Ann Surg Oncol (2019) 26:2912–2932
https://doi.org/10.1245/s10434-019-07417-5

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

CONTINUING EDUCATION– GASTROINTESTINAL ONCOLOGY

In Patients with Localized and Resectable Gastric Cancer, What is the Optimal Extent of Lymph Node Dissection—D1 Versus D2 Versus D3?

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ABSTRACT

Background. Despite advances in the treatment of patients with gastric cancer, the debate over the optimal extent of lymphadenectomy continues.

Method. A review of the classification, rationale for, and boundaries of lymphadenectomy is presented. A review of the available literature comparing D1 versus D2 versus D3 lymphadenectomy was performed and included randomized controlled trials, and prospective and retrospective comparative and non-comparative studies.

Results. Earlier studies demonstrated increased morbidity with D2 compared with D1 lymphadenectomy, with no significant survival benefit. More recent studies have demonstrated survival benefit of a pancreas and spleen-sparing D2 lymphadenectomy in patients with advanced, node-positive tumors. Para-aortic/D3 dissections contribute to increased morbidity, with no survival benefit.

Conclusions. In patients with resectable gastric adenocarcinoma, a D2 lymph node dissection preserving the pancreas and spleen should be considered standard for optimal staging and treatment, provided it is performed by surgeons with sufficient expertise. Extended lymph node dissections beyond D2 should not be routinely performed as it has been shown to have increased morbidity, with no improvement in outcomes. While systemic chemotherapy should be considered standard in patients undergoing D2 lymphadenectomy, the role of adjuvant radiation continues to evolve.

First Received: 30 June 2018;
Published Online: 10 May 2019

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Despite advances in early diagnosis and treatment, gastric cancer remains one of the most common causes of cancer-related deaths worldwide, with almost 1 million cases estimated to occur per year.[1,2] Surgery is the only potentially curative treatment and lymphadenectomy is recommended as a main component of radical gastrectomy to optimally stage the disease, prevent locoregional recurrence, and thereby potentially improve overall survival (OS).[3] While Eastern surgeons have traditionally focused surgical techniques on radical control of the lymph node basins, Western surgeons have been hesitant to adopt this rationale on the basis of several studies that have shown increased perioperative morbidity and mortality with this approach, without any significant benefit of prolonging survival outcomes. The debate over the optimal extent of lymphadenectomy, therefore continues.

EVOLUTION OF THE DEFINITIONS AND CLASSIFICATIONS OF LYMPH NODE STATIONS AND LYMPHADENECTOMY

Prior to the establishment of the American Joint Committee on Cancer (AJCC) system, the first Japanese edition of the Japanese Classification (JC) of Gastric Carcinoma was published in 1962 to standardize pathological classification of gastric cancer.[4] Three English editions of the JC have since been published, corresponding to the 10th, 12th, and 13th Japanese editions in 1981, 1995, and 1998, respectively.[5] The terms D1, D2, and D3, as originally defined in the 2nd English edition of the JC, were used in most large randomized controlled trials (RCTs) of gastric cancer surgery, including the Dutch, Medical Research Council (MRC), and Taipei Veterans study trials[6–11] Based on the seminal work by Sasako et al., which involved calculation of the incidence of metastasis and 5-year

survival for each nodal station independent of overall pathological stage, a complex definition of the nodal groups was established.[12] The regional lymph nodes were classified into one of three *N* 'compartments' (*N*1, 2, 3, or *M*) based on their anatomical position in relation to the geographic location of the primary tumor.[5] These 'compartments' correlated with the extent of lymphadenectomy (D1–3 dissections corresponding with N1–3 lymph node stations). However, outside these fairly well-controlled clinical trials, owing to the complexity of this classification, the terms D1, D2, and D3 have been used loosely and rather erroneously, with N1 referring to perigastric nodes, N2 denoting nodes along the celiac artery and its branches, and N3 corresponding to nodes in the retropancreatic and transverse mesocolic region, with the corresponding dissections designated as D1, D2, and D3, respectively.

Therefore, in 2010, to simplify classification, the Japanese Gastric Cancer Association published an integrated version of the JC and the Japanese Gastric Cancer Treatment Guidelines (JGL), which adopted similar definitions and classifications as the AJCC 7th Edition.[13] Nodal grouping was replaced by the number of metastatic lymph nodes.[13,14] The definition of lymphadenectomy was markedly simplified, with the lymph node dissection in D1, D1 +, and D2 defined for total and distal gastrectomy regardless of the tumor location (Fig. 1).[15] D3 (also called para-aortic lymph node dissection) was not included after the negative results of the Japan Clinical Oncology Group (JCOG) 9501 trial comparing D2 and D3 dissection.[16] With the release of the AJCC 8th Edition, although several changes have been made to the clinical, post-neoadjuvant, and pathological staging, the classification of *N* status based on the number of involved nodes has remained unchanged.[17]

Rationale for the Boundaries of Systematic Lymphadenectomy in Gastric Cancer

The Maruyama Computer Program and Maruyama Index In 1989, the Japanese National Cancer Center database of 3843 prospectively collected cases was used to create the Maruyama computer program.[18] The program estimates the risk of metastasis to each nodal station based on the input of eight variables, including age, sex, endoscopic or Bormann's classification, depth of invasion, maximal diameter, tumor location, position, and WHO histological classification. By matching input variables to a large database of patients, the program gives a percentage likelihood of disease in each of the lymph node stations. An estimate of the added 5-year survival benefit of dissecting each nodal station is calculated by multiplying the frequency of metastasis to the station by the 5-year survival rate of patients with metastasis to this station. The index of estimated benefit from dissection of the various stations was maximum for N2 nodes, providing a rational basis for the boundaries of D2 lymphadenectomy.[12] By determining the 5-year survival of patients with positive nodes independently for each lymph node station without reference to the overall pathological stage, the Maruyama program circumvents the problem of stage migration. The Maruyama Index (MI) has been defined as the sum of Maruyama Program predictions for those Japanese-defined regional node stations (stations 1 through 12) left in situ by the surgeon. For patients enrolled into the Macdonald Chemoradiation Trial (Intergroup 0116) and the Dutch gastric cancer RCT, the MI proved an independent predictor of both overall and disease-specific survival, with low MI demonstrating better long-term prognosis.[19,20] In lieu of the 'one size fits all' approach, the use of a low MI operation guided by prospective use of the Maruyama computer program can potentially better impact survival in patients undergoing radical gastrectomy.[21] However, this approach is limited by the need to preoperatively assess several parameters, lending itself to error and resultant over- or under-treatment during surgery.

Extent of Dissection and Adequacy of Staging The likelihood of adequately determining the truly negative incidence of regional lymph nodes is extremely low when the number of nodes retrieved is < 10.[22,23] The risk of downstaging when an inadequate number of nodes is retrieved is especially high for patients with early *T* stage and N0 tumors, thereby underscoring the need for a more radical lymphadenectomy.[24–27]

Deng et al.[28] showed that a D2 lymphadenectomy with retrieval of at least 16 nodes provided the best prognostication for 5-year OS of patients with resectable gastric cancer. Similarly, in their study of 2090 consecutive patients with noncardia gastric cancer, Marelli et al. demonstrated improved prognosis of patients with N2b (7–15 positive nodes) compared with those with N3b disease ($\geq$ 16 nodes), thus emphasizing the importance of retrieving 16 or more nodes for an adequate lymphadenectomy. While a minimum total number of lymph nodes examined is important to adequately assess *N* stage, some studies from high-volume centers indicate lymph node ratio may be a better way of analyzing stage to assess its effects on survival because it obviates the stage migration phenomenon.[29–31]

Lymph Node Retrieval and Recommended Lymph Node Counts Although the AJCC 7th and 8th editions do not mandate a minimum number of nodes to be considered adequate to assign an appropriate *N* stage, 16 has been suggested as the standard threshold for adequate

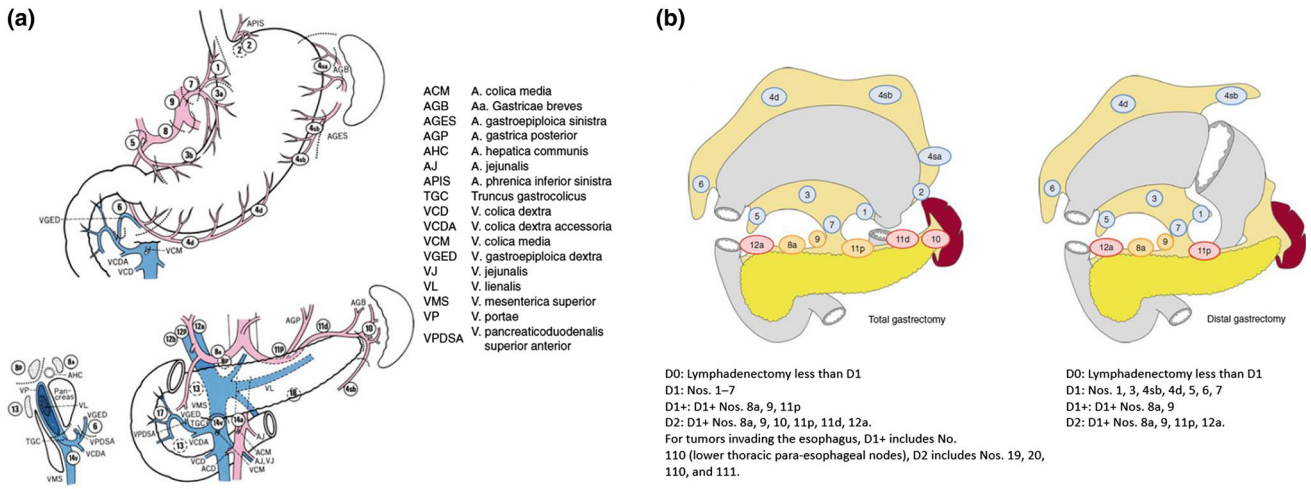

FIG. 1 **a** Location of lymph node stations (from 'Japanese Classification of Gastric Carcinoma: 3rd English edition',[14] with permission). **b** Extent of lymphadenectomy based on type of surgery (from 'Japanese Gastric Cancer Treatment Guidelines 2010 ver. 3',[15] with permission)

lymphadenectomy, and has also been recommended by the Japanese Gastric Cancer treatment guidelines, Clinical Practice Guidelines for Gastric Cancer in Korea, European Society of Radiotherapy and Oncology (ESTRO), and the international RAND/UCLA Expert Panel.[13,14,32–34] The National Comprehensive Cancer Network (NCCN), British Society of Gastroenterology and British Association of Surgical Oncology, and the American College of Surgeons Commission on Cancer (CoC) guidelines recommend retrieval of ≥ 15 nodes for adequate pathologic assessment.[35–37]

However, there is wide variation in practice patterns for lymphadenectomy during curative resection of gastric cancer and the optimal extent continues to be debated. A review of the available literature was therefore performed to better define optimal node dissection in the context of morbidity, mortality, and long-term outcomes.

METHODS

PubMed was searched for articles published from January 1990 through December 2017 that addressed the question of lymphadenectomy in patients with gastric cancer. Combinations of the following Medical Subject Heading (MeSH) terms or keywords were used: 'gastrectomy', 'gastric cancer', 'gastric carcinoma', 'lymphadenectomy', 'lymph node dissection', 'D1', 'D2', 'D3', 'PAND', and 'paraaortic node dissection'. Our initial search yielded 5897 articles. To simplify ease of discussion and avoid the confounding effect of neoadjuvant or adjuvant therapies on outcomes, we excluded articles that included the terms 'neoadjuvant' or 'adjuvant'. This yielded 4814 articles, of which 3242 pertained to human beings and were published in the English language. Articles relevant to the key question were then selected based on whether they addressed the issue of morbidity/mortality and survival in D1, D2, or D3 lymphadenectomies. Studies in which comparison of extended lymph node dissection was made to a historical control group belonging to a previous clinical era were excluded. A total of 47 unique full-text articles were identified from the reviewed abstracts. Twenty articles comprising 11 studies were RCTs (including interim analysis of the data), and 27 studies included prospective or retrospective analyses, of which 19 were comparative and 8 were non-comparative. Each article was then reviewed by two authors (HM and KV) to achieve the final list of suitable studies. The search methodology is summarized in the CONSORT (Consolidated Standards of Reporting Trials) diagram in Fig. 2.

RESULTS

Tables 1, 2 and 3 summarize findings from RCTs and prospective and retrospective comparative and non-comparative studies. Most studies used the Japanese Research Society for Gastric Cancer 1st English edition or the Japanese Classification of Gastric Cancer 2nd English edition in their methods section to define the extent of lymphadenectomy. All of the studies excluded patients with metastatic cancer or obvious metastasis to the paraaortic nodes (considered M1 disease), except one retrospective study by Tokunaga et al.[38] None of the studies (except the study by Galizia et al.[39] comparing D1 + and D2 dissections) used systemic or radiation therapy in a neoadjuvant or adjuvant manner, except when patients were found to have recurrent disease during follow-up. Given the improvement in adjuvant/neoadjuvant protocols

for gastric cancer in recent years, the role of lymphadenectomy in the era of modern chemotherapy and chemoradiotherapy merits further discussion.

DISCUSSION

D1 Versus D2 Lymphadenectomy

Several studies conducted in the 1980s from high-volume Japanese and Korean institutions have demonstrated the role of extended lymphadenectomy in improving survival of patients with gastric cancer. As a result, surgeons from Japan and Korea have considered the need for a randomized trial between D1 and D2 lymphadenectomy rather futile. However, survival results and operative morbidity and mortality that have been noted in many Eastern studies have not been replicated in the Western literature. As a result, two large multicenter randomized trials were conducted by the MRC in the UK and the Dutch group in The Netherlands to assess the short- and long-term results of D2 lymphadenectomy in gastric cancer. Early data from both of these trials showed increased morbidity (43–46%) and mortality (10–13%) rates, with a failure to demonstrate any survival benefit (33–45% 5-year OS).[6–9,40] However, these trials were criticized for the relative lack of experience among participating institutions and surgeons performing extended lymphadenectomy, which is subject to a learning curve. Another criticism was the routine performance of pancreatosplenectomy for patients with proximal tumors. This contributed to the observed excess morbidity and mortality, which is believed to have negated any survival benefit from extended lymphadenectomy. Additionally, patients were older and had more comorbidities than traditional Eastern patients, which may have contributed to a higher complication rate. A high noncompliance rate (failure to remove requisite lymph nodes) of 51% in the D2 arm may have further contributed to understaging and poorer survival outcomes. In the final analysis of the Dutch trial data after mature follow-up, survival was statistically significantly improved after excluding patients who underwent pancreatosplenectomy (35% vs. 22%) and in those with stage II (33% vs. 15%)

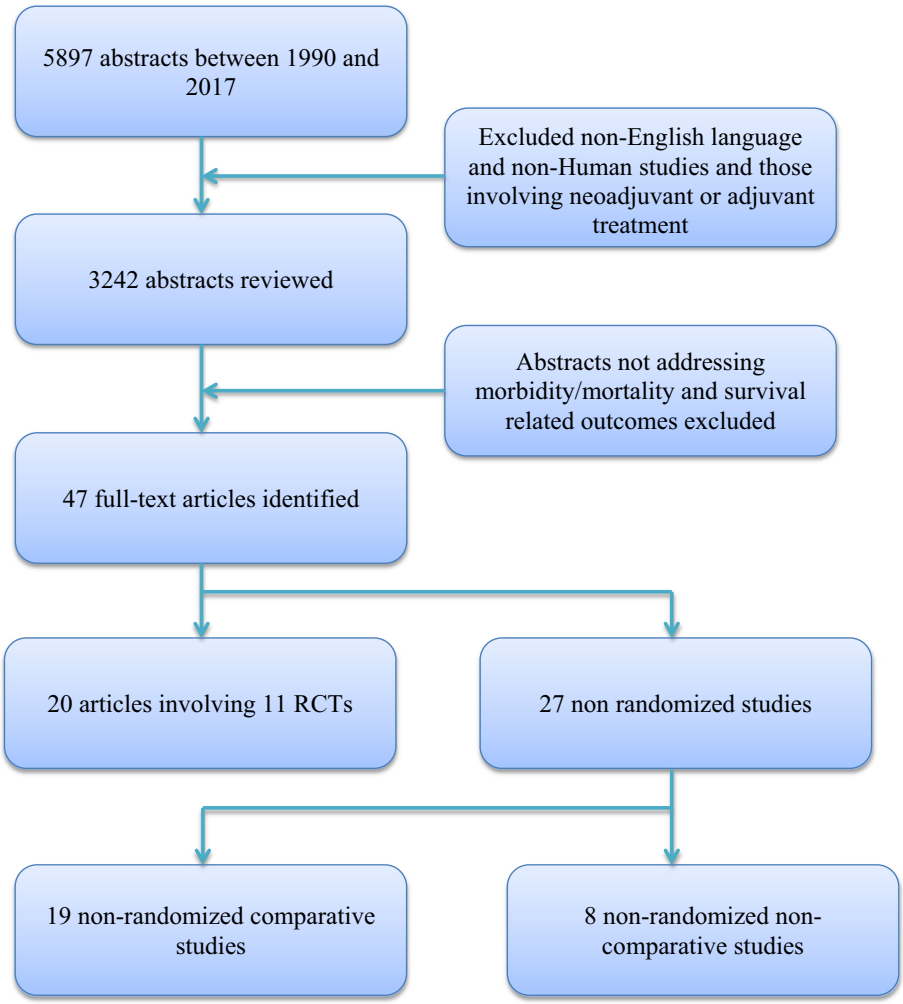

FIG. 2 CONSORT diagram. *CONSORT* Consolidated Standards of Reporting Trials, *RCTs* randomized controlled trials

TABLE 1 Prospective randomized controlled trials comparing limited lymphadenectomy with extended lymphadenectomy

Author/study group/number of patients	Study period	Mean nodes removed	Classification of LN dissection	Median operative time	EBL	Median LOS (days)
MRC ST01/Cuschieri et al.[8]						D1: 14
N = 400						D2: 14
MRC ST01/Cuschieri et al.[9]	1987–1994	D1: **13**	JRSGC 1st English edition/AJCC 4th edition			D1: 14
N = 400		D2: **17**				D2: 14
FINAL analysis						
Dutch gastric cancer trial/Bonenkamp et al.[6]	1989–1990		JRSGC 1st English edition/AJCC 4th edition			R1: **15**
N = 192 (131 curative)						R2: **18**
Dutch gastric cancer trial/Bonenkamp et al.[7]	1989–1993	D1: 18.4	JRSGC 1st English edition/AJCC 4th edition			D1: **18**
N = 996 (711 curative)		D2: 31.5				D2: **25**
Dutch gastric cancer trial/Bonenkamp et al.[40]	1989–1993		JRSGC 1st English edition/AJCC 4th edition			D1: **14**
N = 996 (711 curative)						D2: **16**
Dutch gastric cancer trial/Songun et al.[41]	1989–1993		JRSGC 1st English edition/AJCC 4th edition			D1: 18
N = 737						D2: 25
FINAL analysis						
Italian gastric cancer study group (ISCSG-R01)—interim analysis/Degiuli et al.[42]	1999–2002	D1: 27	JCGC 2nd English edition			D1: 12
		D2: 36.6				D2: 12
N = 162						
Italian Gastric Cancer Study Group (ISCSG-R01)—interim analysis/Degiuli et al.[43]	1998–2005	D1: 28.2	JCGC 2nd English edition			D1: 12.8
		D2: 37.3				D2: 13.1
N = 267						
Italian Gastric Cancer Study Group (ISCSG-R01)/Degiuli et al.[44]	1998–2006	D1: 28	JCGC 2nd English edition			
		D2: 37				
N = 267						
FINAL analysis						
Italian study comparing D2 versus modified D2 (D1 +) dissection/Galizia et al.[39]	2006–2012	D1 + : **19.6**	Japanese gastric cancer treatment guidelines 2010 (ver. 3)			
		D2: **29.6**				
N = 73						
Hong Kong experience comparing R1 subtotal and R3 total gastrectomy for antral cancers/Robertson et al.[45]	1987–1991			R1: **140** min	R1: **300** ml	R1: **8**
				R3: **260** min	R3: **600** ml	R3: **16**
N = 55						
Chilean experience comparing D2 with or without splenectomy/Csendes et al.[46]	1985–1992		JCGC 1st English edition	D2: 208 min		D2: 18.4
				D2 + S: 218 min		D2 + S: 21.6
N = 187						

TABLE 1 continued

Author/study group/number of patients	Study period	Mean nodes removed	Classification of LN dissection	Median operative time	EBL	Median LOS (days)
Taiwanese gastric cancer study/Wu et al.[10]	1993–1999	D1: **19.4**	JCGC 1st	D1: **3.6 h**	D1: **377** ml	D1: **15**
N = 221		D3: **37.2**	English edition	D3: **4.5 h**	D3: **621** ml	D3: **19.6**
Taiwanese gastric cancer study/Wu et al.[11]	1993–1999		JCGC 1st English edition			
N = 221						
Japan Clinical Oncology Group (JCOG9501)/Sano et al.[47]	1995–2001	D2: **54**	JCGC 1st English edition	D2: **237** min	D2: **430** ml	D2: **21**
N = 523		D2 + PAND: **74**		D2 + PAND: **300** min	D2 + PAND: **660**	D2 + PAND: **24**
Japan Clinical Oncology Group (JCOG9501)/	1995–2001		JCGC 1st	D2: **237** min	D2: **430** ml	
Sasako et al.[16]			English edition	D2 + PAND: **300** min	D2 + PAND: **660**	
N = 523						
RCT comparing D3 and D4 gastrectomy/Maeta et al.[48]	1990–1997	D3: **56**	JRSGC, 12th Japanese edition/JCGC 1st edition	D3: **261** min	D3: **536** ml	D3: 38
N = 70		D4: **74**		D4: **298** min	D4: **733** ml	D4: 50
Polish experience. Standard versus extended D2 for gastric cancer/Kulig et al.[49]	1999–2003	D2: **23**	JCGC 2nd English edition	D2: 240	D2: 600 ml	D2: 19.4
N = 275		D2 + : **28**		D2 + : 242.5	D2 + : 600 ml	D2 + : 17.2
East Asia Surgical Oncology Group/Yonemura et al.[50]	1995–2002		JCGC 1st English edition	D2: **273** min	D2: **571** ml	D2: **46**
N = 256				D4: **369** min	D4: **872** ml	D4: **58**
East Asia Surgical Oncology Group/Yonemura et al.[51]	1995–2002	D2: **42.7**	JCGC 1st English edition			
N = 269		D4: **68.7**				

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
MRC ST01/Cuschieri et al.[8]	D1: 28%	D1: **6.5%**	NR		Increased morbidity attributed to pancreas/spleen resection
N = 400	D2: 46%	D2: **13%**			
MRC ST01/Cuschieri et al.[9]	D1: 28%	D1: **6.5%**	D1: 5-year OS 35%		Contamination in D1 and non-compliance in D2 arm
N = 400	D2: 42%	D2: **13%**			Non-pancreas/spleen-preserving D2 dissection
FINAL analysis			D2: 5-year OS 33%		Inadequate surgeon experience with performing D2 dissections
					Increased morbidity attributed to pancreas/spleen resection
					Increased LOS in both D1 and D2 with pancreas/spleen resection

TABLE 1 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Dutch gastric cancer trial/ Bonenkamp et al.[6] *N* = 192 (131 curative)	R1: **36%** R2: **43%**	R1: 4.7% R2: 5.9%	NR		Instruction provided on site by a Japanese surgeon experienced in R dissection, for the first 4 months of the trial No difference in complications between patients operated on by Japanese versus Dutch surgeons Overall increased morbidity attributed to older patients with increased comorbidities and increased obesity among Western patients D2 not recommended
Dutch gastric cancer trial/ Bonenkamp et al.[7] *N* = 996 (711 curative)	D1: **25%** D2: **43%**	D1: **4%** D2: **10%**	NR		Increased morbidity and mortality in the D2 arm persisted in subgroup analysis based on age, sex, ± distal pancreatectomy and splenectomy, blood transfusion and case volume at a single center Overall increased morbidity attributed to older patients with increased comorbidities and increased obesity among Western patients D2 not recommended
Dutch gastric cancer trial/ Bonenkamp et al.[40] *N* = 996 (711 curative)	D1: **25%** D2: **43%**	D1: **4%** D2: **10%**	D1: 45% D2: 47%	D1: 43% D2: 37% RFS for R0 patients	Contamination 6% and 7% in D1 and D2 Non-compliance 36% and 51% in D1 and D2 Splenectomy associated independently with increased morbidity and lower OS in both D1 and D2 arms 30% rate of stage migration in the D2 arm D2 not recommended
Dutch gastric cancer trial/Songun et al.[41] *N* = 737 FINAL analysis	D1: **25%** D2: **43%**	D1: **4%** D2: **10%**	D1: 5-, 11- and 15-year OS 45, 30 and 21%, respectively D2: 5-, 10- and 15-year OS 47, 35 and 29%, respectively	D1: 41 D2: 30 Local recurrence rate	Contamination in D1 and non-compliance in D2 arm Non-pancreas/spleen-preserving D2 dissection Improved OS for D2 versus D1 in TNM stage II patients (33% vs. 15%), N2 disease (19% vs. 0%) and patients not undergoing pancreatosplenectomy (35% vs. 22%) Limited surgeon experience with performing D2 dissections D2 recommended in the setting of pancreas/spleen-preserving dissection
Italian gastric cancer study group (ISCSG-R01)—interim analysis/Degiuli et al.[42] *N* = 162	D1: 10.5% D2: 16.3%	D1: 1.3% D2: 0%	D1: NR D2: NR		Younger patients More early and distal cancers Inclusion of only those surgical teams in which the learning curve for D2 was reached (≥ 25 cases)

TABLE 1 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Italian Gastric Cancer Study Group (ISCSG-R01)—interim analysis/Degiuli et al.[43] *N* = 267	D1: 12.0% D2: 17.9%	D1: 3.0% D2: 2.2%	NR	NR	Spleen and pancreas-preserving D2 dissections 18% contamination in the D1 arm 33.6% non-compliance in the D2 arm
Italian Gastric Cancer Study Group (ISCSG-R01)/Degiuli et al.[44] *N* = 267 FINAL analysis	D1: 12.0% D2: 17.9%	D1: 3.0% D2: 2.2%	D1: 5-year OS 66.4% D2: 5-year OS 65.2	D1: 5-year DSS 71% D2: 5-year DSS 72.6%	Spleen and pancreas-preserving D2 dissections 18% contamination in D1 and 33.6% non-compliance in D2 arm Improved OS in D2 versus D1 (54% vs. 43%) for *N* + tumors Improved DSS in D1 versus D2 (98% vs. 83%) for pT1 tumors Improved DSS in D2 versus D1 for pT2-4 tumors (69% vs. 55%) and *N* + tumors (61% and 46%) For pT2-4 and *N* + tumors, improved 5-year OS (51% and 35%) and DSS (59% and 38%) for D2 versus D1
Italian study comparing D2 versus modified D2 (D1 +) dissection/ Galizia et al.[39] *N* = 73	D1: **19.4%** D2: **48.6%**	D1 + : 0% D2: 5.4%		D1 + : 5-year DFS 42.9% D2: 42.1% 5-year DFS	D1 + , also called modified D2 dissection, includes D1 nodes plus the extraperigastric nodal stations 8a, 9, and 11p Almost all patients received 5-fluorouracil-based adjuvant chemotherapy No difference in the rate or pattern of recurrence—locoregional recurrence 58.3 in D1 + and 60% in D2 No DFS difference in patients with N2 disease Metastases to stations 10, 11d, and 12a show 0% DFS at 5-years by using the IEBLD, therefore likely no DFS benefit of removing these nodes (as in D2 dissection) Removal of stations 8a, 9, and 11p (included in a D1 + dissection) had a 10% benefit using IEBLD analysis
Hong Kong experience comparing R1 subtotal and R3 total gastrectomy for antral cancers/ Robertson et al.[45] *N* = 55	R1: **0%** R3: **46.6%**	R1: 0% R3: 3.2%	R1: 5-year OS 72% (**median OS 1511 days**) R3: 5-year OS 53.3% (**median OS 922 days**)		R3 involved routine distal pancreatectomy and splenectomy All tumors were located in the antrum; R1 was performed with subtotal and R3 was performed with total gastrectomy
Chilean experience comparing D2 with or without splenectomy/ Csendes et al.[46] *N* = 187	Septic complications higher for D2 + s versus D1 patients	D2: 3.1% D2 + S: 4.4%	D2: 5-year OS 36% D2 + S: 5-year OS 42%		No difference in survival for early- or late-stage tumors on subgroup analysis, except stage IIIB where survival was improved with D2 + S

TABLE 1 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Taiwanese gastric cancer study/ Wu et al.[10] *N* = 221	D1: 7.3% D3: 17.1%	D1: 0% D3: 0%			D3, defined as per the JCGC 1st edition, included N2 and N3 nodes, which is equivalent to D2 per the JCGC 2nd edition Extensive experience of surgeons with D3 dissection
Taiwanese gastric cancer study/ Wu et al.[11] *N* = 221	D1: 7.3% D3: 17.1%	D1: 0% D3: 0%	D1: 5-year OS **53.6%** D3: 5-year OS **59.5%**	D1: **5-year DSS 58.5% for R0** D3: **5-year DSS 64.9% for R0**	D3, defined as per the JCGC 1st edition, included N2 and N3 nodes, which is equivalent to D2 per the JCGC 2nd edition Extensive experience of surgeons with D3 dissection MV analyses showed that nodal disease, tumor involving the entire stomach, Borrmann type III and IV, and allocation to D1 arm were associated with poor survival
Japan Clinical Oncology Group (JCOG9501)/Sano et al.[47] *N* = 523	D2: 20.9% D2 + PAND: 28.1	D2: 0.8% D2 + PAND: 0.8%			Only tumors deeper than T2 subserosal were included Strict quality control of surgeon participation High-volume centers Routine pancreatectomy avoided Splenectomy only routinely used for proximal tumors
Japan Clinical Oncology Group (JCOG9501)/ Sasako et al.[16] *N* = 523	D2: 20.9% D2 + PAND: 28.1	D2: 0.8% D2 + PAND: 0.8%	D2: 5-year OS 69.2% D2 + PAND: 5-year OS 70.3%	D2: 5-year RFS 62.6% D2 + PAND: 5-year RFS 61.7%	For node-negative patients, the 5-year OS rate was **78.4%** in D2 versus **96.8%** in D2 + PAND For node-positive patients, the 5-year OS was 65.2% in D2 versus 54.9% in D2 + PAND The above paradoxical findings may have resulted from multiple testing on post hoc subgroup analysis Similar pattern of recurrence in patients receiving D2 or D2 + PAND Pattern of recurrence similar in both arms
RCT comparing D3 and D4 gastrectomy/Maeta et al.[48] *N* = 70	D3: 26% D4: 40%	D3: 1% D4: 1%	No difference in survival between the D3 and D4 arms, although the sample size was too small to detect a difference of 15% in survival, with a p value < 0.05		Only patients with T3 or T4 tumors undergoing total gastrectomy were included D3 defined as D2 + removal of nodes in the hepatoduodenal ligament, In the retropancreatic space and along the vessels of transverse mesocolon D4 defined as D3 + removal of LNs around the abdominal aorta (no. 16 nodes) Authors advocate D4 dissection in selected cases with N2 or N3 involvement

TABLE 1 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Polish experience. Standard versus extended D2 for gastric cancer/ Kulig et al.[49] *N* = 275	D2: 27.7% D2 + : 21.6%	D2: 4.9% D2 + : 2.2%	NR		D2 + defined as D2 with para-aortic LN dissection
East Asia Surgical Oncology Group/Yonemura et al.[50] *N* = 256	D2: **26%** D4: **39%**	D2: 0.8% D4: 3.9%			Strict quality control of participating surgeons D4 defined as D2 + para-aortic node (16a2 and 16b1) dissection No contamination or non-compliance
East Asia Surgical Oncology Group/Yonemura et al.[51] *N* = 269			D2: 5-year OS 52.6% D4: 5-year OS 55%		Recurrence rate similar between the D2 and D4 groups (46.7% and 38.8%)

EBL estimated blood loss, *LOS* length of stay, *OS* overall survival, *DSS* disease-specific survival, *RFS* recurrence-free survival, *JRSGC* Japanese Research Society for Gastric Cancer, *JCGC* Japanese Classification of Gastric Cancer, *NR* not reported, *IEBLD* index of estimated benefit from lymph node dissection, *LN* lymph node, *DFS* disease-free survival, *RCT* randomized controlled trial, *AJCC* American Joint Committee on Cancer, *MRC* Medical Research Council, *PAND* para-aortic lymphadenectomy, *MV* multivariate

Numbers in bold indicate significant values

D4 defined as D3 + removal of lymph nodes around the abdominal aorta (no. 16 nodes)

and N2 disease (19% vs. 0%), leading investigators to recommend D2 as the standard procedure if performed by experienced surgeons and when a spleen- and pancreas-sparing technique was used to dissect nodes around the splenic hilum.[41] In order to circumvent the issue of quality control, the Italian Gastric Cancer Study Group conducted a phase II prospective study in 191 patients and demonstrated that by using a spleen/pancreas-sparing operation performed by surgeons who had reached their learning curve for D2 lymphadenectomy, morbidity/mortality and survival outcomes similar to Eastern series could be achieved.[78,79] This study provided the background for a prospective multicenter RCT initiated by the same group. Long-term analysis showed that although there was no OS advantage between the D1 and D2 arms (66% vs. 65%), disease-specific survival was significantly improved for patients with advanced tumors (T2-4 and node-positive) undergoing D2 lymphadenectomy.[44]

Many retrospective studies have demonstrated improved survival with D2 dissection in patients with higher *T*- and *N*-stage tumors.[53,56–59,62] Whether the improved survival observed in these studies was a result of stage migration (secondary to higher lymph node retrieval for D2 patients) or because of clearance of micrometastatic disease in clinically and pathologically negative nodes is unknown. However, the majority of authors believe that D2 dissection is the recommended procedure in patients with T2-4 disease or *N*+ patients when performed by experienced surgeons and when avoiding routine removal of the distal pancreas and spleen.

Role of Splenectomy

Whether the spleen should routinely be removed in order to improve oncological outcomes, even if this can be performed with relatively low perioperative mortality, has been addressed by two prospective randomized clinical trials from Korea and Chile.[46,80] Both of these studies showed no significant improvement in survival for routine splenectomy in node-negative patients, and only a marginal benefit was noted for stage IIIB patients in the Chilean study. In their study of 73 patients, Galizia et al.[39] demonstrated that using a modified D2 dissection, also called a D1 + dissection, routine dissection of 10, 11d, and 12a can be avoided, with similar oncological outcomes and reduced morbidity, compared with standard D2 dissections, in patients with advanced node-positive, non-junctional gastric carcinomas. However, the study was limited by the small number of patients and resulting low statistical power. A randomized trial by the JCOG study compared splenectomy and spleen preservation in patients with proximal gastric adenocarcinoma of T2-4/N0-2/M0 not invading the greater curvature.[81] Splenectomy was

TABLE 2 Prospective/retrospective comparative studies comparing limited and extended lymphadenectomy

Author/study group/number of patients	Study period	Mean nodes removed	Classification of LN dissection	Median operative time	EBL	Median LOS (days)
Kaibara et al.[52]	1966–1985		JRSGC 1st English edition			
N = 345						
Pacelli et al.[53]	1981–1990	R1: **12.4**	JRSGC 1st English edition	R1: **220** min	R1:	R1:
N = 320		R2/3: **37**		R2/R3: **269** min	R2/R3:	R2/R3:
Siewert et al. (prospective multicenter study)[54]	1986–1989		JRSGC 1st English edition			
N = 1654						
Roukos et al. (retrospective study)[55]	1979–1986		JRSGC 1st English edition			
N = 74						
Volpe et al. (retrospective analysis)[56]	1975–1990		JRSGC 1st English edition			
N = 101						
Harrison et al. (retrospective analysis)[57]	1985–1995	D1: **12**	JRSGC 1st English edition			D1: 14 days
N = 247		D2: **22**				D2: 14 days
Onate-Ocana et al. (retrospective analysis)[58]	1987–1998	D1: **16.8**	JRSGC 1st English edition		D1: 808 ml	
N = 219		D2: **23.6**			D2: 674 ml	
Kasakura et al. (retrospective)[59]	1980–1997					D1: **24.6**
N = 1403						D2: **26.3**
Gunji et al. (retrospective analysis)[60]	1987–1997		JRSGC 1st English edition			D2: 27.9%
N = 436						D3/4: 22.2%
Sierra et al. (retrospective)[61] *N* = 156	1990–1998	D1: **14**	JRSGC 1st English edition	D1: **187.7** min		D1: 12.1
		D2: **31**		D2: **202.9** min		D2: 13.1
Edwards et al. (prospective comparison)[62]	1996–2002	D1: **8**	JRSGC 1st English edition			
N = 118		D2: **15**				
Bostanci et al. (retrospective)[63]	1999–2002	**D2: 28.6**	JCGC 2nd English edition	D2: **240** min		D2: **8.8**
N = 134		**D3: 36.2**		D3: **330** min		D3: **11.6**
Kunisaki et al. (retrospective)[64]	1992–2000		JCGC 2nd English edition	D2: **224** min	**D2: 479** ml	
N = 580				D3: **455** min	**D3: 485** ml	
Marrelli et al. (retrospective)[65] *N* = 330	1994–2005	**D2: 36**	JCGC 2nd English edition			D2: 15
		D3: 53				D3: 13
Hu et al. (retrospective)[66]	2001–2003	D2: 15.7	JCGC 2nd English edition	D2: **206.1**		D2: 9.4
N = 117		D2 + PAND: 26.1		D2 + PAND: **316.6**		D2 + PAND: 12.1
Zhang and Tian (retrospective)[67]	1990–2007		JRSGC 1st English edition	D2: 157 min		**D2: 17**
N = 1792				D2 + PAND: 161 min		**D2 + PAND: 19**

TABLE 2 continued

Author/study group/number of patients	Study period	Mean nodes removed	Classification of LN dissection	Median operative time	EBL	Median LOS (days)
Zhang and Tian (retrospective)[68]	1980–2003	D1: 21	JRSGC 1st English edition			
N = 567		D2: 23				
		D3: 26				
Eom et al. (retrospective)[69]	2001–2006	D2: **47.7**	JCGC 2nd English edition	D2: **212.4** min		
N = 527		D2 + 13D: **57**		D2 + 13D: **259.3** min		
Eom et al. (retrospective)[70]	2001–2007	D2: **43.6**	JCGC 2nd English edition	D2: **208.2** min		D2: **10.5**
N = 1661		D2 + 14v: **52.7**		D2 + 14v: **232.6** min		D2 + 14v: **9.9**

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Kaibara et al.[52]			R2: 5-year OS 48.8%		R2 defined as dissection of group 2 nodes, and R3 defined as dissection of group 3 nodes
N = 345			R3: 5-year OS 50.3%		R3 patients with isolated metastases to hepatoduodenal group 3 nodes had better OS than those with metastases to other group 3 nodes
Pacelli et al.[53]	R1: 22.3%	R1: 3.8%	R1: **5-year OS 50.1%**		R1 included limited lymphadenectomy whereas R2/R3 comprised extensive lymphadenectomy
N = 320	R2/R3: 28.2%	R2/R3: 7.4%	R2/R3: **5-year OS 65.4%**		Survival significantly improved for stage III patients (29.8% for R2/3 versus 48.7% for R2/R3 patients)
					Extent of nodal dissection an independent prognostic factor on MV analysis
Siewert et al. (prospective multicenter study)[54]	R1: 29.0%	R1: 5.2%			Standard dissection (R1) defined as removal of $\leq$ 25 nodes, and radical dissection (R2) defined as removal of $>$ 25 nodes
	R2: 30.6%	R2: 5%			
N = 1654					Radical resection resulted in improved survival for stage II and IIIA patients
Roukos et al. (retrospective study)[55]	D1: 19%	D1: 3.2%	D1: 5-year OS 58%		Comparison of patients with antral cancer undergoing total gastrectomy + D2 or subtotal gastrectomy + D1
	D2: 37%	D2: 7%	D2: 5-year OS 66%		
N = 74					Most complications in the D2 arm resulted from leakage at the esophagojejunal anastomosis
Volpe et al. (retrospective analysis)[56]			D1: 5-year OS 27%		D1 group included both D1 and D1.5
			D2: 5-year OS 49%		D2 group included both D2 and D2.5
N = 101					5-year survival rate for D2 patients with N2 disease was 31%
					Extent of dissection an independent prognostic indicator

TABLE 2 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Harrison et al. (retrospective analysis)[57] *N* = 247		D1: 3.2% D2: 3.2%	No difference in 5-year survival between D1 and D2 for the entire cohort of node-negative patients		Study included only node-negative patients, to examine the effect of the extent of lymphadenectomy in patients with occult metastases For T3N0 patients, 5-year survival significantly improved with D2 versus D1 (54% vs. 39%)
Onate-Ocana et al. (retrospective analysis)[58] *N* = 219	D1: 16.9% D2: 19.5%	D1: 6.8% D2: 8.6%	D1: 5-year OS 35% D2: 5-year OS 64%		D2 node dissection was found to be an independent determinant of OS on MV analysis Pancreatosplenectomy found to be an independent determinant of operative morbidity
Kasakura et al. (retrospective)[59] *N* = 1403	D1: **13.8%** D2: **19.6%**	D1: 1.4% D2: 1.2%	No difference in OS between both groups		Improved OS with D2 dissection in T1, T2, N1, N3, and stage II tumors
Gunji et al. (retrospective analysis)[60] *N* = 436		D2: 2.7% D3: 2.0%	D2: 5-year OS 45.3% D3/4: 5-year OS 51.5%		D3/4 dissections performed only for grossly N2-positive tumors 5-year OS improved in D3/4 only for stage IIIb patients (otherwise similar for all *T* and *N* stages)
Sierra et al. (retrospective)[61] *N* = 156	D1: 48.2% D2: 53.5%	D1: 2.3% D2: 0%	D1: 5-year DSS 50.6% D2: 5-year DSS 44.4%		TNM stage, metastatic LN ratio and type of dissection independent determinants of OS on MV analysis
Edwards et al. (prospective comparison)[62] *N* = 118	D1: 25% D2: 23%	D1: 8.3% D2: 7.3%	D1: 5-year OS 32 D2: 5-year OS 59%		D2 routinely involved pancreas/spleen preservation *T*, *N* stage and extent of lymphadenectomy independent predictors of survival on MV analysis 5-year OS significantly improved in stage III cancers for D2 (33% vs. 8%)
Bostanci et al. (retrospective)[63] *N* = 134	D2: **10%** D3: **35.3%**	D2: **1%** D3: **8%**			Maruyama computer program used to prospectively assess candidates for extended lymphadenectomy—D3 performed in those with likelihood of N3-positive nodes > 10%
Kunisaki et al. (retrospective)[64] *N* = 580		D2: 0.23% D3: 0.67%	D2: 5-year OS 56% D3: 5-year OS 50.4% D2: 5 year DSS 58.8% D3: 5-year DSS 54%	No significant difference in the rate or pattern of recurrence between D2 and D3	D3 defined as superextended/para-aortic lymphadenectomy D3 performed on T2 patients with subserosal invasion Extent of lymphadenectomy not an independent determinant of prognosis on MV analysis Significant difference in DSS in favor of D3 for patients with T measuring 50–100 mm or pN1 Within T 50–100 mm subgroup, significant DSS difference in favor of D3 noted for pN2 No survival benefit for pN0, T < 50 mm, high N stage or T > 100 mm Age > 70 years an independent poor prognostic variable

TABLE 2 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Marrelli et al. (retrospective)[65]	D2: 35%	D2: 4%			D3 dissections included D2 + para-aortic LN
N = 330	D3: 30%	D3: 4%			D3 performed in patients < 75 years of age with cT2-4 tumors
					Spleen/pancreas preservation
					Low albumin and splenectomy ± pancreatectomy were independently associated with morbidity
					Low albumin and age > 75 years were independently associated with mortality
Hu et al. (retrospective)[66]	D2: 27.3%		D2 + PAND: 24.2%	D1: 1.8%	D2: 5-year OS 66.1%
N = 117				D2 + PAND: 0%	D2 + PAND: 5-year OS 65.8%
Higher incidence of PAN metastases in 8a and 9 node-positive patients					
No difference in survivals based on overall TNM and T stage					
Zhang and Tian (retrospective)[67]	D2: 9%		D2 + PAND: 9%	D2: 2%	D2: 5-year OS 26.6%
N = 1792				D2 + PAND: 2%	D2 + PAND: 5-year OS 31.2%
Improved outcomes of D2 for T1 tumors					
Improved outcome for D2 + PAND in T3-4 and N2					
Zhang and Tian (retrospective)[68]	D1: 14%	D1: 1.6	D1: 5-year OS 37.4%; 10-year OS 29%		D3 defined as D2 + nodes in the hepatoduodenal ligament, posterior aspect of the head of the pancreas, and at the root of the mesentery
N = 567	D2: 13%	D2: 0.5			
	D3: 13%	D3: 3.1	D3: 5-year OS 47.8%; 10-year 33.7%		No significant difference in OS between the D1 and D2 groups
					Improved survival for D1 in N3 patients, and for D3 in N0/1 patients (likely false positive from multiple testing on post hoc subgroup analysis)
Eom et al. (retrospective)[69]	D2: 22.7				Patients with resectable middle- and lower-third tumors
N = 527	D2 + 13D: 21.5				13D defined as retropancreatic nodes (group 3 per JCGC 2nd edition)
					Improved survival in stage III/IV patients with D2 + 13D which remained significant on MV analysis

TABLE 2 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Eom et al. (retrospective)[70]	D2: 15.4%	D2: 2%			Patients with resectable middle- and lower-third tumors
N = 1661	D2 + 14v: 15.1%	D2 + 14v: 0%			14v defined as nodes along the superior mesenteric vein (classified as group 2 for lower-third tumors and group 3 for middle-third tumors)
					Higher incidence of locoregional recurrence in the D2-only arm
					Better OS for group III/IV patients in the D2 + 14v arm

EBL estimated blood loss, *LOS* length of stay, *OS* overall survival, *DSS* disease-specific survival, *RFS* recurrence-free survival, *JRSGC* Japanese Research Society for Gastric Cancer, *JCGC* Japanese Classification of Gastric Cancer, *LN* lymph node, *PAND* para-aortic lymphadenectomy, *PAN* para-aortic node, *MV* multivariate

Numbers in bold indicate significant values

associated with higher morbidity and increased blood loss, with no effect on 5-year survival. Routine splenectomy should therefore only be considered for potentially curable T2–T4 tumors invading the greater curvature of the proximal stomach.[15]

Learning Curve for D2 Gastrectomy

Several studies have suggested that gastrectomy with D2 is a complex procedure that is accompanied by a significant learning curve, and that the quality of surgery and lymph node retrieval directly affects outcomes.[82,83] In their study of 2797 patients treated at a single high-volume institution in South Korea, Jang et al.[84] demonstrated that node retrieval and OS of patients improved with institutional experience over time and that surgeon subspecialty association with gastric cancer was an independent predictor of improved outcomes. Most studies, including the Italian Gastric Cancer Collaborative, suggest a learning curve of approximately 15–25 cases or between 8 and 24 months in establishing a plateau, at which point a D2 gastrectomy can be accomplished with reasonable morbidity and mortality.[42,82,85] Similarly, improved quality of surgery, as judged by the adequacy of node retrieval, is affected by cancer center recognition and can indirectly impact outcomes.[86]

Role of Adjuvant Treatment After D1/D2 Lymphadenectomy

While the role of lymphadenectomy in the management of patients with locally advanced, node-positive disease has been established in large-scale RCTs and non-randomized comparative studies, the benefit of adjuvant therapies in regional nodal control in the setting of lymphadenectomy continues to evolve. INT-0116 was an early randomized clinical trial aimed at defining the role of postoperative chemoradiation (CRT) in improving outcomes for patients with resected gastric cancer.[87] In that trial, patients randomized to the surgery plus CRT arm showed improved OS and a decreased recurrence rate compared with patients randomized to the surgery-only arm. However, the trial was heavily criticized for the lack of surgical quality control since only 10% of patients underwent a D2 dissection, and subgroup analysis of these patients showed no survival benefit in the CRT plus surgery arm.[88] Thus, the OS and local control benefit observed in the CRT arm was attributed to the compensatory effect of adding radiation to surgically inadequately treated patients. Western surgeons, especially in the US, have used this study as a rationale for routine postoperative CRT in patients undergoing surgery with limited lymphadenectomy. However, Eastern surgeons have criticized this standard of care, citing equivalent outcomes with a well-performed D2

TABLE 3 Prospective/retrospective non-comparative studies of limited and extended lymphadenectomy

Author/study group/number of patients	Study period	Mean nodes removed	Classification of LN dissection	Median operative time	EBL	Median LOS (days)
Jatzko et al. (retrospective)[71] *N* = 345	1984–1994	26	JRSGC 1st English edition	199 min		
Adachi et al. (retrospective)[72] *N* = 214	1975–1990		JRSGC 1st English edition	**204** min in patients without complications **227** min in patients with complications	671 ml in patients without complications 700 ml in patients with complications	29
Italian Gastric Cancer Study Group/Degiuli et al. (prospective)[73] *N* = 191	1994–1996		JRSGC 1st English edition			
Nitti et al. (retrospective)[74] *N* = 119	1980–2001	24.7	JCGC 2nd English edition			
Biffi et al. (prospective)[75] *N* = 250	1994–2002		JCGC 1st and 2nd English editions			14.8
Kosaka et al. (retrospective)[76] *N* = 244	1991–2004		JCGC 2nd English edition			
Roviello et al. (retrospective)[77] *N* = 254	1993–2006	45	JCGC 2nd English edition			
Tokunaga et al. (retrospective)[38] *N* = 178	1980–2004		JCGC 2nd English edition			

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Jatzko et al. (retrospective)[71] *N* = 345	177.1 in R0 resection	4.9% in R0 resection	5-year OS 51.9% for R0 10-year OS 36.0% for R0	5-year DSS 57.7% for R0 10-year DSS 44.3% for R0	D3 dissection (as defined by the JRSGC 1st English edition) Age > 65 years, increasing pT and pN stage, and total gastrectomy identified as independent predictors of poor OS on MV analysis
Adachi et al. (retrospective)[72] *N* = 214	36%	0%			D2/D3 dissection for node-positive cancers, as defined in the JRSGC 1st English edition Increased morbidity with total gastrectomy and splenectomy No difference in morbidity between the D2/D3 arms
Italian Gastric Cancer Study Group/Degiuli et al. (prospective)[73] *N* = 191	20.9%	3.1%	5-year OS 55%	5-year DSS 65%	Experienced surgeons who attained the learning curve for D2 dissection Spleen and pancreas-preserving technique used

TABLE 3 continued

Author/study group/number of patients	Operative morbidity	Operative mortality	OS	DSS/RFS	Comments/important findings
Nitti et al. (retrospective)[74]			5-year OS 85.4%		D2 dissection for early gastric cancers (T1 tumors)
N = 119					5-year OS 85.9% for N0 patients and 83.0% for *N* + patients
					No change in the number of metastatic nodes, with an increase in the number of examined lymph nodes
					2.5% survival benefit to D2 dissection
					Majority of recurrences were distant
Biffi et al. (prospective)[75]	18%	1.2%			Spleen and pancreas-preserving D2 dissection performed by two experienced surgeons
N = 250					
Kosaka et al. (retrospective)[76]	35.6%	2.4%	5-year OS 28% for clinically PAN-negative patients and 5% for clinically PAN-positive patients		Para-aortic LN dissection included D2 + 16a2 and 16b1
N = 244					Mortality predicted by increasing age and postoperative complications
					Morbidity predicted by comorbidities, extent of surgery and positive distal margin
					27.5% incidence of PAN metastases
					Increasing rate of PAN metastases with increasing T stage
Roviello et al. (retrospective)[77]	28%	2.1%	5-year OS 52.2%		Advanced gastric cancers with R0 resection and D3 + PAND
N = 254					Dissection of PAN station 16a2 and 16b1 performed
					12.9% incidence of PAN metastases
					No increase in PAN involvement noted with increasing *T* stage
					Poorer survival with increasing *N* stage
					Long-term survival possible in a small group of PAN-positive patients
Tokunaga et al. (retrospective)[38]	30%	2%	5-year OS 13%		PAND for PAN-positive patients included D2 + 16a2 and 16b1
N = 178					5-year OS increased to 19.0% in those with macroscopically negative nodes, and to 28.6% in patients with $\leq$ 15 positive nodes

EBL estimated blood loss, *LOS* length of stay, *OS* overall survival, *DSS* disease-specific survival, *RFS* recurrence-free survival, *JRSGC* Japanese Research Society for Gastric Cancer, *JCGC* Japanese Classification of Gastric Cancer, *PAND* para-aortic lymphadenectomy, *PAN* para-aortic node, *MV* multivariate

Numbers in bold indicate significant values

lymphadenectomy with no added morbidity, and simultaneously avoiding the added morbidity and cost of CRT.[89] This differential treatment paradigm is also reflected in more recent trials of adjuvant CRT in the West, such as the Cancer and Leukemia Group B (CALGB) 80101 RCT, which compared 5-fluorouracil plus leucovorin with epirubicin, cisplatin, and 5-fluorouracil (ECF) to assess which chemotherapeutic regimen combined with radiation would yield better outcomes after gastrectomy with D0/D1/D2 lymphadenectomy. Overall, there was no difference in OS and disease-free survival (DFS) between study arms, including within any specific patient subgroup, based on the number of nodes retrieved. However, only 55% of patients in this trial had $\geq$ 15 nodes, with no comparisons made between different nodal subgroups within each arm.[90] The ARTIST (Adjuvant Chemoradiation Therapy in Stomach Cancer) trial randomized patients with gastric cancer who received gastrectomy with D2 lymph node dissection to either postoperative chemotherapy or postoperative chemotherapy with CRT, and observed no significant benefit with the addition of radiotherapy to adjuvant capecitabine and cisplatin compared with capecitabine and cisplatin alone after resection of gastric cancer with D2-lymphadenectomy.[91] With 7 years of follow-up, OS (hazard ratio [HR] 0.740, 95% confidence interval [CI] 0.520–1.050; $p = 0.0922$) and DFS (HR 1.130, 95% CI 0.775–1.647; $p = 0.5272$]) remained similar between treatment arms. However, post hoc subgroup analyses showed that chemoradiotherapy significantly improved DFS in patients with node-positive disease. Whether there is selective benefit of adjuvant CRT in node-positive patients after an adequate D2 dissection is currently being studied in the prospective ARTIST-2 RCT (ClinicalTrials.gov identifier: NCT0176146). Similarly, the Dutch Gastric Cancer Group recently reported on the CRITICS trial, which compared postoperative CRT with preoperative chemotherapy versus perioperative chemotherapy in resected patients with gastric cancer.[92] Surgical quality in this study was good, with a median lymph node yield of 20, with 89% of patients undergoing at least a D1 + dissection, an R0 resection rate of at least 81%, and an MI of 1. OS was not improved with the addition of CRT to preoperative chemotherapy. At a median follow-up of 61.4 months, median OS was 43 months in the chemotherapy group and 37 months in the chemoradiotherapy group (HR 1.01, 95% CI 0.84–1.22; $p = 0.90$).[92] Given the lack of benefit of adjuvant therapies in patients undergoing adequate nodal dissection, the CRITICS II trial is currently comparing neoadjuvant strategies (chemotherapy vs. chemotherapy followed by CRT vs. CRT) to assess the benefit of these adjunct therapies when administered upfront. Contrary to this, in the East, adjuvant radiation is routinely avoided. Additionally, chemotherapy after D2 lymphadenectomy has only recently been adopted as standard of care for adjuvant treatment of stage II/III gastric cancer after the results of the ACTS-GC Japanese RCT comparing surgery alone with surgery and adjuvant chemotherapy using *S*-1, which demonstrated that there was a significant survival benefit to adjuvant chemotherapy (3-year OS 80.1% vs. 70.1%, and HR for death 0.68, 95% CI 0.52–0.87; $p = 0.003$).[93] The Korean phase III CLASSIC study reported a significant benefit in DFS with adjuvant combination chemotherapy versus observation in stage II–IIIb gastric cancer after curative D2 gastrectomy.[94] Thus, while perioperative chemotherapy is standard in patients undergoing curative gastrectomy with D2 lymphadenectomy, the role of adjuvant/neoadjuvant CRT continues to evolve, with potential benefit noted in node-positive patients.

D1/D2 Versus Para-Aortic Lymph Node Dissection

The JCOG 9501 trial randomized patients to D2 versus D2 with para-aortic lymphadenectomy (PAND). While operative times (300 vs. 237 min; $p < 0.001$), blood loss (660 ml vs. 430 ml; $p < 0.001$), and minor complications (20.0% vs. 9.1%; $p < 0.001$) were significantly higher in the PAND plus D2 arm versus the D2-only arm, there was no OS (HR 1.03, 95% CI 0.77–1.37; $p = 0.85$]) or recurrence-free survival (HR 1.08, 95% CI 0.83–1.42; $p = 0.56$]) benefit. Five-year OS was 69.2% in the D2 lymphadenectomy arm versus 70.3% in the D2 plus PAND arm. In fact, the pattern of relapse was similar in both arms and PAND did not prevent recurrence in the regional nodes.[16,47] Two studies by Yonemura et al.[50,51] from the East Asia Oncology group showed similar findings, with no improvement in oncological outcomes. However, some retrospective studies suggest a small benefit for PAND in clinically or macroscopically node-negative patients, with a possibility of long-term survival.[38, 76,77] Yet others have investigated the utility of adding dissection of only 13D (retropancreatic) or 14v (superior mesenteric) nodes, which likely act as 'gate-keepers' to the para-aortic nodes. When performed by experienced surgeons, additional 13D and 14v dissections achieved modest survival benefit compared with D2-only dissections in patients with advanced stage middle- and lower-third tumors, with no added morbidity or mortality risk.[69,70]

Overall, although D3 and PAND may be performed relatively safely by surgeons experienced in super-extended lymphadenectomy, the oncological benefit is negligible and is limited to an extremely small subset of patients. With improvements in adjuvant systemic therapy options, this could change; however, based on available data, it should not be routinely recommended.

CONCLUSIONS

A D2 dissection without routine distal pancreatectomy and splenectomy should be considered the standard approach for all patients with resectable gastric carcinoma, and can be carried out safely provided it is performed by surgeons with sufficient experience in the conduct of this surgery. In patients with T1 tumors, advanced age, poor functional status, or multiple comorbidities, D1 dissections may be considered on an individual basis when the treating physicians feel that the increased morbidity of D2 lymph node dissection may outweigh the potential benefit of an extended lymph node dissection. Extended para-aortic node dissections (D3 and beyond) are not associated with survival benefit and should be performed selectively. While perioperative chemotherapy should be considered standard in patients undergoing curative gastrectomy with D2 lymphadenectomy, the role of CRT continues to be defined, with potential benefit in node-positive patients.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer.* 2015;136(5):E359–86.
2. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomark Prev.* 2010;19(8):1893–907.
3. Schmidt B, Yoon SS. D1 versus D2 lymphadenectomy for gastric cancer. *J Surg Oncol.* 2013;107(3):259–64.
4. Sano T, Aiko T. New Japanese classifications and treatment guidelines for gastric cancer: revision concepts and major revised points. *Gastric Cancer.* 2011;14(2):97–100.
5. Japanese Gastric Cancer Association. Japanese Classification of Gastric Carcinoma—2nd English Edition. *Gastric Cancer.* 1998;1(1):10–24.
6. Bonenkamp JJ, van de Velde CJ, Sasako M, Hermans J. R2 compared with R1 resection for gastric cancer: morbidity and mortality in a prospective, randomised trial. *Eur J Surg.* 1992;158(8):413–8.
7. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. *Lancet.* 1995;345(8952):745–8.
8. Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. *Lancet.* 1996;347(9007):995–9.
9. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. *Br J Cancer.* 1999;79(9–10):1522–30.
10. Wu CW, Hsiung CA, Lo SS, Hsieh MC, Shia LT, Whang-Peng J. Randomized clinical trial of morbidity after D1 and D3 surgery for gastric cancer. *Br J Surg.* 2004;91(3):283–7.
11. Wu CW, Hsiung CA, Lo SS, et al. Nodal dissection for patients with gastric cancer: a randomised controlled trial. *Lancet Oncol.* 2006;7(4):309–15.
12. Sasako M, McCulloch P, Kinoshita T, Maruyama K. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg.* 1995;82(3):346–51.
13. Edge SB, Byrd DR, Compton CC. AJCC cancer staging manual. 7th ed. New York: Springer; 2010.
14. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer.* 2011;14(2):101–12.
15. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer.* 2011;14(2):113–23.
16. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med.* 2008;359(5):453–62.
17. Amin MB, ed. AJCC cancer staging manual. 8th ed. Berlin: Spinger; 2018.
18. Kampschoer GH, Maruyama K, van de Velde CJ, Sasako M, Kinoshita T, Okabayashi K. Computer analysis in making preoperative decisions: a rational approach to lymph node dissection in gastric cancer patients. *Br J Surg.* 1989;76(9):905–8.
19. Hundahl SA, Macdonald JS, Benedetti J, Fitzsimmons T. Surgical treatment variation in a prospective, randomized trial of chemoradiotherapy in gastric cancer: the effect of undertreatment. *Ann Surg Oncol.* 2002;9(3):278–86.
20. Peeters KC, Hundahl SA, Kranenbarg EK, Hartgrink H, van de Velde CJ. Low Maruyama index surgery for gastric cancer: blinded reanalysis of the Dutch D1–D2 trial. *World J Surg.* 2005;29(12):1576–84.
21. Douglass HO Jr, Hundahl SA, Macdonald JS, Khatri VP. Gastric cancer: D2 dissection or low Maruyama Index-based surgery—a debate. *Surg Oncol Clin N Am.* 2007;16(1):133–55.
22. Bouvier AM, Haas O, Piard F, Roignot P, Bonithon-Kopp C, Faivre J. How many nodes must be examined to accurately stage gastric carcinomas? Results from a population based study. *Cancer.* 2002;94(11):2862–6.
23. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. *J Clin Oncol.* 2005;23(28):7114–24.
24. Cozzaglio L, Doci R, Celotti S, Roncalli M, Gennari L. Gastric cancer: extent of lymph node dissection and requirements for a correct staging. *Tumori.* 2004;90(5):467–72.
25. Shen JY, Kim S, Cheong JH, et al. The impact of total retrieved lymph nodes on staging and survival of patients with pT3 gastric cancer. *Cancer.* 2007;110(4):745–51.
26. Liu C, Lu Y, Jun Z, et al. Impact of total retrieved lymph nodes on staging and survival of patients with gastric cancer invading the subserosa. *Surg Oncol.* 2009;18(4):379–84.
27. Son T, Hyung WJ, Lee JH, et al. Clinical implication of an insufficient number of examined lymph nodes after curative resection for gastric cancer. *Cancer.* 2012;118(19):4687–93.
28. Deng J, Zhang R, Pan Y, et al. Comparison of the staging of regional lymph nodes using the sixth and seventh editions of the tumor-node-metastasis (TNM) classification system for the evaluation of overall survival in gastric cancer patients: findings of a case-control analysis involving a single institution in China. *Surgery.* 2014;156(1):64–74.
29. Kong SH, Lee HJ, Ahn HS, et al. Stage migration effect on survival in gastric cancer surgery with extended lymphadenectomy: the reappraisal of positive lymph node ratio as a proper N-staging. *Ann Surg.* 2012;255(1):50–8.
30. Marchet A, Mocellin S, Ambrosi A, et al. The ratio between metastatic and examined lymph nodes (N ratio) is an independent prognostic factor in gastric cancer regardless of the type of lymphadenectomy: results from an Italian multicentric study in 1853 patients. *Ann Surg.* 2007;245(4):543–52.
31. Xu DZ, Geng QR, Long ZJ, et al. Positive lymph node ratio is an independent prognostic factor in gastric cancer after d2 resection

regardless of the examined number of lymph nodes. *Ann Surg Oncol.* 2009;16(2):319–26.
32. Coburn N, Seevaratnam R, Paszat L, et al. Optimal management of gastric cancer: results from an international RAND/UCLA expert panel. *Ann Surg.* 2014;259(1):102–08.
33. Waddell T, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D. Gastric cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi57–63.
34. Lee JH, Kim JG, Jung HK, et al. Clinical practice guidelines for gastric cancer in Korea: an evidence-based approach. *J Gastric Cancer.* 2014;14(2):87–104.
35. National Comprehensive Cancer Network Practice Guidelines in Oncology (NCCN Guidelines), Gastric Cancer, version 1. 2019. https://www.nccn.org. Accessed 5 May 2019.
36. Allum WH, Blazeby JM, Griffin SM, Cunningham D, Jankowski JA, Wong R. Guidelines for the management of oesophageal and gastric cancer. *Gut.* 2011;60(11):1449–72.
37. Cancer Programs Practice Profile Reports (CP^3R). https://www.facs.org/~/media/files/quality%20programs/cancer/ncdb/measure%20specs%20gastric.ashx. Accessed 15 Feb 2019.
38. Tokunaga M, Ohyama S, Hiki N, Fukunaga T, Aikou S, Yamaguchi T. Can superextended lymph node dissection be justified for gastric cancer with pathologically positive para-aortic lymph nodes? *Ann Surg Oncol.* 2010;17(8):2031–6.
39. Galizia G, Lieto E, De Vita F, et al. Modified versus standard D2 lymphadenectomy in total gastrectomy for nonjunctional gastric carcinoma with lymph node metastasis. *Surgery.* 2015;157(2):285-296.
40. Bonenkamp JJ, Hermans J, Sasako M, et al. Extended lymph-node dissection for gastric cancer. *N Engl J Med.* 1999;340(12):908–14.
41. Songun I, Putter H, Kranenbarg EM, Sasako M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. *Lancet Oncol.* 2010;11(5):439–49.
42. Degiuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian gastric cancer study group (IGCSG) randomised surgical trial. *Eur J Surg Oncol.* 2004;30(3):303–8.
43. Degiuli M, Sasako M, Ponti A. Morbidity and mortality in the Italian gastric cancer study group randomized clinical trial of D1 versus D2 resection for gastric cancer. *Br J Surg.* 2010;97(5):643–9.
44. Degiuli M, Sasako M, Ponti A, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. *Br J Surg.* 2014;101(2):23–31.
45. Robertson CS, Chung SC, Woods SD, et al. A prospective randomized trial comparing R1 subtotal gastrectomy with R3 total gastrectomy for antral cancer. *Ann Surg.* 1994;220(2):176–82.
46. Csendes A, Burdiles P, Rojas J, Braghetto I, Diaz JC, Maluenda F. A prospective randomized study comparing D2 total gastrectomy versus D2 total gastrectomy plus splenectomy in 187 patients with gastric carcinoma. *Surgery.* 2002;131(4):401–7.
47. Sano T, Sasako M, Yamamoto S, et al. Gastric cancer surgery: morbidity and mortality results from a prospective randomized controlled trial comparing D2 and extended para-aortic lymphadenectomy. Japan Clinical Oncology Group study 9501. *J Clin Oncol.* 2004;22(14):2767–73.
48. Maeta M, Yamashiro H, Saito H, et al. A prospective pilot study of extended (D3) and superextended para-aortic lymphadenectomy (D4) in patients with T3 or T4 gastric cancer managed by total gastrectomy. *Surgery.* 1999;125(3):325–331.
49. Kulig J, Popiela T, Kolodziejczyk P, Sierzega M, Szczepanik A. Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial. *Am J Surg.* 2007;193(1):10–5.
50. Yonemura Y, Wu CC, Fukushima N, et al. Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons. *Hepatogastroenterology.* 2006;53(69):389–94.
51. Yonemura Y, Wu CC, Fukushima N, et al. Randomized clinical trial of D2 and extended paraaortic lymphadenectomy in patients with gastric cancer. *Int J Clin Oncol.* 2008;13(2):132–7.
52. Kaibara N, Sumi K, Yonekawa M, et al. Does extensive dissection of lymph nodes improve the results of surgical treatment of gastric cancer? *Am J Surg.* 1990;159(2):218–21.
53. Pacelli F, Doglietto GB, Bellantone R, Alfieri S, Sgadari A, Crucitti F. Extensive versus limited lymph node dissection for gastric cancer: a comparative study of 320 patients. *Br J Surg.* 1993;80(9):1153–6.
54. Siewert JR, Bottcher K, Roder JD, Busch R, Hermanek P, Meyer HJ. Prognostic relevance of systematic lymph node dissection in gastric carcinoma. German Gastric Carcinoma Study Group. *Br J Surg.* 1993;80(8):1015–8.
55. Roukos D, Schmidt-Mathiesen A, Encke A. Adenocarcinoma of the gastric antrum: does D2 total gastrectomy with splenectomy improve prognosis compared to D1 subtotal gastrectomy? A long-term survival analysis with emphasis on Lauren classification. *Surg Oncol.* 1995;4(6):323–32.
56. Volpe CM, Koo J, Miloro SM, Driscoll DL, Nava HR, Douglass HO, Jr. The effect of extended lymphadenectomy on survival in patients with gastric adenocarcinoma. *J Am Coll Surg.* 1995;181(1):56–64.
57. Harrison LE, Karpeh MS, Brennan MF. Extended lymphadenectomy is associated with a survival benefit for node-negative gastric cancer. *J Gastrointest Surg.* 1998;2(2):126–31.
58. Onate-Ocana LF, Aiello-Crocifoglio V, Mondragon-Sanchez R, Ruiz-Molina JM. Survival benefit of D2 lympadenectomy in patients with gastric adenocarcinoma. *Ann Surg Oncol.* 2000;7(3):210–7.
59. Kasakura Y, Mochizuki F, Wakabayashi K, Kochi M, Fujii M, Takayama T. An evaluation of the effectiveness of extended lymph node dissection in patients with gastric cancer: a retrospective study of 1403 cases at a single institution. *J Surg Res.* 2002;103(2):252–9.
60. Gunji Y, Suzuki T, Kobayashi S, et al. Evaluation of D3/D4 lymph node dissection for patients with grossly N2 positive advanced gastric cancer. *Hepatogastroenterology.* 2003;50(52):1178–82.
61. Sierra A, Regueira FM, Hernandez-Lizoain JL, Pardo F, Martinez-Gonzalez MA, Javier AC. Role of the extended lymphadenectomy in gastric cancer surgery: experience in a single institution. *Ann Surg Oncol.* 2003;10(3):219–26.
62. Edwards P, Blackshaw GR, Lewis WG, Barry JD, Allison MC, Jones DR. Prospective comparison of D1 vs modified D2 gastrectomy for carcinoma. *Br J Cancer.* 2004;90(10):1888–92.
63. Bostanci EB, Kayaalp C, Ozogul Y, Aydin C, Atalay F, Akoglu M. Comparison of complications after D2 and D3 dissection for gastric cancer. *Eur J Surg Oncol.* 2004;30(1):20–5.
64. Kunisaki C, Akiyama H, Nomura M, et al. Comparison of surgical results of D2 versus D3 gastrectomy (para-aortic lymph node dissection) for advanced gastric carcinoma: a multi-institutional study. *Ann Surg Oncol.* 2006;13(5):659–67.
65. Marrelli D, Pedrazzani C, Neri A, et al. Complications after extended (D2) and superextended (D3) lymphadenectomy for gastric cancer: analysis of potential risk factors. *Ann Surg Oncol.* 2007;14(1):25–33.
66. Hu JK, Yang K, Zhang B, Chen XZ, Chen ZX, Chen JP. D2 plus para-aortic lymphadenectomy versus standardized D2

lymphadenectomy in gastric cancer surgery. *Surg Today.* 2009;39(3):207–213.
67. Zhang Y, Tian S. Does D2 plus para-aortic nodal dissection surgery offer a better survival outcome compared to D2 surgery only for gastric cancer consistently? A definite result based on a hospital population of nearly two decades. *Scand J Surg.* 2013;102(4):251–7.
68. Zhang H, Liu C, Wu D, et al. Does D3 surgery offer a better survival outcome compared to D1 surgery for gastric cancer? A result based on a hospital population of two decades as taking D2 surgery for reference. *BMC Cancer.* 2010;10:308.
69. Eom BW, Joo J, Kim YW, et al. Is there any role of additional retropancreatic lymph node dissection on D2 gastrectomy for advanced gastric cancer? *Ann Surg Oncol.* 2013;20(8):2669–75.
70. Eom BW, Joo J, Kim YW, et al. Improved survival after adding dissection of the superior mesenteric vein lymph node (14v) to standard D2 gastrectomy for advanced distal gastric cancer. *Surgery.* 2014;155(3):408–16.
71. Jatzko GR, Lisborg PH, Denk H, Klimpfinger M, Stettner HM. A 10-year experience with Japanese-type radical lymph node dissection for gastric cancer outside of Japan. *Cancer.* 1995;76(8):1302–12.
72. Adachi Y, Mimori K, Mori M, Maehara Y, Sugimachi K. Morbidity after D2 and D3 gastrectomy for node-positive gastric carcinoma. *J Am Coll Surg.* 1997;184(3):240–4.
73. Degiuli M, Sasako M, Ponti A, Calvo F. Survival results of a multicentre phase II study to evaluate D2 gastrectomy for gastric cancer. *Br J Cancer.* 2004;90(9):1727–32.
74. Nitti D, Marchet A, Mammano E, et al. Extended lymphadenectomy (D2) in patients with early gastric cancer. *Eur J Surg Oncol.* 2005;31(8):875–81.
75. Biffi R, Chiappa A, Luca F, et al. Extended lymph node dissection without routine spleno-pancreatectomy for treatment of gastric cancer: low morbidity and mortality rates in a single center series of 250 patients. *J Surg Oncol.* 2006;93(5):394–400.
76. Kosaka T, Usami K, Ueshige N, et al. Paraaortic lymph node dissection for gastric cancer in 244 consecutive cases. *Hepatogastroenterology.* 2006;53(70):629–33.
77. Roviello F, Pedrazzani C, Marrelli D, et al. Super-extended (D3) lymphadenectomy in advanced gastric cancer. *Eur J Surg Oncol.* 2010;36(5):439–46.
78. Degiuli M, Sasako M, Ponti A, Soldati T, Danese F, Calvo F. Morbidity and mortality after D2 gastrectomy for gastric cancer: results of the Italian gastric cancer study group prospective multicenter surgical study. *J Clin Oncol.* 1998;16(4):1490–3.
79. Maruyama K, Sasako M, Kinoshita T, Sano T, Katai H, Okajima K. Pancreas-preserving total gastrectomy for proximal gastric cancer. *World J Surg.* 1995;19(4):532–6.
80. Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. *Br J Surg.* 2006;93(5):559–63.
81. Sano T, Sasako M, Mizusawa J, et al. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma. *Ann Surg.* 2017;265(2):277–283.
82. Lee JH, Ryu KW, Park SR, et al. Learning curve for total gastrectomy with D2 lymph node dissection: cumulative sum analysis for qualified surgery. *Ann Surg Oncol.* 2006;13(9):1175–81.
83. Woodall CE 3rd, Scoggins CR, McMasters KM, Martin RC, 2nd. Adequate lymphadenectomy results in accurate nodal staging without an increase in morbidity in patients with gastric adenocarcinoma. *Am J Surg.* 2008;196(3):413–7.
84. Jang YJ, Park MS, Park SS, et al. Surgeon subspecialty as a factor in improving long-term outcomes for gastric cancer: twenty years of experience in Korea. *Arch Surg.* 2010;145(11):1091–6.
85. Parikh D, Johnson M, Chagla L, Lowe D, McCulloch P. D2 gastrectomy: lessons from a prospective audit of the learning curve. *Br J Surg.* 1996;83(11):1595–9.
86. Morgan JW, Ji L, Friedman G, Senthil M, Dyke C, Lum SS. The role of the cancer center when using lymph node count as a quality measure for gastric cancer surgery. *JAMA Surg.* 2015;150(1):37–43.
87. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Engl J Med.* 2001;345(10):725–30.
88. Macdonald JS. Role of post-operative chemoradiation in resected gastric cancer. *J Surg Oncol.* 2005;90(3):166–70.
89. Kurokawa Y, Sasako M. Recent advances in chemotherapy and chemoradiotherapy for gastrointestinal tract cancers: adjuvant chemoradiotherapy for gastric cancer. *Int J Clin Oncol.* 2008;13(6):479–82.
90. Fuchs CS, Niedzwiecki D, Mamon HJ, et al. Adjuvant chemoradiotherapy with epirubicin, cisplatin, and fluorouracil compared with adjuvant chemoradiotherapy with fluorouracil and leucovorin after curative resection of gastric cancer: results from CALGB 80101 (Alliance). *J Clin Oncol.* 2017;35(32):3671–7.
91. Park SH, Sohn TS, Lee J, et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. *J Clin Oncol.* 2015;33(28):3130–6.
92. Cats A, Jansen EPM, van Grieken NCT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. *Lancet Oncol.* 2018;19(5):616–28.
93. Sakuramoto S, Sasako M, Yamaguchi T, et al. Adjuvant chemotherapy for gastric cancer with S-1, an oral fluoropyrimidine. *N Engl J Med.* 2007;357(18):1810–20.
94. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15(12):1389–96.