Outcomes of Extended Lymphadenectomy for Gastroesophageal Carcinoma: A Large Western Series

Selena S Li, BA, Christina L Costantino, MD, David W Rattner, MD, FACS, John T Mullen, MD, FACS

BACKGROUND: The extent of lymph node dissection for patients with gastroesophageal carcinoma remains controversial. We sought to examine the perioperative risk and survival outcomes in a large Western series of patients undergoing limited (D0/D1) vs extended (D1+/D2) lymphadenectomy (LAD) for gastroesophageal carcinoma.

STUDY DESIGN: Clinicopathologic and treatment factors for 520 patients with gastroesophageal carcinoma undergoing potentially curative resection at a single institution from 1995 to 2017 were analyzed for their impact on perioperative morbidity and mortality, lymph node yield, and overall survival.

RESULTS: A total of 362 (70%) patients underwent D0/D1 LAD and 158 (30%) underwent D1+/D2 LAD. Median follow-up was 3.1 years. Patients undergoing D1+/D2 LAD were more likely to have distal tumors, to undergo distal/subtotal/total gastrectomy, and to undergo operation at a more contemporary time than patients undergoing D0/D1 LAD. The median number of lymph nodes examined and the percentage of patients with 16 or more lymph nodes examined was 16 and 53%, respectively, in the D0/D1 group vs 27 and 89%, respectively, in the D1+/D2 group. There were no differences in the rates of major complications (16.6% vs 14.6%) or operative mortality (2.8% vs 0.6%) between the D0/D1 and D1+/D2 groups, respectively. Patients undergoing D1+/D2 LAD had significantly improved overall survival (hazard ratio 0.74; $p = 0.035$) compared with those undergoing D0/D1 LAD on univariate analysis, but this survival benefit disappeared when controlling for the time period of operation.

CONCLUSIONS: Gastrectomy with extended (D1+/D2) LAD can be performed safely at a high-volume Western center, and it improves nodal yield significantly and ensures accurate pathologic staging. (J Am Coll Surg 2019;228:879–891. © 2019 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Gastric cancer is the third leading cause of cancer mortality in the world,[1] and operation remains the only potentially curative treatment. Gastric adenocarcinoma commonly metastasizes to the regional lymph nodes (LNs), and regional LN involvement is one of the most important prognostic factors for this cancer.[2] The National Comprehensive Cancer Network Clinical Practice Guidelines for the treatment of gastric cancer recommends the examination of at least 15 LNs for accurate staging,[3] although other authors have concluded that the staging accuracy improves with increasing numbers of LNs examined,[4] with one large international database study demonstrating that the maximal survival advantage is achieved by examining a minimum of 29 LNs.[5]

Significant differences exist around the world in extent of LN dissection performed at the time of potentially curative gastrectomy. The Japanese Gastric Cancer Association has carefully defined the anatomic nodal stations around the stomach and the vasculature of the celiac axis.[6] Briefly, a D1 lymphadenectomy (LAD) includes the LNs in the first tier adjacent to the stomach, and a

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From the Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA.

Correspondence address: John T Mullen, MD, FACS, Department of Surgery, Massachusetts General Hospital, Yawkey Center for Outpatient Care, 32 Fruit St, YAW-7-7926, Boston, MA 02114. email: JMULLEN@mgh.harvard.edu

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Abbreviations and Acronyms
GEC = gastroesophageal carcinoma
HR = hazard ratio
LAD = lymphadenectomy
LN = lymph node
OR = odds ratio

D2 LAD additionally includes the LNs in the second tier along the branches of the celiac axis. In the East, a D2 LAD is the recommended standard treatment for all gastric cancers staged T2 or higher.[7] However, in the West, surgeons have been reluctant to perform the more technically demanding D2 LAD, given the typically higher BMI of patients in the West, and the lack of evidence for a survival advantage for this procedure. In fact, 2 large randomized trials conducted in the 1990s in the UK and the Netherlands demonstrated that D2 LAD was accompanied by significantly higher postoperative morbidity and mortality, without a concomitant improvement in survival compared with D1 LAD.[8,9] The high morbidity and mortality rates reported in these studies was due in large part to the high percentage of distal pancreatectomies and splenectomies performed in the patients assigned to a D2 LAD, when in fact, the resection of these organs should not be routinely necessary in the performance of a proper D2 LAD. In recent years, with the publication of 15-year follow-up data on the Dutch trial showing a significant reduction in gastric cancer-specific mortality in those patients undergoing D2 LAD,[10] combined with the demonstration of improved survival outcomes with D2 LAD in several retrospective studies and meta-analyses,[11-14] there has been increased enthusiasm for the performance of extended (D1+/D2) lymphadenectomies at the time of gastrectomy in the West.

In the past decade or so, many Western surgeons have made a concerted effort to learn the technique of D2 LAD from their colleagues in Korea and Japan, and they have demonstrated that Western surgeons can perform a D2 LAD safely and with excellent nodal yields.[15-17] We published our early outcomes with D2 LAD in a total of 46 patients, for whom the median number of LNs examined was 27, and 93% had at least 16 LNs examined.[18] There were no differences in the 30-day major complication rates (17.4% vs 15.8%) or mortality rates (0% vs 2.5%) between the D2 and D1 LAD groups, respectively. In addition, we reported an improved 5-year overall survival rate in those patients undergoing D2 LAD (71.3%) compared with those undergoing D1 LAD (47.1%). In fact, for the past 10 years or so in our center, we have routinely performed a D1+ or D2 LAD at the time of potentially curative gastrectomy or esophagogastrectomy, consequently increasing our patient volume and follow-up significantly during this time. In this current analysis of a much larger cohort of patients, we sought to expand on our earlier work by assessing our short-term perioperative and long-term survival outcomes after extended LAD for gastroesophageal carcinoma (GEC).

METHODS

This study was approved by the IRB of Partners Healthcare (IRB 2008P000578). A comprehensive database of patients undergoing potentially curative resection for GEC at the Massachusetts General Hospital from 1995 to 2017 was examined. Patient information, including demographics, hospital courses, and outcomes, was extracted from electronic medical records and the Massachusetts General Hospital Cancer Registry. Survival data were obtained from the Social Security Death Index and validated by chart review.

Of the 634 patients included in the database between the 1995 and 2017 study period, 114 were excluded from this analysis based on the following reasons: patients undergoing palliative (n = 23) or prophylactic (n = 23) procedures, those with stage IV disease (n = 47), gastrointestinal stromal tumor resections (n = 12), local tumor excisions (n = 2), and missing data (n = 7). The final study cohort consisted of 520 patients who underwent resection with curative intent, including 395 patients with gastric adenocarcinoma and 125 patients with adenocarcinoma of the gastroesophageal junction (Fig. 1).

Patients were subcategorized into type of LAD: D0/D1 (n = 362) vs extended (D1+/D2) dissections (n = 158). The extent of LAD was defined according to guidelines from the Japanese Gastric Cancer Association, precisely defining nodal stations based on anatomic locations.[19] A D1 LAD is defined as including removal of the first tier of perigastric nodes (stations 1 to 6), as well as those nodes in station 7 along the left gastric artery. D2 LAD includes resection of the D1 perigastric nodes in addition to all of the LNs along the main branches of the celiac axis, including (when appropriate) stations 8, 9, 10, 11, and 12.[19] We define a "D1+" LAD to mean an extended LN dissection, which includes all but one of the LN stations resected as part of a standard D2 LAD (eg leaving the splenic hilar nodes in station 10 undissected during the course of a total gastrectomy for an advanced proximal gastric cancer). The extent of LN dissection was determined by careful review of the operative notes, in which

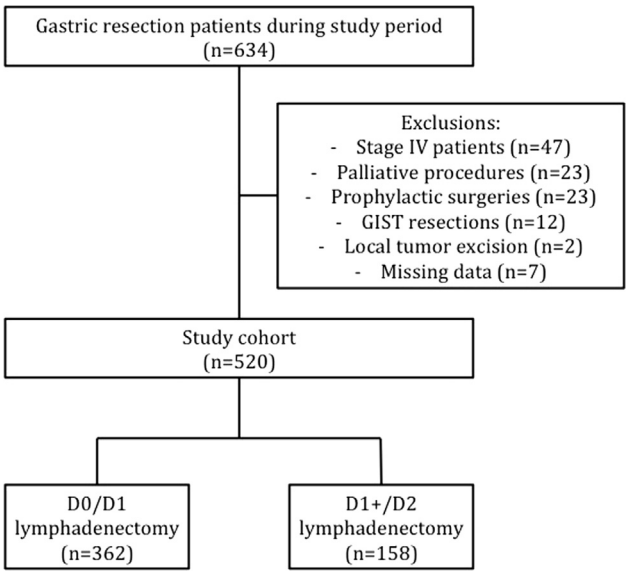

Figure 1. Single-institution retrospective study cohort including 362 patients undergoing D0/D1 lymphadenectomy and 158 patients undergoing D1+/D2 lymphadenectomy. GIST, gastrointestinal stromal tumor.

all D1+ and D2 dissections were clearly described as such and in which the remainder were assumed to be a more limited dissection, defined as D0/D1 LAD. Pathologic staging was determined using the 8th edition of the American Joint Committee on Cancer cancer staging manual.[20] Complications were classified according to Clavien-Dindo grading classification, with severe complications defined as grade 3 or 4.[21]

Statistical analysis was performed in R statistical computing language. Comparison of demographic, pathologic, and treatment-specific factors between D0/D1 and D1+/D2 groups was conducted using Pearson chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. Univariate and multivariate survival analyses were evaluated using the Cox proportional hazards method, and significant variables ($p < 0.05$) found on univariate analysis were included in the multivariate model. Overall survival plots were generated using Kaplan-Meier estimates.

RESULTS

Patient demographics and operative details

Between the study period from 1995 to 1997, 520 patients undergoing gastrectomy for GEC with curative intent were evaluated. D0/D1 LAD was performed in 362 (69.6%) patients, and extended LAD (D1+/D2) dissections were performed in 158 (31.4%) patients (Fig. 1). The median follow-up of the entire cohort was 3.1 years. Patient characteristics are summarized in Table 1, with significant differences in sex ($p = 0.011$) and racial distribution ($p < 0.001$), but not in age, comorbidities, or social history. The percentage of patients receiving a D1+ or D2 LAD at the time of (esophago)gastrectomy comprised only 9.4% of

Table 1. Clinical Characteristics of the Patients

Characteristic	Overall (n = 520)	D0/D1 (n = 362)	D1+/D2 (n = 158)	p Value
Age, y, median (IQR)	68 (58–77)	68 (59–77)	67 (56–78)	0.261
Male sex, n (%)	353 (67.6)	258 (71.3)	94 (59.5)	0.011
Race, n (%)				<0.001
White	447 (86.0)	328 (90.6)	119 (75.3)	
Asian	34 (6.5)	17 (4.7)	17 (10.8)	
Hispanic	20 (3.8)	7 (1.9)	13 (8.2)	
Black	12 (2.3)	5 (1.4)	7 (4.4)	
Unrecorded	7 (1.3)	5 (1.4)	2 (1.3)	
Earlier comorbidity, n (%)				
Diabetes	103 (19.8)	70 (19.3)	33 (20.9)	0.773
Coronary artery disease	87 (16.7)	64 (17.7)	23 (14.6)	0.454
Hypertension	260 (50.0)	188 (51.9)	72 (45.6)	0.215
Arrhythmia	70 (13.5)	53 (14.6)	17 (10.8)	0.292
Asthma	25 (4.8)	16 (4.5)	8 (5.1)	>0.999
COPD	39 (7.5)	29 (8.0)	10 (6.3)	0.625
Other cancer	88 (16.9)	61 (16.9)	27 (17.1)	0.964
Other	300 (57.7)	215 (59.4)	85 (53.8)	>0.999
Smoking history, n (%)	264 (50.8)	194 (53.6)	70 (44.3)	0.137
Alcohol history, n (%)	101 (19.4)	69 (19.1)	32 (20.3)	0.146

IQR, interquartile range.

operations from 1995 to 2000 and 9.0% of operations between 2001 and 2005, and in the recent decade, extended LAD was performed at the time of (esophago)gastrectomy in 36.5% of operations between 2006 and 2010 and in 49.4% of operations between 2011 and 2017 (Fig. 2). D0/D1 LAD was performed more often in esophagogastric procedures, and extended LAD was performed more commonly at the time of a total gastrectomy ($p < 0.001$) (Table 2). A laparoscopic approach was first used in the year 2000 and was more often used with extended dissections (D0/D1: 11.0%, D1+/D2: 23.4%; $p < 0.001$). Patients undergoing D1+/D2 LAD were also more likely to receive pre- or postoperative chemotherapy or radiation therapy ($p < 0.001$).

The number of LNs examined differed significantly between D0/D1 and D1+/D2 LAD. A median of 16 LNs were examined in patients undergoing D0/D1 LAD compared with 27 LNs in those undergoing D1+/D2 LAD ($p < 0.001$) (Fig. 3). The groups differed significantly in pathologic characteristics, as summarized in Table 3. Tumors located proximally and at the gastroesophageal junction were associated with D0/D1 LAD, and D1+/D2 LAD more often accompanied the resection of diffuse or distal tumors. Extended LAD correlated with higher TNM stages due to the greater number of LNs examined, with significantly higher percentages of patients with stage IIIB (D0/D1: 10.7%, D1+/D2: 15.2%) and IIIC (D0/D1: 4.4%, D1+/D2: 12.0%) disease. Patients undergoing D1+ or D2 LAD were also more likely to be pathologically staged as N3a and N3b (D0/D1: 18.5%, D1+/D2: 25.9%; $p = 0.034$).

Postoperative outcomes

There were no significant differences in type or severity of complications experienced by patients undergoing D0/D1 vs D1+/D2 LAD. Postoperative outcomes are summarized in Table 4. Overall, 16% of patients experienced a severe complication, classified as a Clavien-Dindo grade 3 or 4 complication, and there were no differences between the 2 groups (16.6% for D0/D1 and 14.6% for D1+/D2; $p > 0.999$). Importantly, the occurrence of a postoperative complication did not affect the receipt of either adjuvant chemotherapy ($p = 0.496$) or adjuvant radiation therapy ($p = 0.615$) in either cohort. The anastomotic leak rate was 4.7% in patients undergoing a D0/D1 LAD and 3.8% in those undergoing a D1+/D2 LAD ($p = 0.821$). However, patients undergoing an extended LAD were more likely to be readmitted within 30 days (D0/D1: 12.4%, D1+/D2: 27.8%; $p < 0.001$). Of the 27 patients readmitted after extended LAD, 19 (70.3%) patients underwent a total gastrectomy, which, in an earlier publication, we found to be an independent risk factor for readmission.[22] The significant differences in readmission were primarily due to nonsurgical complications, such as inadequate oral intake and *Clostridium difficile* colitis, as summarized in Table 5. The 30-day postoperative mortality rate in those patients undergoing D0/D1 LAD was 2.8% ($n = 10$) vs 0.6% ($n = 1$) for those patients undergoing D1+/D2 LAD ($p = 0.222$). At 90 days, the mortality rate for the D0/D1 cohort was 4.1% ($n = 15$) vs 2.5% ($n = 4$) for the D1+/D2 cohort ($p = 0.517$). One- and 5-year mortality rates were 20.7% and 49.7%, respectively, for the D0/D1 cohort and 15.2% and 39.9%, respectively, for the extended LAD cohort.

The performance of a pancreatectomy did not affect the complication rate (odds ratio [OR] 2.4; $p = 0.21$), but did increase the risk of 90-day mortality (OR 8.4; $p = 0.002$), and the performance of a splenectomy was associated with an increased complication rate (OR 3.1; $p = 0.02$), but did not affect the 90-day mortality rate (OR 1.95; $p = 0.304$). The nodal yield was not significantly impacted by either the performance of a pancreatectomy (median LN harvest: 18 vs 24.5; $p = 0.100$) or a splenectomy (median LN harvest: 18 vs 21; $p = 0.212$). However, it is important to note that rather few pancreatectomies ($n = 14$) and splenectomies ($n = 47$) were performed in this series, potentially limiting our ability to identify findings of statistical significance.

Clinicopathologic factors that significantly predicted overall survival were evaluated by univariate and multivariate Cox proportional regression analysis, as summarized in Table 6. Age, African-American race, earlier coronary artery disease, additional pancreatectomy or splenectomy, higher tumor grade, higher TNM stage, and positive resection margins were identified as independent negative prognostic factors for overall survival on univariate analysis. Conversely, factors that were positively correlated

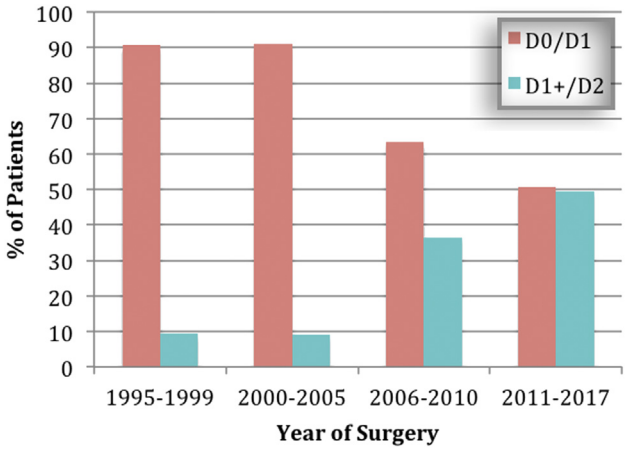

Figure 2. Distribution of D0/D1 vs D1+/D2 LAD performed according to year of operation.

Table 2. Treatment Detail

Variable	Overall (n = 520)	D0/D1 (n = 362)	D1+/D2 (n = 158)	p Value
Earlier gastric resection, n (%)	29 (5.6)	25 (6.9)	4 (2.5)	0.073
Year of operation, median (IQR)	2008 (2002–2011)	2006 (2000–2010)	2011 (2008–2012)	<0.001
Resection, n (%)				<0.001
Esophagogastrectomy/proximal gastrectomy	181 (34.8)	151 (41.7)	30 (19.0)	
Distal/subtotal	188 (36.2)	117 (32.3)	71 (44.9)	
Total	151 (29.0)	94 (26.0)	57 (36.1)	
Reconstruction, n (%)				<0.001
Esophagogastrostomy	170 (32.7)	144 (39.8)	26 (16.5)	
Billroth I	2 (0.4)	2 (0.6)	0 (0.0)	
Billroth II	154 (29.6)	105 (29.0)	49 (31.0)	
Roux-en-Y	194 (37.3)	111 (30.7)	83 (52.5)	
Laparoscopic procedure, n (%)	77 (14.8)	40 (11.0)	37 (23.4)	<0.001
Additional pancreatectomy, n (%)	14 (2.7)	8 (2.2)	6 (3.8)	0.462
Additional splenectomy, n (%)	47 (9.0)	25 (6.9)	22 (13.9)	0.016
Nodes examined, median (IQR)	18 (13–26)	16 (10–21)	27 (20–34)	<0.001
≥16 nodes examined, n (%)	332 (63.8)	191 (52.8)	141 (89.2)	<0.001
Positive nodes, n, median (IQR)	1 (0–5)	1 (0–5)	1 (0–7)	0.065
Chemotherapy, n (%)				<0.001
Preoperative only	84 (16.2)	51 (14.1)	33 (20.9)	
Postoperative only	115 (22.1)	70 (19.3)	45 (28.5)	
Pre- and postoperative	81 (15.6)	52 (14.4)	29 (18.4)	
Radiation, n (%)				<0.001
Preoperative only	87 (16.7)	60 (16.6)	27 (17.1)	
Postoperative only	118 (22.6)	72 (19.9)	46 (29.1)	
Pre- and postoperative	9 (1.7)	9 (2.5)	0 (0)	

IQR, interquartile range.

with survival were Hispanic race, year operation was performed, laparoscopic approach, and importantly, extended (D1+/D2) LAD. Included in the multivariate survival analysis were variables with a p value <0.05 on univariate analysis and important clinical covariates, such as sex, type of operation, and adjuvant chemotherapy or radiation therapy.

On adjusted multivariate analysis, age, African-American race (hazard ratio [HR] 2.83; p = 0.0008), earlier coronary artery disease (HR 1.48; p = 0.022), TNM stage II (HR 14.75; p = 0.018), TNM stage III (HR 28.67; p = 0.004), and positive resection margins (HR 2.74; p < 0.001) predicted an increased risk of death. Patients undergoing surgical resection in the most recent decade (2006 to 2017) experienced a significantly decreased risk of death compared with those undergoing operations in earlier eras (HR 0.61; p = 0.040). Importantly, when adjusting for the year of operation in multivariate analyses, undergoing an extended LAD compared with a D0/D1 LAD no longer conferred a survival benefit (p = 0.648).

Kaplan-Meier survival analysis of the total cohort (n = 520) demonstrated an improved overall survival rate in patients undergoing an extended LAD (p = 0.033) (Fig. 3). The median overall survival for D0/D1 patients was 35.5 months, and D1+/D2 patients had a median

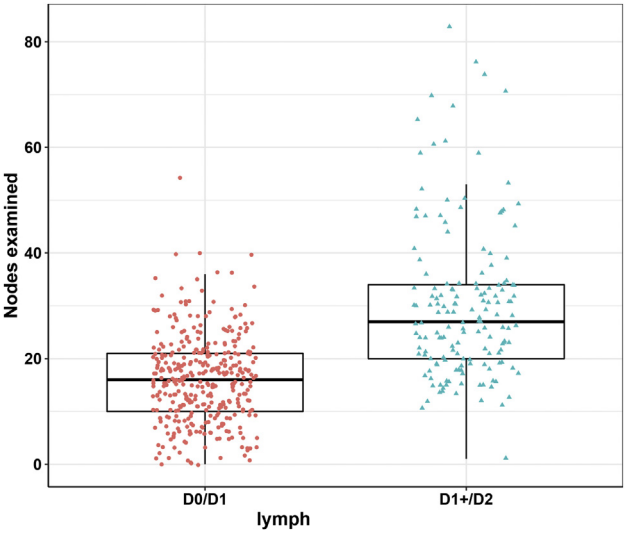

Figure 3. Distribution of nodal yield in D0/D1 vs D1+/D2 lymphadenectomy

Table 3. Pathology Characteristics

	Overall (n = 520)		D0/D1 (n = 362)		D1+/D2 (n = 158)		
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**p Value**
Tumor site							<0.001
Gastroesophageal junction	125	24.0	104	28.7	21	13.3	
Proximal/cardia	100	19.2	78	21.5	22	13.9	
Distal/antrum	239	46.0	160	44.1	79	50.0	
Body or diffuse	56	10.8	20	5.5	36	22.8	
Tumor grade							<0.001
Well differentiated	29	6.4	23	6.4	6	3.8	
Moderately differentiated	151	33.2	120	33.1	31	19.6	
Poorly differentiated	269	59.1	163	45.0	106	67.1	
Undifferentiated	33	7.3	27	7.5	6	3.8	
Unknown	38	8.4	29	8.0	9	5.7	
AJCC 8th ed T status							<0.001
ypCR	27	5.2	22	6.1	5	3.2	
T1a	48	9.2	37	10.2	11	7.0	
T1b	64	12.3	41	11.3	23	14.6	
T2	126	24.2	97	26.7	29	18.4	
T3	203	39.0	141	38.8	62	39.2	
T4a	34	6.5	13	3.6	21	13.3	
T4b	18	3.5	11	3.0	7	4.4	
AJCC 8th ed N status							0.147
N0	232	44.6	167	46.0	65	41.1	
N1	88	16.9	67	18.5	21	13.3	
N2	90	17.3	61	16.8	29	18.4	
N3a	84	16.2	50	13.8	34	21.5	
N3b	26	5.0	17	3.0	7	5.7	
Positive nodes >7 (N3a, N3b)	110	21.2	67	18.5	41	25.9	0.034
AJCC 8th ed TNM stage group							0.035
ypCR	26	5.0	20	5.5	6	3.8	
IA	84	16.2	58	16.0	26	16.5	
IB	77	14.8	60	16.5	17	10.8	
IIA	83	15.9	60	16.5	23	14.6	
IIB	65	12.5	46	12.7	19	12.0	
IIIA	87	16.7	63	17.4	24	15.2	
IIIB	63	12.1	39	10.7	24	15.2	
IIIC	35	6.7	16	4.4	19	12.0	
Resection margin							0.613
Uninvolved	467	89.8	323	89.2	144	91.1	
Involved	53	10.2	39	10.8	14	8.9	

AJCC, American Joint Committee on Cancer; ypCR, pathologic complete response after neoadjuvant treatment.

overall survival of 39.5 months (p = 0.033). However, when stratifying the cohort into early (1995 to 2005) and late (2006 to 2017) periods based on when the surgical procedure was performed, performance of an extended LAD no longer conferred a survival benefit (Figs. 4A-4C). The separation of the curves in the overall cohort (Fig. 4C) is explained by the differences in survival due to the year that operation was performed. That is, most (or all) of the survival benefit seen in Figure 4C for the D1+/D2 cohort is due to the fact that these patients tended to undergo treatment in a more contemporary time period and is not due to the more extensive node dissection itself. In addition, this finding of a lack of a survival benefit for extended LAD is not due to a difference

Table 4. Perioperative Outcomes

Outcome	Overall (n = 520)	D0/D1 (n = 362)	D1+/D2 (n = 158)	p Value
Complication severity (Clavien-Dindo), n (%)				0.549
0	254 (48.8)	177 (48.9)	77 (48.7)	
I	23 (4.4)	16 (4.4)	7 (4.4)	
II	160 (30.8)	109 (30.1)	51 (32.3)	
IIIa	21 (4.0)	13 (3.6)	8 (5.1)	
IIIb	37 (7.1)	26 (7.2)	11 (7.0)	
IVa	11 (2.1)	8 (2.2)	3 (1.9)	
IVb	3 (0.6)	3 (0.8)	0 (0)	
V	11 (2.1)	10 (2.8)	1 (0.6)	
Severe complication, n (%)	83 (16.0)	60 (16.6)	23 (14.6)	>0.999
Complication, n (%)				
Anemia	54 (10.4)	40 (11.0)	14 (8.9)	0.551
Arrhythmia	92 (17.7)	65 (18.0)	27 (14.3)	0.910
Respiratory complication	88 (16.9)	67 (18.5)	21 (15.5)	0.183
Anastomotic leak	23 (4.4)	17 (4.7)	6 (3.8)	0.821
Duodenal leak	5 (1.0)	3 (0.8)	2 (1.3)	>0.999
Abscess	21 (4.0)	12 (3.3)	9 (5.7)	0.305
Wound dehiscence or infection	20 (3.8)	17 (4.7)	3 (1.9)	0.201
Acute kidney injury	11 (2.1)	11 (3.0)	0 (0)	0.060
Length of stay, d, median (IQR)	8 (7−11)	9 (7−11)	8 (6−10)	0.010
Readmission, n (%)				
30-d	88 (16.9)	44 (12.2)	44 (27.8)	<0.001
Mortality, n (%)				
Admission	10 (1.9)	10 (2.8)	0 (0)	0.078
30 d	11 (2.1)	10 (2.8)	1 (0.6)	0.222
90 d	19 (3.7)	15 (4.1)	4 (2.5)	0.517
1 y	99 (19.0)	75 (20.7)	24 (15.2)	0.335
5 y	243 (46.7)	180 (49.7)	63 (39.9)	0.117
Recurrence, n (%)	102 (19.6)	74 (20.4)	27 (17.1)	0.443
Median follow-up time, y, median (IQR)	3.1 (1.2−7.5)	3.0 (1.2−8.5)	3.3 (1.3−6.8)	0.574

IQR, interquartile range.

in median follow-up, as the median follow-up of the modern cohort (2006 to 2017, n = 324) is 36 months, no different than the median follow-up of the older cohort (1995 to 2005, n = 196) at 36.5 months, which is likely due to the lethal nature of gastric cancer. In addition, when analyzing the D1, D1+, and D2 patient cohorts separately, there remains no statistically significant difference in overall survival (Fig. 5). Lastly, when one excludes the patients who died in the first 90 days after operation, there remains no difference in survival, which is not surprising because the 90-day mortality for the D1+/D2 cohort in this study was only 2.5% (compared with 4.1% for the D0/D1 cohort).

Given concern for the heterogeneity of our patient cohort in terms of year of operation and type of resection, a smaller subset of the entire data set was analyzed with the same statistical approach to determine whether a survival benefit could be elicited when examining a stricter, more homogenous data set. Siewert type 1 and 2 gastroesophageal junction tumors were excluded, and patients who underwent operations between 2001 and 2015 were analyzed (n = 190). When examining extent of LN dissection on survival benefit by univariate regression or Kaplan-Meier analysis, there was no effect (p = 0.683, data not shown).

DISCUSSION

For patients with localized, resectable gastric cancer, gastrectomy with D2 LAD has long been the standard of care in eastern Asia; and in the West, the practice of routinely performing a D2 LAD at the time of curative

Table 5. Reason for Readmission

	Overall (n = 520)		D0/D1 (n = 362)		D1+/D2 (n = 158)		
Variable	**n**	**%**	**n**	**%**	**n**	**%**	**p Value**
Oral tolerance difficulty	18	16.7	5	8.5	13	26.5	0.008
Abdominal pain or dysphagia	12	11.1	7	11.9	5	10.2	0.798
Respiratory complication	7	6.5	5	8.5	2	4.1	0.596
Cardiac complication	8	7.4	5	8.5	3	6.1	0.897
Surgical complication							
Obstruction or stricture	11	10.2	8	13.6	3	6.1	0.263
Anastomotic or duodenal stump leak	7	6.5	5	8.5	2	4.2	0.596
J-tube obstruction or leak	8	7.4	4	6.8	4	8.2	0.304
Gastric necrosis	3	2.8	3	5.1	0	0.0	0.278
Infection	8	7.4	7	11.9	1	2.0	0.112
Abscess	9	8.3	3	5.1	6	12.2	0.233
Clostridium difficile colitis	5	4.6	0	0.0	5	10.2	0.006
Hemorrhage	3	2.8	2	3.4	1	2.0	0.761
Other	9	8.3	5	8.5	4	8.2	0.175

gastrectomy has not been widely embraced. With the publication of studies from high-volume Western centers demonstrating that a D2 LAD can be performed safely, that it improves nodal yield and ensures more accurate staging, and that it can even confer a survival benefit for higher-stage cancers,[23] the National Comprehensive Cancer Network Guidelines now emphasize that a D2 LAD should be performed if done by experienced surgeons in high-volume Western centers.[3] In this study, we confirm that gastrectomy with extended (D1+/D2) LAD can be performed safely at a high-volume Western center and that it significantly improves nodal yield and ensures accurate pathologic staging. However, we were not able to demonstrate a survival benefit from the performance of an extended LAD.

Importantly, the demonstration of the safety of extended LAD must first be established before recommending its routine performance. High-volume centers in Asia have published countless studies demonstrating very low rates of postoperative morbidity and mortality for D2 LAD in patients undergoing both open and minimally invasive gastrectomy, and this procedure is now standard there. Early studies of D2 LAD from the West included the Dutch Gastric Cancer Group Trial and the British Cooperative trial conducted by the Medical Research Council, both of which showed unacceptably high postoperative morbidity rates (in excess of 40%) and mortality rates (at or in excess of 10%).[8,9] In light of the high risk of this procedure, as well as the fact that both of these trials also failed to show a survival benefit for D2 LAD over D1 LAD, many surgeons in the West concluded that D2 LAD was of no or limited benefit for patients undergoing potentially curative gastrectomy. However, Degiuli and colleagues[24,25] in the Italian Gastric Cancer Study Group recently demonstrated, in a prospective, multicenter, randomized clinical trial, that Western surgeons expertly trained in extended LN dissections can perform D2 LAD safely and with morbidity rates comparable to D1 LAD ($p = 0.178$). In this current study, we also found that at our high-volume center, where extended LADs are performed by surgeons trained in the technique, that the procedure can be done with very acceptable postoperative morbidity and mortality, confirming the findings of our initial, much smaller study on this topic.[18] Notably, patients undergoing D1+/D2 LAD were more likely to be readmitted within 30 days of discharge, but we believe this is due in part to the larger proportion of patients undergoing total gastrectomy in the D1+/D2 cohort compared with the D0/D1 cohort. We have previously identified these patients to be at higher risk for readmission due to nutritional difficulties and/or complications related to their feeding jejunostomy tube.[22]

Another reported benefit of extended LN dissection is improved nodal yield and, accordingly, more accurate pathologic staging.[7] In our series, we demonstrate a significantly increased nodal yield with extended LAD, from a median of 16 examined nodes in the D0/D1 group to a median of 27 nodes examined in D1+/D2 patients. In addition, receipt of neoadjuvant therapy did not significantly impact LN yield in our data; however, when examining the patients who did not meet the recommended 16-node harvest, a majority of these patients had received neoadjuvant radiation, suggesting that it is preoperative radiation rather than chemotherapy that can lead to

Table 6. Univariate and Multivariate Analyses for Overall Survival

Variable	HR	95% CI	p Value	HR	95% CI	p Value
Age	1.02	1.01–1.03	0.002	1.02	1.01–1.04	<0.001
Male sex	1.23	0.95–1.59	0.119	0.95	0.70–1.28	0.734
Race						
White	ref	ref	ref	ref	ref	ref
Asian	0.76	0.46–1.26	0.287	0.80	0.45–1.40	0.430
Hispanic	0.34	0.14–0.82	0.016	0.44	0.18–1.10	0.078
Black	1.97	1.01–3.84	0.045	2.83	1.31–6.08	0.008
Earlier comorbidity						
Diabetes	1.00	0.74–1.36	0.982	—	—	—
Coronary artery disease	1.66	1.24–2.23	<0.001	1.48	1.15–2.21	0.022
Hypertension	0.93	0.74–1.18	0.574	—	—	—
Arrhythmia	1.15	0.82–1.60	0.425	—	—	—
Asthma	1.32	0.76–2.25	0.318	—	—	—
COPD	1.35	0.88–2.07	0.171	—	—	—
Smoking history	1.15	0.90–1.46	0.263	—	—	—
Alcohol history	1.09	0.82–1.46	0.547	—	—	—
Year of operation						
1995–1999	ref	ref	ref	ref	ref	ref
2000–2005	0.64	0.46–0.88	0.007	1.19	0.82–1.72	0.362
2006–2010	0.49	0.36–0.68	<0.001	0.95	0.64–1.42	0.814
2011–2017	0.41	0.29–0.58	<0.001	0.61	0.38–0.98	0.040
Prior resection	1.04	0.63–1.73	0.878			
Laparoscopic procedure	0.65	0.45–0.95	0.027	0.96	0.62–1.47	0.845
Resection						
Esophagogastric/proximal	ref	ref	ref	ref	ref	ref
Distal/subtotal	0.89	0.67–1.19	0.433	0.87	0.62–1.23	0.440
Total	1.29	0.97–1.73	0.081	1.21	0.86–1.70	0.264
Reconstruction						
Esophagogastric	ref	ref	ref	—	—	—
Billroth I	0.61	0.09–4.41	0.628	—	—	—
Billroth II	0.94	0.70–1.27	0.697	—	—	—
Roux-en-Y	1.04	0.79–1.38	0.773	—	—	—
Additional pancreatectomy	2.11	1.16–3.87	0.015	1.50	0.69–3.25	0.309
Additional splenectomy	1.56	1.08–2.24	0.016	0.84	0.50–1.41	0.502
Lymph node dissection						
D0/D1	ref	ref	ref	ref	ref	ref
D1+/D2	0.74	0.56–0.98	0.035	0.92	0.65–1.31	0.648
Chemotherapy						
None	ref	ref	ref	ref	ref	ref
Preoperative only	0.79	0.53–1.16	0.220	0.81	0.42–1.58	0.543
Postoperative only	1.08	0.81–1.44	0.613	0.73	0.43–1.22	0.233
Pre- and postoperative	1.00	0.71–1.41	0.996	0.63	0.36–1.11	0.110
Radiation						
None	ref	ref	ref	ref	ref	ref
Preoperative only	1.06	0.75–1.50	0.733	2.07	1.11–3.86	0.022
Postoperative only	1.12	0.85–1.48	0.420	0.07	0.67–1.71	0.786
Pre- and postoperative	0.60	0.19–1.88	0.380	0.12	0.31–4.10	0.857

(Continued)

Table 6. Continued

Variable	HR	95% CI	p Value	HR	95% CI	p Value
Tumor grade						
Well differentiated	ref	ref	ref	ref	ref	ref
Moderately differentiated	2.93	1.35–6.34	0.006	1.56	0.70–3.47	0.277
Poorly differentiated	3.48	1.63–7.41	0.001	1.50	0.67–3.34	0.322
Undifferentiated	3.54	1.51–8.28	0.004	1.21	0.47–3.05	0.692
AJCC 8th ed TNM stage						
ypCR	ref	ref	ref	ref	ref	ref
I	7.06	0.97–51.17	0.053	5.05	0.54–47.45	0.156
II	20.44	2.85–146.63	0.003	14.75	1.57–138.45	0.018
III	31.92	4.46–228.28	<0.001	28.67	3.01–273.27	0.004
Resection margin						
Uninvolved	ref	ref	ref	ref	ref	ref
Involved	3.00	2.17–4.15	<0.001	2.74	1.87–4.01	<0.001
Severe complication	1.42	1.12–1.80	0.003	0.98	0.74–1.31	0.916
Complication						
Anemia	1.19	0.83–1.72	0.341	—	—	—
Arrhythmia	1.05	0.77–1.43	0.762	—	—	—
Respiratory complication	1.58	1.18–2.11	0.002	1.34	0.94–1.92	0.108
Anastomotic leak	0.95	0.53–1.69	0.853	—	—	—
Duodenal leak	1.56	0.50–4.86	0.447	—	—	—
Abscess	1.40	0.78–2.49	0.259	—	—	—
Wound dehiscence or infection	0.88	0.47–1.66	0.694			
Renal dysfunction	4.06	2.22–7.43	<0.001	1.81	0.93–3.54	0.082
Length of stay	1.02	1.01–1.02	<0.001	1.00	0.99–1.01	0.680
Readmission						
30-day	1.30	0.95–1.78	0.097	—	—	—

AJCC, American Joint Committee on Cancer; HR, hazard ratio; ypCR, pathologic complete response after neoadjuvant treatment.

reduced LN yield.[26,27] Ultimately, increase in nodal yield leads to stage migration, reflected in major differences in nodal status and TNM staging. The percentage of patients staged as N3a or N3b was 18.5% in D0/D1 patients and 25.9% in D1+/D2 patients, a difference that almost certainly reflects more accurate detection of node-positive disease in the extended LAD group, which had significantly more LNs examined. If nothing else, the performance of an extended LAD is warranted to ensure the accurate pathologic staging of patients with GEC, as this has obvious implications for the clinician in terms of adjuvant therapy recommendations and patient prognosis.

A much more controversial issue is whether a more extensive LAD confers a survival benefit to patients with GEC. Two large, prospective randomized trials from Europe failed to show a survival benefit for D2 LAD over D1 LAD.[8,9] However, longer-term follow-up of the Dutch trial did, in fact, demonstrate that D2 LAD was associated with both lower locoregional recurrence rates and lower death rates from gastric cancer.[10] In addition, a large randomized trial from Taiwan also demonstrated a survival benefit from a more extended LAD over a D1 LAD (5-year overall survival rate of 59.5% compared with 53.6%).[12] In our current study, patients undergoing a more extensive LN dissection did have a significantly improved overall survival compared with those undergoing D1 LAD on univariate analysis. However, after controlling for the year that the operation was performed on multivariate analysis, this survival advantage disappeared. In fact, patients operated on in a more contemporary time period, which is when most of the extended LN dissections were performed, had significantly better outcomes than those operated on more than 10 years ago, which is likely due to a number of factors, including improvements in our surgical skill, perioperative care, systemic therapies, and in the percentage of patients receiving multimodality therapy, as we have more routinely adopted neoadjuvant therapy before operation.

Our study is not without limitations. First, we have limited data on the site of recurrence, such that we could not accurately determine the difference in locoregional

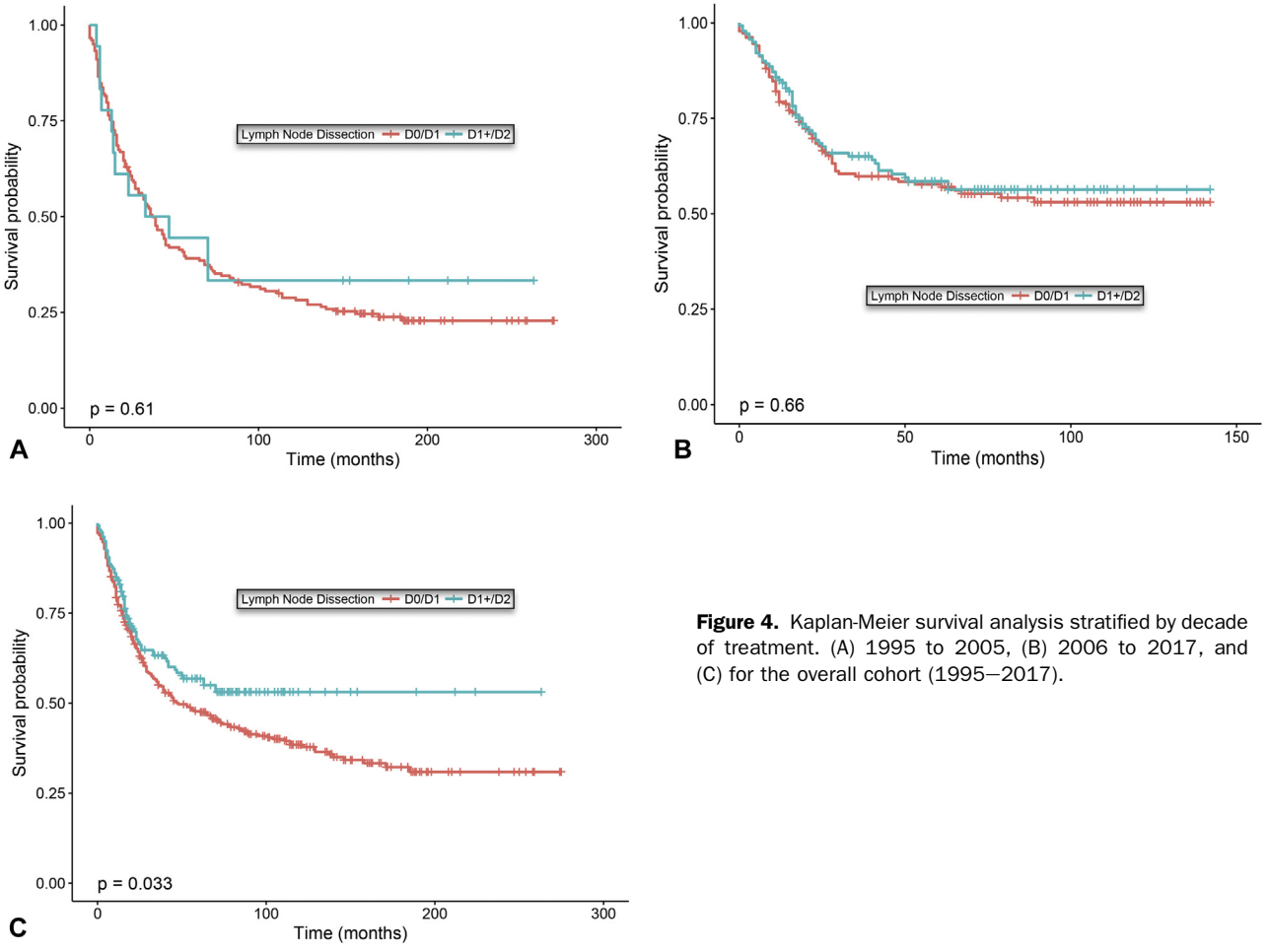

Figure 4. Kaplan-Meier survival analysis stratified by decade of treatment. (A) 1995 to 2005, (B) 2006 to 2017, and (C) for the overall cohort (1995–2017).

recurrence rates for D1 vs D1+/D2 LAD. Second, we chose overall survival as our outcomes measure because many of our patients received their long-term follow-up care at outside hospitals. As such, for many of these patients we could only determine their vital status overall and not their exact cause of death, such that we could not reliably calculate disease-specific survival for our patients. Additional limitations to our study include potential time bias, as this study spans a long period of time (22 years) with variations in the duration of patient follow-up depending on the year of operation. Given this limitation, it is possible that there might be a difference in overall survival that is not captured in our analysis. Lastly, as a nonrandomized study, we recognize the issue of selection bias for patients receiving extended LN dissections vs those receiving only a limited (D0/D1) LAD. However, we attempted to control for this bias by accounting for differences in demographic and clinicopathologic characteristics between the 2 groups in our multivariate analysis.

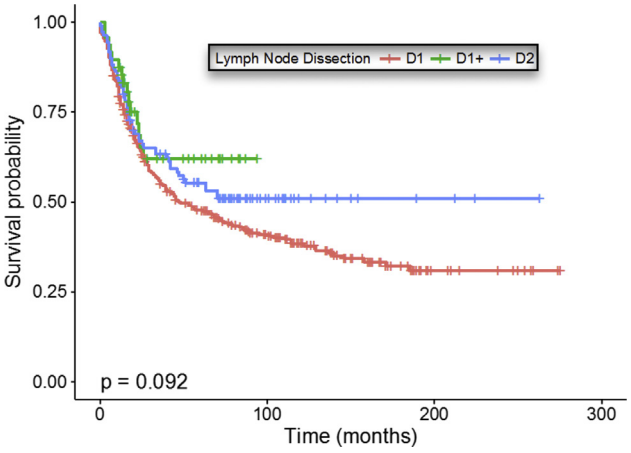

Figure 5. Kaplan-Meier survival analysis stratified by extent of lymph node dissection (D1 vs D1+ vs D2).

CONCLUSIONS

In the contemporary era, gastrectomy with extended (D1+/D2) LAD can be performed safely with low morbidity and minimal mortality. Importantly, although it might not confer a survival advantage, extended LAD does improve nodal yield and ensures accurate pathologic staging for patients with GEC undergoing potentially curative resection.

Author Contributions

Study conception and design: Li, Costantino, Rattner, Mullen

Acquisition of data: Li, Costantino

Analysis and interpretation of data: Li, Costantino, Rattner, Mullen

Drafting of manuscript: Li, Costantino, Rattner, Mullen

Critical revision: Li, Costantino, Rattner, Mullen

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Invited Commentary

Timothy L Fitzgerald, MD
Portland, ME

Dr Li and colleagues present a single-institutional experience with extended lymphadenectomy for gastric cancer. The series includes 520 patients undergoing operation for gastroesophageal carcinoma over 2 decades. The authors uniquely classify patients as having D0/D1 vs D1+/D2 lymphadenectomy. In this nomenclature, D1+ is a D2 dissection that does not include station 10 (splenic hilum). Patients did not routinely undergo pancreatosplenectomy. The extent of dissection was classified retrospectively by review of the operative notes for details describing an extended lymphadenectomy; if this description was not included, it was assumed a D0 or D1 lymphadenectomy was performed.

The authors noted about 70% of the patients had a D0/D1 lymphadenectomy. Those undergoing more limited lymphadenectomy were more likely to be in earlier cohorts and have proximal tumors. The D1+/D2 cohort had a greater number of lymph nodes and improved survival on univariate analysis. When accounting for year of diagnosis on multivariate analysis, the survival difference did not persist. The authors hypothesized that improved outcomes in more contemporary cohorts were likely secondary to improved surgical technique, perioperative care, and a higher percentage of patients receiving multimodal care. It is important to note that extended lymphadenectomy was not associated with morbidity or operative mortality.

In this manuscript, the primary benefit of D1+/D2 lymphadenectomy was staging. There was a slight decrease in the number of patients with node-negative disease with D1+/D2 dissection. However, the primary difference was an increase in the number of positive nodes for those with positive node disease. The percentage of patients with N3 disease increased by almost 10%.

For surgeons to understand the clinical implications of adopting extended lymphadenectomy in patients with gastric cancer, it is imperative to distinguish between what one can do and what one should do. It is clear from this manuscript, and other surgical data, that when performed by trained surgeons who avoid splenectomy/pancreatectomy, extended lymphadenectomy is associated with little additional perioperative risk. However, there has been a failure to consistently demonstrate a meaningful clinical benefit.

Five randomized trials, 3 of which were performed in Europe, have examined extended lymphadenectomy for gastric cancer.[1] Two seminal western trials are the Dutch Gastric Cancer and UK Medical Research Council (MRC) trials.[2,3] The Dutch trial, originally published in 1999, enrolled 711 patients and reported similar 5-year survival with increased morbidity, mortality, and hospital length of stay with D2 lymphadenectomy.[4] In a 2004 publication, 11 years of follow-up data from the Dutch trial demonstrated a trend in improved survival limited to N2 disease.[2] A smaller, randomized Italian study demonstrated similar findings of benefit for patients with positive node cancers.[5] The 15-year follow-up of the Dutch study demonstrated lower local-regional recurrence and gastric cancer-related mortality, but no difference in overall and disease-free survival.[6]

Similarly, the UK MRC trial noted higher morbidity and mortality with D2 resection with no advantage at 6 years of follow-up.[7] Both the Dutch and MRC trials attribute this increased morbidity and mortality to splenectomy and distal pancreatectomy.[3,6] The authors of both studies suggest that if splenectomy and pancreatectomy were omitted, D2 dissection would be superior to D1.[6,7]

Taking this manuscript in the context of the current literature is imperative. The data presented here illustrate that at a high-volume center, extended lymph node dissection can be performed safely for gastric cancer. Also, the authors noted improved staging, as evidenced by increased lymph node yield and an increased number of patients with N3 disease. However, this study fails to demonstrate a clear therapeutic advantage. The additional clinical data provided by improved staging in lymph node-positive patients are unlikely to affect adjuvant therapy.

Patterns of adjuvant treatment have evolved in the decades after the previously mentioned seminal European trial was conducted. Most gastric cancer patients receive adjuvant therapy.[8] The current National Comprehensive Cancer Network (NCCN)-preferred approach to treatment is perioperative chemotherapy. It is unclear what impact effective preoperative treatment will have on the potential benefits of extended lymph node dissection.

Overall, the authors provide a significant contribution to the literature and further define the role of extended lymphadenectomy. Given that large prospective randomized trials have demonstrated increased morbidity and mortality after extended lymphadenectomy, this technique must be applied with caution. The morbidity of a traditional Japanese D2 lymphadenectomy can be potentially mitigated with modifications such as omitting pancreatectomy/splenectomy and D1+ rather than D2 dissection. It would be reasonable to use extended lymphadenectomy at high-volume centers by trained surgeons if this can be done without additional morbidity. However, if these criteria cannot be met, the disadvantages of increased morbidity would likely outweigh the benefits of extended lymphadenectomy.

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