)	
DCF*** regimen	10 (%26.3)	17 (%21.3)	
Adjuvant radiotherapy (+)	26 (68.4%)	52 (65%)	0.71

*D1-LND: D1 lymphadenectomy
**D2-LND: D2 lymphadenectomy
***DCF: docetaxel, cisplatin, 5 fluorouracil
pts: patients

Table 2. The demographic and clinico-pathological characteristics

Age (years)	58.6±11.9	62.5±12.3	0.11
Gender:			
Male	28 (73.7%)	54 (67.5%)	0.495
Female	10 (26.3%)	26 (32.5)	
Co-morbid disease	15 (39.5%)	30 (37.5%)	0.84
Additional organ surgery	2(5.3%)	4(5%)	0.63
TNM Stage			
IIA and IIB	9(23.7%)	20(25%)	0.62
IIIA	10(26.3%)	15(18.8%)	
IIIB	6(15.8%)	20(25%)	
IIIC	13(34.2%)	25(31.3%)	
Signet-ring cell, mucinous and poorly differentiated histology	15(39.5%)	30(37.5%)	0.84
Lymphovascular and neural invasion	20 (52.6%)	42 (52,5%)	0.99
Location of tumor:			
1/3 proximal stomach	7(18.4%)	21(26,3%)	0.009
1/3 mid-stomach	24(63.2%)	27(33,8%)	
1/3 distal stomach	7(18.4)	32(40%)	
Number of retrieved lymph nodes	27.5±14.3	35.7±18.8	0.02

*D1-LND: D1 lymphadenectomy
**D2-LND: D2 lymphadenectomy

Table 3. The distribution of morbidity and mortality in the D1 lymphadenectomy and D2 lymphadenectomy groups

	D1-LND* group (n=38)	D2-LND** group (n=80)
Bacterial pneumonia	9 (23.6%)	5 (6.3%)
Minor leak from the esophagojejunal anastomosis	2 (5.3%)	5 (6.3%)
Duodenal stump leakage	2 (5.3%)	2 (2.4%)
Death	-	1 (1.2%)

*D1-LND: D1 lymphadenectomy
**D2-LND: D2 lymphadenectomy

porting R0 resection,at least 15 nodes removed in the D2 cohort Stages II and III tumors based on the 7th edition of the UICC/AJCC criteria (9), and no neoadjuvant chemotherapy ± radiotherapy.

Thus, 153 patients were eligible for the final analysis. Of those, 118 patients (38 D1 vs. 80 D2) who have survived at least 1 year after surgery were enrolled in the study. Thirty-five patients were excluded because they were lost to follow-up, incomplete clinical history, incompliance during adjuvant therapy, or short-term follow-up. Surgical quality was assessed solely by the pathological confirmation of R0 resection in standard D1 and D2 lymphadenectomy. This prevented the contamination of results by disparities of surgical skills and techniques. Clinical database and follow-up information were complete for the whole study group. In-hospital mortality is defined as the number of deaths from any cause within 30 days of surgical intervention.

Written informed consent was obtained from patients who participated in this study. The research was conducted according to the principles of the World Medical Association, the Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects," (amended in October 2013).

Surgical Procedures and Quality Assessment

The methodology of D1 and D2 resection was essentially based on the guidelines of the Japanese Research Society for the Study of Gastric Cancer (10). The details were explained in a previous study by our group, elsewhere. The sine qua non of quality was the ultimate pathology report indicating R0 resection with the removal of at least 15 lymph nodes in D2 gastrectomy (11). All patients underwent total gastrectomy through the Roux-en-Y reconstruction. Esophagojejunostomyanostomosis was performed by a circular stapler or by hand in the D1 group, but unexceptionally by hand-sewn single-layer 3:0 atraumatic single sutures in the D2 group.

Adjuvant Chemotherapy and Radiotherapy

Adjuvant chemotherapy was conducted when possible in all patients having the SWOG performance status score between 0 and 2. While almost all patients with Stage IIA (T3N0M0, T2N1M0) have received the Mayo regimen, patients with pathological T1N2M0 and Stage IIB or greater receiveda cisplatin-based regimen ora docetaxel-containing regimen after 2011, when possible.

The chemotherapy protocols with the distribution of chemotherapy and radiotherapy among the D1 and D2 groups are shown in Table 1. The Mayo regimen consisted of 5FU plus a low-dose leucovorin (5FU 425mg/m^2 plus leucovorin 20mg/m^2) intravenous push daily for 5 days with courses repeated at 4-week intervals. Cisplatin (CDDP) plus an UFT regimen consisted of intravenous CDDP 30 mg/m^2 administered on Days 1–3 and a single oral UFT dose of 400 mg/m^2/day administered on Days 1 through 28, and they were repeated every 28 days. Docetaxel has been administered to patients since 2011, which is when itwas approved for use in adjuvant treatment of gastric cancer. DCF consisted of docetaxel (75mg/m^2 day 1), CDDP (75mg/m^2 day 1), and 5FU (750mg/m^2 by 24-h continuous infusion for 5 days) administered every 3 weeks in 6 cycles.

All patients who had pT3, T4, and pN+ were referred for radiotherapy. However, 2 patients in the D1 and 8 patients in the D2 group did not receive or complete radiotherapy due to a low clinical performance, advance age, or treatment adverse effects.

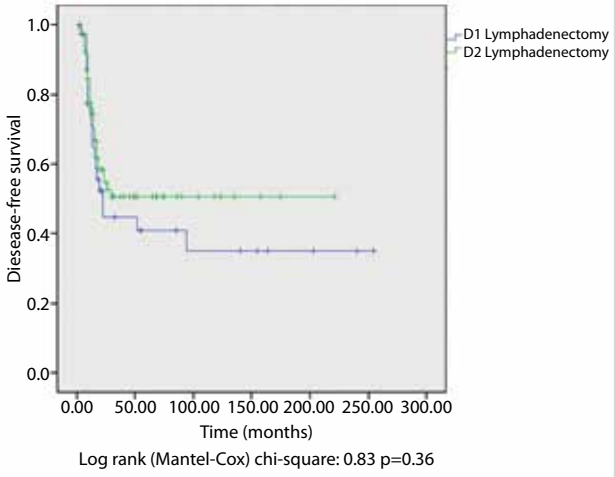


Figure 1. The Kaplan–Meier disease-free survival curve

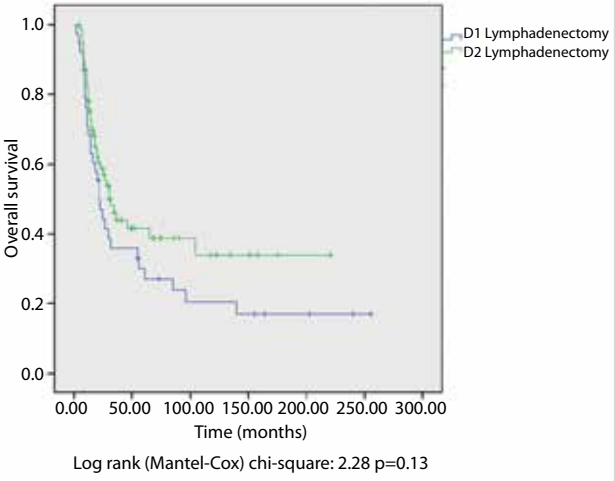


Figure 2. The Kaplan–Meier overall survival curve

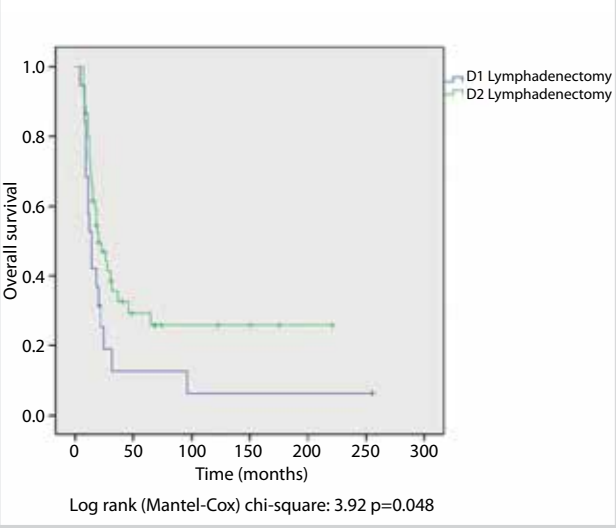


Figure 3. The Kaplan–Meier estimate of the overall survival for the pathologic stages IIIB and C patients in the D1 lymphadenectomy vs. D2 lymphadenectomy groups

Statistical Analysis

Overall survival (OS) and disease-free survival (DFS) were defined as the time from D1 or D2 resection to death and to the occurrence of the first locoregional recurrence or distant organ metastasis, respectively.

We calculated the OS and DFS status using the Kaplan–Meier method. Log-rank tests were performed to compare OS and DFS. Independent two-sample t-test was used to detect the differences among demographic data and histopathological variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The demographic and clinico-pathological characteristics of the patients are shown in Table 2. There was no difference between demography of the groups with respect to age, gender, the UICC TNM stage, co-morbid disease and additional organ surgery, the rate of poorly differentiated tumor histology and protocol, and total sessions of adjuvant chemotherapy and radiotherapy. The anatomic location of the primary tumor was predominantly the middle one-third of the stomach in the D1 group (63%) and distal one-third in the D2 group (40%) (p=0.009). As expected, the number of retrieved lymph nodes was significantly higher in the D2 group (p=0.02).The TNM stage distribution was 25% Stage II and 75% Stage III for both groups. Extended surgery was applied in two patients from the group D1. One had distal one-third esophagectomy, and the other had splenectomy with segmental colon resection. Four patients from the D2 group underwent splenectomy, distal pancreatectomy, segmental resection of the transverse colon, and the liver segment III resection, respectively. In-hospital mortality was 0.8% (1 patient).

Postoperative Complications

The most frequent morbid event was post-operative bacterial pneumonia, which occurred in 9 (23.6%) and 5 (6.3%) cases in the D1- and D2-LND groups, respectively. All patients had uneventful course by proper antibiotics, pulmonary toilet, oxygen supplementation, and respiratory exercises.

A minor anastomotic leak at esophagojejunal anostomosis occurred in 2 (5.3%) and 5 (6.3%) patients in the D1 and D2-LND groups. Two patients in the D2-LND group required jejunal stent replacement and 3 weeks of enteral nutrition. Of those, one had subphrenic abscess and was treated successfully by percutaneous catheter drainage. The remaining patients completely recovered by cessation of per-oral feeding, accompanied by 2 weeks of parenteral nutrition. Duodenal stump leakage was observed in 2 cases for both groups. All stumps were closed by linear-staplers. These 2 patients recovered uneventfully with conservative measures.

One patient died suddenly at home 32 days after the operation. He had congestive cardiomyopathy with ejection fraction of 35%. Although we think the death was of cardiac origin, the exact cause of death determined by an autopsy is not available. The distribution of morbidity and mortality in the D1 and D2 groups are shown in Table 3.

Survival Analysis

The mean follow-up was 42.6±52.5 months (mo.). Eighteen patients (47.4%) in the D1 and 47 patients (58.8%) in the D2 group were free from locoregional recurrence or distant organ metastasis. The median DFS was 22.0±4.1 mo. for the D1 and 28.0±4.3 mo. for the D2 group (p=0.36) (Figure 1). Eight patients (21%) in the D1 and 39 patients (49%) in the D2 group were alive at the last follow-up. The median OS was 22.0±3.7 mo. for the D1 and 31.0±5.4 mo. for the D2 group (p=0.13) (Figure 2).

Although a statistical survival advantage has not been obtained for all patients with the D2 lymph node dissection, an overall survival difference in favor of a D2 dissection has emerged for the pathologic stages IIIB and IIIC patients in the subgroup analysis. Nineteen patients in the group D1 and forty-five patients in the group D2 had pathologically assessed stage IIIB and IIIC tumors. The median 5-year OS was 14.0±2.2 mo.for the D1 and 20.0±5.0 mo. for D2 groups with a corresponding p-value of 0.048 (Figure 3).

DISCUSSION

In this study, compared to D1-LND, D2-LND with R0 resection have yielded to a trend toward better survival outcomes in patients with primary gastric adenocarcinoma. The five-year DFS and OS by the Kaplan–Meier estimates were 41% vs. 51% and 30% vs. 42% in the D1 and D2 groups, respectively. There was an absolute 10% difference in favor of the D2 group with respect to the 5-year DFS and OS, but this has not reached statistical significance. These results are derived from a prospectively collected database of a single oncological surgery unit in which surgery, adjuvant chemotherapy, and routine follow-up have been carried through with a multidisciplinary approach for years. The number of the lymph nodes retrieved in this study meets the precondition of the new classification system that underlines the strong association between the survival outcomeand the lymph node count (12) and reveals the quality of surgery.

As demonstrated in the latest randomized controlled trials, the rationale underlying D2 dissection is the ability of the procedure to cure almost 20% of patients with N2-disease (13). In addition, post-hoc analysis of randomized trials in a recent meta-analysis of extended lymphadenectomy for gastric cancer suggested a possible survival benefit in Stage T3+ tumors, non-randomized comparisons revealed the benefit in Stage II and IIIA, and observational studies reported better survival outcomes of D2 surgery (14). In a recent retrospective study conducted on 533 gastric cancer patients, the median survival by Stages IIIB and IIIC were 28.0 and 14.8 mo., and D2-LND appeared as the major prognosticator of survival (15). These findings are consistent with our results in which patients with gastric cancer and the pathological Stage III and beyond, that had at least a loco-regional or a distant metastases, had benefited much from D2-LND with regard to OS, with a median OS of 20.0±5.0 months.

In contrast to equivalent survival outcomes of common solid tumors such as colorectal and breast cancer in the Eastern and Western societies, the West has worse out comes of gastric cancer surgery compared with Japanese trials (5, 13, 14, 16). The mortality rate of D2 dissection is still improving, and it is almost 0.8% in Japan, with a cumulative 5-year survival of 70%, thus bringing D2 dissection as standard routine surgery for cT1N+ and potentially curable cT2-T4 disease (17-19). Two meta-analyses of randomized controlled trials comprised of nearly 1900 and over 2000 gastric cancer patients favored D1 over D2, essentially in terms of significantly reduced postoperative complications and a 30-day mortality rate, with no significant difference in the 5-year survival between the groups (20, 21). These reports and the observation of 10%~13% perioperative mortality with a 5-year survival of 33%~35%, which did not meet the expectations in two major European trials (22, 23), have lead Western proponents to recommend at least D1 dissection, but not to favor a routine application of D2 universally at present (24, 25).

The difference in the survival outcome has been partially attributed to an earlier diagnosis and less aggressive biology of tumors in the East, but this thesis was subsequently refuted via reports indicating a better outcome in patients with comparable pathological stages in the East than in the West. Two studies from the Memorial Sloan-Kettering Cancer Center demonstrated survival differences for T1–T3 tumors in favor of Japanese patients and improved survival after matching by T stage and location in Korean patients compared to the US patients (26, 27). However, as observed in our recent and previous study, it is promising that the inconsistency of the surgical approach between Japan and the Western groups, particularly in terms of the extent of nodal resection, is being eliminated, such that better outcomes in the D2 groups with an operative mortality rate of less than 4% and an increased rate of cases having at least 15 lymph nodes removed is being reported both in randomized control trials and observational studies by surgical teams who had acquired experience through the years spent in Western countries (11, 28-36). The results of the Dutch and UK trials have been criticized for the unacceptably high mortality and poor survival rates, as well as the non-compliance of surgeons (24). On the contrary, Italian Gastric Cancer Study Group reported 2.2% operative mortality in D2-LND and have proven that they can doas well as the Eastern surgeons. Moreover, they have demonstrated the survival advantage resulting from D2 surgery, particularly for patients with the pT2-4 status and positive lymph nodes (32).

CONCLUSION

Therefore, in view of our results and current literature mentioned above, we may conclude the following:

The operative mortality after D2 gastrectomy can be reduced via surgical subspecialization, and D2-LND is already being performed safely by many Western surgical teams. Although a clear-cut evidence about the cumulative survival advantage of D2-LND is still lacking, patients who are perceived to be in an advanced stage, but without distant metastasis, seem to benefit from D2 surgery.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects" (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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